AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Chronic Pain

Effective December 19, 2024

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SUMMARY OF RECOMMENDATIONS

The Evidence-based Practice Chronic Pain Panel's recommendations are based on critically-appraised higher-quality research evidence and on expert consensus observing First Principles when higher-quality evidence is unavailable or inconsistent (see Methodology). The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, preceding testing or conservative treatment, and contraindications that are elaborated in more detail for each test or treatment in the body

of this Guideline in using these recommendations in clinical practice or medical management. These recommendations are not simple “yes/no” criteria.

All ACOEM guidelines include analyses of numerous interventions, whether or not FDA-approved. For non-FDA-approved interventions, recommendations are based on the available evidence; however, this is not an endorsement of their use. In addition, many of the medications recommended are utilized off-label. (For example, anti-epileptic agents have been used off-label since the 1960s to treat chronic pain.)

Recommendations are made under the following categories:

- Strongly Recommended, “A” level
- Moderately Recommended, “B” level
- Recommended, “C” level
- Insufficient - Recommended (consensus-based), “I” level
- Insufficient - No Recommendation (consensus-based), “I” level
- Insufficient - Not Recommended (consensus-based), “I” level
- Not Recommended, “C” level
- Moderately Not Recommended, “B” level
- Strongly Not Recommended, “A” level

DIAGNOSTIC RECOMMENDATIONS

Intervention	Recommendation	Evidence
ANSAR Testing	ANSAR Testing for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	ANSAR Testing for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	ANSAR Testing for Diagnosing Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
Antibody Testing	Antibodies for Diagnosing Chronic Pain with Suspicion of Rheumatological Disorder	Recommended, Insufficient Evidence (I)
	Antibody Testing to Diagnose Fibromyalgia	Strongly Recommended, Evidence (A)
Bone Scanning	Bone Scanning for Diagnosing Complex Regional Pain Syndrome	Moderately Recommended, Evidence (B)
Cytokine Tests	Cytokine Tests for Diagnosing Complex Regional Pain Syndrome and Chronic Pain	Not Recommended, Insufficient Evidence (I)
Electromyography	Needle Electromyography (EMG) and Nerve Conduction Studies to Diagnose Fibromyalgia	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Needle Electromyography (EMG) and Nerve Conduction Studies to Evaluate Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Surface Electromyography (EMG) for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Surface Electromyography (EMG) for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Surface Electromyography for Diagnosing Complex Regional Pain Syndrome and Chronic Pain	Not Recommended, Insufficient Evidence (I)
FCEs	Functional Capacity Evaluations (FCEs) for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Functional Capacity Evaluations for Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
Injections	Local Anesthetic Injections for Diagnosing Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Local Anesthetic Injections for Diagnosing Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Local Anesthetic Injections for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Laboratory Tests	Antibodies to Confirm Specific Disorders	Recommended, Insufficient Evidence (I)
	Cytokine Tests for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Laboratory Tests for Peripheral Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Nonspecific Inflammatory Markers to Screen for Inflammatory Disorders	Recommended, Evidence (C)
	Occupational Neurotoxin Exposure Measurement for Diagnosis of Neuropathic Pain	Recommended, Insufficient Evidence (I)
MRI	Functional Magnetic Resonance Imaging (fMRI) for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Functional Magnetic Resonance Imaging (fMRI) for Diagnosing Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Functional Magnetic Resonance Imaging (fMRI) for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
QSART	Quantitative Sudomotor Axon Reflex Testing (QSART) for Diagnosing Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
SPECT / PET	Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Single-Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) for Diagnosing Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Single-Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Thermography	Thermography for Diagnosing Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
X-Rays	X-Rays for Diagnosis of Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)

TREATMENT RECOMMENDATIONS

Intervention	Recommendation	Evidence
Acupuncture	Acupuncture for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Acupuncture for Fibromyalgia	Recommended, Evidence (C)
	Acupuncture/Electroacupuncture for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Anticonvulsants	Anticonvulsant Medications for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Anticonvulsant Medications for Neuropathic Pain	Moderately Recommended, Evidence (B)
	Anticonvulsant Medications for Fibromyalgia	Moderately Recommended, Evidence (B)
	Gabapentin or Pregabalin for Complex Regional Pain Syndrome	Recommended, Evidence (C)

Intervention	Recommendation	Evidence
Antidepressants	Antidepressants for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Bupropion, Trazodone, or Pramipexole for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Duloxetine for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Noradrenergic and Specific Serotonergic Antidepressants for Fibromyalgia	Moderately Recommended, Evidence (B)
	Norepinephrine Reuptake Inhibitors (NRIs) for Fibromyalgia	Recommended, Evidence (C)
	Selective Serotonin Reuptake Inhibitors (SSRIs) and Norepinephrine-Dopamine Reuptake Inhibitors (NDRIs) for Neuropathic Pain	Recommended, Evidence (C)
	Selective Serotonin Reuptake Inhibitors for Fibromyalgia	Moderately Recommended, Evidence (B)
	Serotonin Norepinephrine Reuptake Inhibitors (Duloxetine, Milnacipran) for Fibromyalgia	Moderately Recommended, Evidence (B)
	Serotonin Receptor Antagonists for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Tricyclic, Tetracyclic, and Serotonin-Norepinephrine Reuptake Inhibitor Antidepressants for Neuropathic Pain	Moderately Recommended, Evidence (B)
Antihypertensives	Clonidine for Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Clonidine for Neuropathic Pain	Recommended, Evidence (C)
	Ketanserin for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
Anti-inflammatories	Glucocorticosteroids for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Oral Glucocorticosteroids for Complex Regional Pain Syndrome	Moderately Recommended, Evidence (B)

Intervention	Recommendation	Evidence
Antipsychotics	Antipsychotic Medications for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Atypical Antipsychotics for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Antivirals	Antiviral Medications for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Valcyclovir for Fibromyalgia	Not Recommended, Evidence (C)
Aquatic Therapy	Aquatic Therapy for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Aquatic Therapy for Fibromyalgia	Moderately Recommended, Evidence (B)
Bed Rest	Bed Rest for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Reduced Activity or Bed Rest for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Reduced Activity or Bed Rest for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Behavioral Interventions	Acceptance and Commitment Therapy for Chronic Pain	Recommended, Evidence (C)
	Biofeedback for Chronic Pain	Recommended, Insufficient Evidence (I)
	Cognitive Behavioral Therapy (CBT) for Chronic Pain	Moderately Recommended, Evidence (B)
	Emotional Awareness and Expression Training for Chronic Pain	Recommended, Evidence (C)
	Fear Avoidance Belief Training for Chronic Pain	Moderately Recommended, Evidence (B)
	Fear Avoidance Belief Training for Fibromyalgia	Recommended, Insufficient Evidence (I)
	Mindfulness-based Stress Reduction and Mindfulness Meditation for Chronic Pain	Moderately Recommended, Evidence (B)

Intervention	Recommendation	Evidence
	Psychological Evaluation for Chronic Pain	Recommended, Insufficient Evidence (I)
Bisphosphonates	Bisphosphonates for Complex Regional Pain Syndrome	Strongly Recommended, Evidence (A)
Desensitization	Desensitization Techniques for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
Electrical Stimulation	Cortical Electrostimulation for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Direct Current Stimulation for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Microcurrent Cranial Electrical Stimulation for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Microcurrent Electrical Stimulation for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Microcurrent Electrical Stimulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Sympathetic Electrotherapy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Sympathetic Electrotherapy for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Transcranial Direct Current Stimulation for Fibromyalgia	Recommended, Evidence (C)
	Transcranial Direct Current Stimulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Transcranial Magnetic Stimulation for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Electrical Therapies	H-Wave® Device Stimulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Other Electrical Therapies for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Electromagnetic	Pulsed Electromagnetic Field Therapy for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Pulsed Electromagnetic Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Repetitive Transcranial Magnetic Stimulation (rTMS) for Neuropathic Pain	Moderately Recommended, Evidence (B)
Exercise	Aerobic Exercise for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Aerobic Exercise for Fibromyalgia	Moderately Recommended, Evidence (B)
	Aerobic Exercise for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Aquatic Therapy for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Strengthening Exercise for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Strengthening Exercises for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Strengthening, Stabilization, and Resistance Exercise for Fibromyalgia	Moderately Recommended, Evidence (B)
	Stretching Exercises for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Stretching Exercises For Fibromyalgia (Non-Yoga)	Not Recommended, Insufficient Evidence (I)
Galvanic Therapy	High-voltage Galvanic Therapy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	High-voltage Galvanic Therapy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Graded Motor Imagery	Graded Motor Imagery for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
Heat	Diathermy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Diathermy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Fluidotherapy for Complex Regional Pain Syndrome	Recommended, Evidence (C)

Intervention	Recommendation	Evidence
	Hot and Cold Therapies for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Self-application of Heat Therapy for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Ultrasound for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Homeopathy	Homeopathic and Herbal Treatments for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Homeopathic and Herbal Treatments for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Hormones	Calcitonin for Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Calcitonin for Fibromyalgia	Not Recommended, Evidence (C)
	Dehydroepiandrosterone (DHEA) for Fibromyalgia	Not Recommended, Evidence (C)
	Growth Hormone for Fibromyalgia	Recommended, Evidence (C)
	Hormone Replacement Therapy for Fibromyalgia	Not Recommended, Evidence (C)
	Melatonin for Fibromyalgia	Recommended, Evidence (C)
	Oxytocin for Fibromyalgia	Not Recommended, Evidence (C)
	Raloxifene for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Hyperbaric Oxygen	Hyperbaric Oxygen for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Hyperbaric Oxygen for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Ice	Cryotherapies for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Cryotherapy (Self-Application or In-Office) for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Hot and Cold Therapies for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Immunomodulators	Thalidomide and Lenalidomide for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
Immunosuppressants	Mycophenolate for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
Infrared Therapy	Infrared Therapy (Clinician-Based or Self-Application) for Neuropathic Pain	Not Recommended, Evidence (C)
	Infrared Therapy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
Injections	Adenosine for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Botulinum Injections for Neuropathic Pain	Recommended, Evidence (C)
	C2 Nerve Stimulation for Fibromyalgia	Not Recommended, Evidence (C)
	Corticosteroids for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Immunoglobulin for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Intrapleural Bupivacaine Infusions for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Intrapleural Bupivacaine Infusions for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Intrathecal Baclofen for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Intrathecal Glucocorticosteroids for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Intravenous Adenosine for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Intravenous Immunoglobulin (IVIG) for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Intravenous NSAIDs for Complex Regional Pain Syndrome	Recommended, Evidence (C)

Intervention	Recommendation	Evidence
	Ketamine for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Ketamine Infusion for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Ketamine Infusions for Fibromyalgia	Not Recommended, Evidence (C)
	Ketorolac Injections for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Kinase Inhibitors for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Lidocaine Infusion for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Lidocaine Infusion for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Lidocaine Infusions for Fibromyalgia	Moderately Not Recommended, Evidence (B)
	Mannitol for Treatment of Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Monoclonal Antibody Injections for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Prolotherapy Injections for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Tumor Necrosis Factor-Alpha Blockers for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
Interferential / Ultrasound	Interferential and Ultrasound Therapies for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Interferential Therapy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Interferential Therapy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Iontophoresis	Iontophoresis for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Iontophoresis for Fibromyalgia	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Iontophoresis for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Laser Therapy	Low-level Laser Therapy for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Low-Level Laser Therapy for Fibromyalgia	Moderately Not Recommended, Evidence (B)
	Low-level Laser Therapy for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Light Therapy	Polarized Polychromatic Light Therapy for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
Magnets	Magnets and Magnetic Stimulation for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Magnets and Magnetic Stimulation for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Magnets or Magnetic Stimulation for Fibromyalgia	Not Recommended, Evidence (C)
Manipulation	Manipulation and Mobilization for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Manipulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Massage	Massage for Fibromyalgia	Recommended, Insufficient Evidence (I)
	Massage for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Mechanical Massage Devices for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Mirror Therapy	Mirror Therapy and Guided Imagery for Complex Regional Pain Syndrome	Recommended, Evidence (C)
Muscle Relaxants	Muscle Relaxants for Acute Exacerbations of Neuropathic Pain	Recommended, Evidence (C)
	Skeletal Muscle Relaxants for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Music Therapy	Music Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
Myofascial Release	Myofascial Release for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Myofascial Release for Fibromyalgia	Not Recommended, Evidence (C)
	Myofascial Release for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Nerve Blocks	Brachial Plexus Blocks and Infusions for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Bretylium Bier Blocks for Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Dorsal Ganglion Destruction for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Ganglion Blocks for Fibromyalgia	Moderately Not Recommended, Evidence (B)
	Guanethidine Bier Blocks for Complex Regional Pain Syndrome	Strongly Not Recommended, Evidence (A)
	Methylprednisolone Bier Blocks for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	Nerve Blocks for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Phentolamine Bier Blocks for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Regional Nerve Blocks for Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Reserpine Bier Blocks for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Stellate and Lumbar Ganglion Blocks for Complex Regional Pain Syndrome	Recommended, Evidence (C)
NMDA Receptor Antagonists	NMDA Receptor Antagonists for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
NSAIDs	Acetaminophen for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Acetaminophen for Neuropathic Pain	Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Acetaminophen for Treatment of Fibromyalgia	Recommended, Insufficient Evidence (I)
	Nonsteroidal Anti-inflammatory Drugs (NSAIDs) for Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Oral Nonsteroidal Anti-inflammatory Drugs (NSAIDs) for Fibromyalgia	Recommended, Insufficient Evidence (I)
	Oral NSAIDs for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Topical NSAIDs for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
Opioids	Opioids for Complex Regional Pain Syndrome	See ACOEM Opioids guideline
	Opioids for Fibromyalgia	Not Recommended, Evidence (C)
Other Medications	Acetyl-1-Carnitine for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Alpha1-Antitrypsin for Fibromyalgia	Not Recommended, Evidence (C)
	Alpha-lipoic Acid for Fibromyalgia	Not Recommended, Evidence (C)
	Antidiencephalon for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Coenzyme Q for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Creatine for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Dextromethorphan for Neuropathic Pain	Recommended, Evidence (C)
	Dolasetron for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Memantine for Neuropathic Pain	Not Recommended, Evidence (C)
	Naltrexone for Fibromyalgia	Not Recommended, Evidence (C)

Intervention	Recommendation	Evidence
	Ondansetron for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Pyridostigmine for Fibromyalgia	Not Recommended, Evidence (C)
	Ritanserin for Fibromyalgia	Not Recommended, Evidence (C)
	S-Adenosylmethionine for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Sodium Oxybate for Fibromyalgia	Moderately Recommended, Evidence (B)
	Suvorexant for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Terguride for Fibromyalgia	Not Recommended, Evidence (C)
	Tumor Necrosis Factor-alpha Blockers for Neuropathic Pain	Not Recommended, Evidence (C)
	Zolpidem for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Zopiclone for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Ozone	Ozone for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Pain Exposure	Pain Exposure Physical Therapy for Treatment of Complex Regional Pain Syndrome	Recommended, Evidence (C)
Qigong	Qigong for Fibromyalgia	Not Recommended, Evidence (C)
Radiation	External Radiation for Sympathetic Blockade for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)
	External Radiation for Sympathetic Blockade for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Reflexology	Reflexology for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Reflexology for Fibromyalgia	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
	Reflexology for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Rehabilitation	Acceptance and Commitment Training for Fibromyalgia	Recommended, Evidence (C)
	Attention Modification for Fibromyalgia	Not Recommended, Evidence (C)
	Education for Fibromyalgia	Recommended, Evidence (C)
	Exposure Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Guided Imagery for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
	Mindfulness Intervention for Fibromyalgia	Recommended, Evidence (C)
	Participatory Ergonomics Programs for Chronic Pain	Recommended, Insufficient Evidence (I)
	Physical or Occupational Therapy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Psychoeducational Treatment for Fibromyalgia	Recommended, Insufficient Evidence (I)
	Shared Decision-Making for Fibromyalgia	Recommended, Insufficient Evidence (I)
	Tertiary Pain Programs for Treatment of Chronic Pain (Interdisciplinary Pain Rehabilitation, Multidisciplinary Rehabilitation, Chronic Pain Management, Functional Restoration)	Recommended, Insufficient Evidence (I)
	Virtual Reality for Fibromyalgia	Recommended, Evidence (C)
	Work Conditioning, Work Hardening, Early Intervention Programs, and Back Schools for Chronic Pain	Recommended, Insufficient Evidence (I)
Reiki	Reiki for Fibromyalgia	Not Recommended, Evidence (C)
Spa Therapy	Spa Therapy and Balneotherapy for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Splints	Occlusal Splint for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)

Intervention	Recommendation	Evidence
Surgery	Amputation for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Intrathecal Drug Delivery Systems for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
	Motor Cortex Stimulation for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Peripheral Nerve Stimulation for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Preoperative Intravenous Regional Anesthesia with Clonidine for Prevention of Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Spinal Cord Stimulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Spinal Cord Stimulators for Complex Regional Pain Syndrome	Recommended, Evidence (C)
	Surgical Decompression for Neuropathic Pain	Recommended, Insufficient Evidence (I)
	Sympathectomy for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
Tai Chi	Tai Chi for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Tai Chi for Fibromyalgia	Moderately Recommended, Evidence (B)
Taping	Kinesiotaping or Taping for Fibromyalgia	Not Recommended, Evidence (C)
	Taping and Kinesiotaping for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
TENS / PENS	Percutaneous Electrical Nerve Stimulation (PENS) for Complex Regional Pain Syndrome	Not Recommended, Insufficient Evidence (I)
	Percutaneous Electrical Nerve Stimulation (PENS) for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
	Transcutaneous Electrical Nerve Stimulation (TENS) for Complex Regional Pain Syndrome	Recommended, Evidence (C)

Intervention	Recommendation	Evidence
	Transcutaneous Electrical Nerve Stimulation (TENS) for Fibromyalgia	Not Recommended, Evidence (C)
	Transcutaneous Electrical Nerve Stimulation (TENS) for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Topical Medications	Capsaicin Patches for Neuropathic Pain	Moderately Recommended, Evidence (B)
	Capsicum Creams for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Dimethyl Sulfoxide (DMSO) for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	EMLA Cream for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Lidocaine Patches for Complex Regional Pain Syndrome	No Recommendation, Insufficient Evidence (I)
	Lidocaine Patches for Neuropathic Pain	Moderately Recommended, Evidence (B)
	N-Acetylcysteine (NAC) for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Topical Ketamine and Amitriptyline (Alone or in Combination) for Neuropathic Pain	Moderately Not Recommended, Evidence (B)
	Topical Medications and Lidocaine Patches for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
	Topical NSAIDs for Chronic Pain	Recommended, Evidence (C)
Vibration	Whole Body Vibration for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Virtual Reality	Virtual Reality Therapy for Complex Regional Pain Syndrome	Recommended, Evidence (C)
Vitamins / Minerals	Magnesium For Neuropathic Pain	Moderately Not Recommended, Evidence (B)
	Magnesium Sulfate for Complex Regional Pain Syndrome	Not Recommended, Evidence (C)

Intervention	Recommendation	Evidence
	Vitamin B for Neuropathic Pain	Not Recommended, Evidence (C)
	Vitamin C for Prevention of Complex Regional Pain Syndrome	Moderately Recommended, Evidence (B)
	Vitamin D for Fibromyalgia	Not Recommended, Evidence (C)
Weight Loss / Nutrition	Dietary Interventions for Fibromyalgia	Not Recommended, Evidence (C)
	Weight Reduction for Fibromyalgia	Recommended, Evidence (C)
Yoga / Pilates	Pilates for Fibromyalgia	Recommended, Evidence (C)
	Yoga for Complex Regional Pain Syndrome	Recommended, Insufficient Evidence (I)
	Yoga for Fibromyalgia	No Recommendation, Insufficient Evidence (I)

INTRODUCTION

The American College of Occupational and Environmental Medicine (ACOEM) Chronic Pain Guideline is designed to provide clinicians (the primary target users of this guideline) with evidence-based guidance on the evaluation and treatment of working-age adults who have chronic pain. While the primary patient population target is working adults, the principles may apply more broadly, especially as the evidence base is almost identical. This guideline does not address guidance for numerous specific disorders, including chronic phases of those conditions (see recommendations available in other ACOEM guidelines). Instead, it addresses a general approach to the evaluation and management of patients with chronic pain, while also including guidance for a few specific disorders (i.e., complex regional pain syndrome, fibromyalgia, neuropathic pain) not found elsewhere in the ACOEM guidelines. This guideline also addresses psychological and behavioral aspects of chronic pain in far greater depth than in the other ACOEM guidelines. This is due to the major influences of psychological and behavioral issues in many, if not most, chronic pain patients (see Figure 1).

The objectives of the Chronic Pain Guideline include examinations of baseline status, diagnostic tests, imaging, physical activity, return to work, medications, physical therapy, injections, rehabilitation psychological evaluations, and behavioral treatment. The comparative effectiveness of various treatment options is addressed where research is available. It is recognized that there are differences in workers' compensation systems [(1)].

There also are regional differences in treatment approaches [2,3,4]. The Evidence-based Practice Chronic Pain Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine and Reed Group, which have not influenced the Guidelines. The literature is routinely monitored and evaluated for quality publications that would modify this guidance. The guideline is planned to be comprehensively updated at least every five years, or more frequently should evidence require it. The health questions for chronic pain disorders (including for complex regional pain syndrome, neuropathic pain, fibromyalgia, chronic pain syndrome) addressed by this guideline include the following:

- What evidence supports the initial assessment and diagnostic approach?
- What red flags signify potentially serious underlying condition(s)?
- What diagnostic approaches and special studies are needed to clarify the clinical pathology?
- What initial treatment approaches have evidence of efficacy?
- What is the evidence of work-relatedness for various diagnoses?
- What modified duty, activity prescriptions, and/or limitations are effective and recommended?
- When is it acceptable to return the individual to work?
- When initial treatment options fail, what evidence supports other interventions?
- When and for what conditions are injections and other invasive procedures recommended?
- When and for what conditions is surgery recommended?
- What management options are recommended for delayed recovery?
- What evidence of effectiveness is available for psychological and behavioral interventions for chronic pain conditions?

A detailed methodology document used for guideline development, including evidence selection, scoring, incorporation of cost considerations [5,6], and formulation of recommendations, is available online as a full-length document and has also been summarized in *JOEM*. All evidence garnered from seven databases was included in this guideline (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro). Comprehensive searches for evidence were performed with both PubMed and Google Scholar up through 2023 to help assure complete capture. There was no limit on year of publication. Search terms are listed with each table of evidence. Guidance was developed with sufficient detail to facilitate assessment of compliance [5] and auditing/monitoring [6]. Alternative options to manage conditions are provided.

This guideline has undergone extensive external peer review. All AGREE II [6], IOM [5], AMSTAR, and GRADE criteria are adhered to in this guideline. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers [5].

Recommendations on assessing and treating adults with chronic pain are presented herein. Topics include the initial assessment and diagnosis of patients with chronic pain, identification of red flags that may suggest the presence of a serious underlying medical condition, initial clinical evaluation, management, diagnostic considerations, and special studies to identify clinical pathology, work-relatedness, modified duty and activity, rehabilitative strategies, return to work, psychological evaluation, behavioral treatments, and further management considerations including delayed recovery. Another ACOEM

guideline addresses disability prevention and management in more detail (see the ACOEM Work Disability Prevention and Management Guideline).

BASIC PRINCIPLES AND DEFINITIONS

Active Exercise Therapy: "Active exercise therapy" describes treatments requiring the patient to perform active exercises for their individualized treatment plan. For most patients with chronic pain, this includes aerobic exercises, cardiovascular training, strengthening, motor control exercises, and muscle reconditioning (weight lifting or resistance training) [7,8,9]. Active exercise therapy is used as a primary treatment for chronic pain, is usually initiated in the course of treating acute and subacute pain, and also is a primary treatment after various surgeries. Active exercise therapy would be considered to include stretching exercises, but only among those patients with significant reductions in range(s) of motion; for most patients with chronic pain, stretching is not considered active exercise because stretching exercises produce a lack of functional gains[8]. The word "active" is used to differentiate individualized exercise programs designed to address and rehabilitate specific functional, anatomic or physiologic deficits from passive treatment modalities or from forms of "exercise" that require very little effort or investment on the part of the patient or clinician.

Acute Pain: Pain with a duration of 1 month or less. Pain lasting >1 month but <3 months is termed "subacute."

Advocagenic: An *advocagenic illness* is a response to legal counsel or legal system, induced or magnified by the counsel or system itself; usually used for unfavorable responses [10,11].

Allodynia: Pain due to a stimulus which does not normally provoke pain (e.g., light touch causes pain).

Catastrophization (Pain Catastrophization). The propensity to exaggerate the pain and disorder, and to typically project the worst outcome on the situation, future surgical outcome, recovery, prognosis and any other factor. It is often accompanied by expressions of helplessness.

Central Pain: Pain that is due to a lesion or other abnormality that is located in the central nervous system. Examples of disorders in this category include tumors, strokes, and traumatic brain injury (TBI) sequelae.

Central Sensitization and Central Sensitivity Syndromes: Central sensitization is considered a condition of the central nervous system that produces and maintains a chronic pain state. While the exact mechanism(s) is(are) not known, the entity is believed to involve an up-regulation from a normal state of perceptions of pain. Patients may have increased sensitivity to pain, thus experiencing as painful something that normal individuals would not generally consider painful (e.g., touch, pressure), also known as allodynia. They also frequently experience more pain than usual to a mildly painful stimulus (hyperalgesia). The prototypical diseases for central sensitization have been generally considered to be post-stroke and spinal cord injury. Other diseases commonly theorized as developing by a central sensitization mechanism include fibromyalgia, traumatic brain injury, and multiple sclerosis. There is some evidence this may also occur in some patients with knee osteoarthrosis and lateral elbow pain.

Chronic Pain: Pain categorized purely based on duration is defined as chronic when lasting at least 3 months. This may be divided into chronic malignant pain and chronic non-malignant pain, although evidence of meaningful differences between those 2 categories is negligible.

Pain is known to be associated with sensory, affective, cognitive, social and other processes [1,2,3,4]. The pain sensory system itself is organized into two parts, often called first and second pain. A-ð nerve fibers conduct first pain via the neospinalthalamic tract to the somatosensory cortex, and provide information about pain location and quality. In contrast, unmyelinated C fibers conduct second pain via the paleospinalthalamic tract, and provide information about pain intensity. Second pain is more closely associated with emotion and memory neural systems than it is with sensory systems [5,6,12].

As a patient's condition transitions through the acute, subacute and chronic phases, the central nervous system is reorganized. The temporal summation of second pain produces a sensitization or "windup" of the spinal cord [8], and the connections between the brain regions involved in pain perception, emotion, arousal, and judgment are changed by persistent pain [13]. The person is thought to process signals in terms of pain or more pain than would be usual for a given stimulus [1,2,3,4]. CNS reorganization occurs that is also associated with changes in the volume of brain areas [14], decreased grey matter in the prefrontal cortex [14], and the brain appearing to age more rapidly [15]. As pain continues over time, the CNS remodels itself so that pain becomes less closely associated with sensation, and more closely associated with arousal, emotion, memory and beliefs [12,16]. Because of these CNS processes, the physician should be aware that as the patient enters the subacute phase, it becomes increasingly important to consider the psychosocial context of the disorder being treated, including the patient's social circumstances, arousal level, emotional state, and beliefs about the disorder. However, behavioral complications and physiological changes associated with chronicity and central sensitization may also be present in the acute phase, and within hours of the initial injury [17].

Chronic Non-malignant Pain (CNMP): Pain lasting over 3 months that is not due to neoplasms, cancers, or tumors. It is also referred to as chronic non-cancer pain (CNCP).

Chronic Pain Syndrome: Pain over 3 months duration with additional features such as limited functional status, vocational status, and/or significant psychological features are present.

Cognitive Behavioral Therapy: One of a set of heterogenous but related psychotherapies that assist workers in living with pain and/or physical debility and/or mental health issues and in so doing help improve functional recovery.

Delayed Recovery: An increase in the period of time prior to returning to work or usual activities compared with the length of time expected based on reasonable expectations, severity of disorder, age, and treatments provided.

Factitious Illness: A mental disorder wherein the patient either falsifies or self-induces symptoms of illness. It is thought to involve both conscious and non-conscious factors. The primary drive is thought to be assuming the role of being a patient or being sick. By definition it is not occupational.

Fear Avoidant Beliefs (Kinesiophobia): Beliefs that one may (re)injure oneself by movement and/or participation in exercises, ADLs, chores, work and/or modified ("light duty") work duty assignments. Fear avoidant belief training addresses these fears.

Flags: Signs, symptoms, attributes, historical findings, or screening/questionnaire test results that are typically correlated with serious conditions, worse prognosis, and/or the need to consider an alternate evaluative or treatment approach. These include red, orange, yellow, blue and black flags [(18)]:

- **Red Flag:** Symptoms and/or signs of a serious underlying disorder (e.g., cancer, serious infection, cauda equina syndrome).
- **Orange Flag:** Symptoms and/or signs of psychological disorders (e.g., depressive, anxiety, personality disorders).
- **Yellow Flag:** Counterproductive beliefs (e.g., kinesiophobia/fear avoidant beliefs, catastrophization, pain equates to damage), emotional responses (e.g., anxiety, worry, fear, depression), pain behaviors (e.g., avoidance of work, avoidance of ADLs, undue antalgia). Yellow flags also include poor coping strategies (e.g., overreliance on passive treatments/modalities).
- **Blue Flag:** Perceptions regarding the relationships between work and health (e.g., belief that work is injurious, coworkers/supervisor is unsupportive).
- **Black Flag:** Firm limits that are sometimes considered to include "dark red" flags that denote severe or serious situations. Firm limits include legislative restrictions for return to work, union/contractual issues that block potential performance of a modified/light duty job, conflicts with worker's compensation insurance staff/policies, interference or oversolicitousness of family and/or healthcare providers.

Functional Capacity Evaluation (FCE): A comprehensive battery of performance-based tests used to attempt to assess an individual's ability for work and ADLs [(19)]. An FCE may be done to identify an individual's ability to perform specific job tasks associated with a job (job-specific FCE), or the individual's ability to perform physical activities associated with any job (general FCE). The term "capacity" used in an FCE may be misleading in cases where there appears to be functional limitations, since an FCE generally measures performance rather than capacity, thus understatements of true capacity are likely whereas overstatements are less likely. There is also significant variation in study quality, generally reflecting, at least in part, both the experience and overall orientation of the clinician performing the study.

Functional Deficit: The degree of loss(es) of function compared with the individual's baseline.

Functional Improvement (especially Objective Evidence): Evaluation of the patient prior to the initiation of treatment should include documentation regarding objective physical findings and current functional abilities both at home and at work. This should include a clear statement regarding what objective or functional goals are to be achieved through the use of treatment. These measures should be tracked during treatment and evidence of progress towards meeting these functional goals should be sought (see Initial Approaches to Treatment Guideline). Examples of the best functional goals to track are: increased physical capabilities including job specific activities, return to work, return from off-duty-status to modified duty, performance of exercise goals, measures of strength, aerobic capacity, participation in progressive active exercises, and other activities of daily living. Instrumental ADLs may be included if appropriate, although or most chronic pain patients these are not

materially affected (e.g., managing finances of managing medications). Questionnaires/ tool(s), such as the Modified Oswestry Questionnaire and Roland-Morris Disability Questionnaire, may be used to help track progress, although they are less robust in an occupational setting due to their subjective nature and should not substitute for tracking with objective measures.

Functional Limitations: Functional limitation(s) for a worker include a barrier, activity limitation, and/or impairment in the ability to perform a job, essential work task(s), and/or activities of daily living. These limitation(s) are addressed with an individualized, tailored functional restoration plan that specifically addresses each limitation.

Functional Restoration: The term functional restoration is often used for a variant of interdisciplinary pain alleviation or at least amelioration characterized by objective measurement of physical function, intensive graded exercise and multi-modal pain/disability management with both psychological and case management features [20,21,22,23,24,25,26]. The term has become popular as a philosophy and an approach to medical care and rehabilitation. In that sense, the term refers to a blend of various techniques (both physical and psychosocial) for evaluating and treating the chronic non-malignant pain patient, particularly in the workers' compensation setting.

Hyperalgesia: Increased or markedly painful response to a stimulus which is normally painful (e.g., light pinprick leads to extreme and prolonged pain). This is distinguished from *allodynia*, pain due to a stimulus which does not normally provoke pain (e.g., light touch causes pain).

Impairment: Impairment is "a significant deviation, loss, or loss of use of any body structure or body function in an individual with a health condition, disorder, or disease" (adapted from AMA Guides, 6th edition).

Long-Term Care Plan (LTCP): A plan that is typically formulated at the end of Maximum Medical Improvement to project reasonably necessary and/or essential clinical needs. A well-formulated plan is thoughtful and helps insurers plan resource demands. Some LTCPs include unfounded and unnecessary expenses that then increase settlement costs.

Major Depressive Disorder: Major depressive disorder is a psychiatric condition that may or may not be related to chronic pain as it is common without pain. However, there is a high occurrence rate with chronic pain. Co-morbid psychiatric conditions including major depressive disorder may interfere with treatment as well as outcomes.

Malignant Pain: Pain associated with cancer, or treatment effects of cancer is commonly termed malignant pain. This pain should be distinguished from non-malignant pain or chronic non-malignant pain.

Malingering: The conscious feigning, manufacturing, or exaggeration of symptoms for purposes of secondary gain (e.g., monetary, avoidance of work, obtaining drugs). Though relatively uncommon, malingering is likely substantially more prevalent in chronic workers' compensation settings than other contexts due to monetary and other incentives. It is usually suggested, in part, through atypical clinical presentations, psychological evaluation, psychometric testing, or discrepancies with surveillance or videotaping [27]. Malingering is not considered a mental disorder.

Maximum Medical Improvement: A medically determined state in which there is the attainment of a plateau in healing. A healing plateau is generally considered to have been reached after there is no functional gain and after there are no other therapies to be employed that are reasonably likely to result in material improvement. The time to attain MMI varies widely by disorder, and severity and can range from days (e.g., mild low back pain, laceration) to 2 years (e.g., traumatic brain injury).

Modified Duty (Light Duty, Transitional Work): A job that is generally performed on a time-limited basis as a transition to normal work for that worker that typically involves lower physical and/or mental demands.

Musculoskeletal Pain: Pain attributed to and/or experiences in any aspect(s) of the musculoskeletal system to include muscles, tendons, myotendinous junctions, ligaments, the spine and the extremities. *Work-related musculoskeletal pain* in workers' compensation systems' definitions are defined in case law and vary, but are generally considered to have been caused or substantially aggravated by work task(s).

Negative Belief System: A mental state or set of beliefs that are excessively negative compared with truth or reality.

Neuralgia: Pain that is thought to be nerve related and is present in the distribution of a nerve or nerve root.

Neuritis: Neuritis technically describes an inflammation of a nerve(s). In practice it is often inaccurately used to label any pain thought to be nerve-related, regardless of whether or not there is an inflammatory process.

Neurogenic Pain: Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system.

Neuropathic Pain: Pain caused by abnormal function of the nervous system due to injury or disease. There is generally no relationship between end-organ damage and pain perception as is thought to be present in nociceptive pain. Although an affected individual perceives pain as emanating from some bodily structure (e.g., the distal lower extremity in sciatica), the pathophysiologic basis for the pain is believed to be an abnormality in the functioning of the central or peripheral nervous system, rather than an abnormality in the location where the pain is perceived. Neuropathic pain can be due to a lesion in the central nervous system, as is seen in post-stroke pain or thalamic pain, (central neuropathic pain) or due to lesions in the peripheral nervous system. Postherpetic neuralgia, painful neuropathies (e.g., diabetes mellitus), and what was previously referred to as causalgia (CRPS II) are all examples of conditions characterized by peripheral neuropathic pain. Note: Neuropathic pain is a clinical description (not a diagnosis) that requires a demonstrable lesion or disease that satisfies established neurological diagnostic criteria.

Neuropathy: A disturbance of function or pathological change in a nerve. This is called a mononeuropathy if involving one nerve. If diffuse and bilateral, it is called a peripheral or polyneuropathy.

Nociceptive Pain: Pain caused by a lesion or disease of the somatosensory nervous system. Pain that arises through the normal activation of pain pathways. In the acute stage, it serves as a protective mechanism to alerting the individual to the presence of potentially damaging stimuli. Stimuli are transduced at the injury site with chemical, mechanical, and thermal

stimuli all eliciting responses in specific subsets of neurons. These stimuli result in increased firing rates in pain-specific neurons with *transmission* of neural signals resulting ultimately in pain *perception* at the cortical level. Once the inciting stimulus is removed and healing has occurred, nociceptive pain typically resolves. While nociceptive pain can be somatic (carried along the sensory fibers) or visceral (transmitted through the autonomic nervous system), most injuries lead to somatic pain.

Nociplastic Pain: Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Note: Patients can have a combination of nociceptive and nociplastic pain.

Nocebo Effect: The opposite of placebo effect, occurring when the patient believes that exposure to treatment, activity, or event may be harmful and leads to adverse effects or results in less benefit than expected.

Outcome Measure for Psychological Testing: In contrast to screening measures or psychological tests, it is preferable if an outcome measure contains only changeable "state" items, not unchanging "fixed" items (e.g. a history of suicide attempt is an indication of depressive vulnerability, but treatment cannot change this fixed historical fact). An outcome measure is scored using an ipsative method which compares patients to themselves (e.g. is your score today better than when you started?). Outcome measures may assess physical functioning, quality of life, psychological states, or satisfaction with care. An example of outcome measures is the PROMIS test.

Pain Behavior: Verbal and non-verbal actions (e.g., grimacing, groaning, limping, using pain relieving or support devices, requesting pain medications, etc.) which communicate the concept of pain to others.

Pain Disorder: Pain disorders have two subtypes. The first, "Pain disorder associated with psychological factors," is a psychological or stress-related condition that is neither precipitated by nor associated with any objective pathophysiology (e.g. chronic tension headache). The second, "Pain disorder with related psychological factors," is a biopsychosocial diagnosis where pain is believed to be associated with both medical and psychological diagnoses (e.g. herniated lumbar disc and depression). Note that Pain Disorder is more closely associated with DSM-IV-TR concepts than it is with DSM5-TR, and that the DSM5-TR diagnosis of "Somatic Symptom Disorder, Pain Predominant" has no ICD equivalent. While the DSM-IV-TR diagnosis of Pain Disorder was diagnosed in part by "medically unexplained symptoms," this is now believed to be a misleading criterion.

Pain Documentation: Pain is most commonly assessed via patient report using numeric or visual analog scales. It cannot yet be commonly measured objectively. Assessing the physiology of peripheral structures which may be involved in nociceptive or other afferent transmission is often not germane to the clinical issue of pain. While tools such as functional MRI have been used experimentally [(28)], imaging studies and other diagnostic procedures that "document" the existence of centrally mediated or experienced chronic pain, and/or identify increased or decreased activity in specific CNS structures in association with chronic pain states, have not yet been shown to be clinically relevant.

Pain Rehabilitation Programs: See Rehabilitation Overview.

Participation Restrictions: These are limitations that preclude full participation in an activity, such as therapy exercises.

Passive Modality: Various types of clinician-given treatments in which the patient is passive and not required to take an active part in the treatment. These treatments include medication, injection, surgery, skilled non-medical therapies (such as massage, acupuncture, and manipulation), and various physical modalities such as hydrotherapy (whirlpools, hot tubs, spas, etc.), ultrasound, TENS, other electrical therapies, heat, and cryotherapies.

Peripheral Pain: Pain that is due to pathology in a location other than in the central nervous system. This includes some examples of neuropathic pain (e.g., pain from an entrapment neuropathy) and all types of nociceptive pain (e.g., pain from muscle-tendon unit abnormalities).

Placebo Effect: A placebo effect is a beneficial effect that is not attributable to the "intervention" itself. This effect may be based on patient and clinician belief(s) and/or expectation(s). This includes clinical improvement or benefit (which can be objective or purely subjective) seen when a patient's belief that a "sugar pill" or sham medication or treatment will help them get well, even when there is no reason to believe that any "true" or specific therapeutic effect has occurred.

Psychiatric Comorbidity: The coexistence of two or more psychiatric disorders, which may include substance(s) use.

Psychological Recovery Barriers: Mental factors that delay or impair recovery, including stigmas, lack of a sense of safety, locus of control other than self, and lack of self-efficacy. May be considered to include kinesiophobia/fear avoidant beliefs. Some definitions of psychological recovery barriers also include lack of access to healthcare, which is less relevant for most patients being treated under worker's compensation plans.

Psychological Tests: Psychological tests are part of the standard for assessing chronic pain and are generally indicated by a positive psychological screening test or by other indications. The length of a psychological test is much longer than a typical screening test or outcome measure. They are usually multidimensional and have multiple validity scales. These tests are typically standardized with test results compared to norms which produce a percentile rank. Standardized tests are protected by test security (e.g., not posted on the internet, requiring a credentials check to obtain), and typically have a published peer review by the Buros Institute. These are interpreted by a psychologist and/or physician with appropriate training. A minimum of two standardized psychological tests specific to the reported concern, when possible, are generally required. In contrast, brief nonstandardized psychological tools may be freely available (e.g., The Pain Catastrophizing Scale, the CES-D, the Pain Anxiety Symptom Scale, the Pain Self Efficacy Scale) and scoring keys for these scales are publicly available. The public nature of these scales increases the ease of manipulating the results if financial incentives are present. These tools do not have validity measures, and typically use cutoff scores rather than standardized scores with percentile ranks. These measures require less training to administer.

Psychotherapy: Psychological treatment that traditionally involves individual and/or group talk therapy to change behavior, increase happiness, and overcome problems. More recently, psychotherapy has been augmented to include cognitive behavioral therapy, which emphasizes development of self-efficacy to address mental and/or physical limitations.

Reconditioning: The process of regaining function(s) lost, usually to include specific active exercises.

Return to Work: A status of returning to employment. Unless otherwise clarified, this is presumed to be return to work in the same job position (i.e., not a modified duty assignment) and employer as the employer of injury. Sometimes, the injured worker may return to either another job position or to another employer.

Screening Tool: A screening tool is generally succinct, and may be as short as one or two questions. It is usually administered to either an entire population, or an entire cohort of patients with a given condition. The frequency is usually at least in the initial exam and/or once a year. The objective of most screening tests is optimization of sensitivity, but not specificity. A screening tool is often also designed to be administered by persons with minimal training.

Secondary Gain: A factor or advantage that is generally considered to (sub)consciously amplify symptoms and/or delay recovery. Examples include financial reward (e.g., worker's compensation claim), avoidance of work, and positive attention from family, friends, and coworkers.

Skilled Therapies: Treatment approaches that require extensive training and development of specific skills. These treatments include manipulation, mobilization, massage, and acupuncture.

Somatic Symptom Disorders: Somatic symptom and related disorders is a category of conditions described by the DSM5-TR, and which is an alternative to the ICD-10 category of somatoform disorders. Somatic symptom disorders consist of somatic symptom disorder [confusingly the same name as the category], illness anxiety disorder, conversion disorder, psychological factors affecting other medical conditions and factitious disorder. Unlike somatoform disorders where unexplained medical symptoms were a central construct, somatic symptom disorders are thought to commonly co-occur with objective medical conditions.

Somatoform Disorders*:* A category of related mental disorders found in the ICD10 but not the DSM5, in which there are symptoms and complaints which are not medically explained. This group of disorders includes pain disorder, conversion disorder, somatization disorder, hypochondriasis, and body dysmorphic disorder. Pain disorder, which also falls into this category, may or may not be associated with a medical condition. With the exception of pain disorder, the somatoform disorders are infrequently encountered in association with a work injury and are not generally considered occupational disorders. However, they are prominent in the differential diagnosis for patients with chronic pain. Body dysmorphic disorder is sometimes found in chronic non-malignant pain patients with burn injuries or amputations. These diagnoses are important diagnostic considerations in the chronic pain population and are often difficult to detect without formal psychological evaluation and testing.

Subacute Pain: Pain lasting >1 but <3 months.

Symptom Magnification: This is a term that commonly denotes conscious or unconscious increases in reported pain levels beyond those the patient is experiencing. This usually is accompanied by pain behaviors such as exaggerated impacts on gait, range of motion, strength and other functions.

Tender Points: Unusual tenderness on palpation at a tendon insertion or origin, muscle belly or over bone. Some examiners require palpation of a taut muscle band or knot to qualify as a tender point. The most widely used criteria are palpation of the area(s) involved with the thumb or forefinger, applying pressure (palpation) approximately equal to a force of 4 kilograms (blanching of the entire nail bed) with a requirement for the patient to acknowledge that the palpation is not merely a discomfort, but would be described as pain. Tender points are specific places on the body (18 specific points at 9 bilateral locations) that are exceptionally sensitive to the palpation in patients with fibromyalgia, although the most common definition for fibromyalgia no longer requires tender points. Tender points are not limited to these locations and can occur elsewhere.

Trigger Points: Frequently used as a synonym for tender points, but is technically reserved for a subset of tender points in which there is elicitation of distal symptoms, usually accompanied with local symptoms, on palpation of the tender point. Trigger points are traditionally associated with myofascial pain, but few clinical trials differentiate these two conditions, thus the potential importance of this traditional distinction is unknown. (See the ACOEM Shoulder Disorders Guideline.)

Visual Analog Scale (VAS): Measures a patient's reported level of pain, ranging from "no pain" to "worst pain" by indicating a mark on a line, frequently 10 cm long. The distance from the low end of the line to the patient's "x" is the pain score.

Work Conditioning/Work Hardening: See Rehabilitation Overview.

DEFINITIONS OF PAIN AND PAIN TERMINOLOGY

The definition of pain was revised by the International Association for the Study of Pain (IASP) in 2020. The IASP definition is: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," and was noted to include the following added concepts:

- "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain" [(29)].

Both research on and treatment of chronic pain require clear conceptualization of painful conditions. In the past, diagnoses for chronic pain conditions have been faulted for numerous reasons. These include, a) pain diagnoses were not based on an accepted definition of pain developed by the International Association for the Study of Pain (IASP), b) pain diagnoses were unrelated to the etiology of the painful condition, and c) diagnostic

systems lacked a systematic manner of categorizing painful conditions. The lack of a scientific method of categorizing painful conditions has also been a barrier to the acquisition of accurate epidemiological data related to subcategories of chronic pain. Additionally, as pain diagnostic categories are a primary method of identifying target diseases and disease groups for research, this has been a barrier in research studies as well. Thus, the International Association for the Study of Pain (IASP) and the World Health Organization (WHO) established the Task Force for the Classification of Chronic Pain to develop a systematic method of categorizing chronic pain conditions based on the best available science. This task force concluded that both the ICD-10 and DSM-5 diagnostic categories were primarily based on pain research published prior to the year 2000, and thus did not utilize more recent science. In order to address these problems, it will be necessary to replace outdated pain concepts and diagnoses with ones based on the best available science.

Outdated Conceptualizations of Pain

In the process of renewing the definition of pain, both IASP and ICD-11 wished to expunge outdated terms and pejorative language from pain diagnostic conceptualizations. For example, “psychogenic pain” is an archaic term having its origins in DSM I. Originally, if there was no obvious explanation for pain it was thought to be “psychogenic,” and attributable to some form of psychopathology, such as a conversion disorder or factitious disorder. In the case of a conversion disorder, recent brain imaging studies suggest that conversion disorder is associated with altered brain functioning that often involves emotion-related parts of the brain, so medical explanations are being found to be at least associated with, if not fully explaining this “medically unexplained” condition.

Alternately, psychogenic pain has sometimes been misconstrued as being a type of factitious disorder, but these disorders are commonly misunderstood. A factitious disorder is a rare condition involving primary gain: A compulsion to assume a patient role *in the absence of any monetary, work avoidance or other incentive for doing so*. Thus, if there are indications that a patient is reporting pain for monetary gain, obtaining opioids or work avoidance, that secondary gain rules out a factious disorder. Metaphorically, the primary gain in factitious disorders could be explained by considering how while one person may have a strong desire to be a doctor or to have tattoos, a person with a factitious disorder may want nothing more than to be a patient and to have surgical scars because they look good and could even perhaps even aspire as a life goal to be an amputee. Given that factitious disorders are rare, this is generally an unlikely explanation for mysterious pain symptoms. Overall, the term “psychogenic pain” has historically been used in a pejorative way to dismiss pain symptoms that are not easily understood, and because of that its use has been eliminated from DSM-5 and ICD-11. This term is not informed by current pain science, and its use is discouraged.

Sometimes pain is attributed to malingering. In contrast with factitious disorder, malingering is the conscious and intentional fabrication of symptoms for the purpose of secondary gain. Because of that, malingering may constitute an act of fraud. This makes malingering a potential criminal act that may be prosecuted, as it is not a psychological condition that requires treatment. Because malingering may be criminal behavior, this is a determination for the Court to make, and not a means to explain away “unexplained” symptoms.

DSM-III, DSM-IV, ICD-9, and ICD-10 all used the diagnostic construct of "somatoform disorders," and a central diagnostic feature of these disorders was the presence of "medically unexplained symptoms" or "MUS." The concepts of somatoform disorders and medically unexplained symptoms were introduced by the ICD-9 in 1977 and persist today in the ICD-10. However, over the course of the decades since the publication of ICD-9, science has increased our ability to explain many of these MUS. In retrospect, the use of diagnostic construct MUS is now seen as unfortunate, as there has been a tendency to attribute MUS to psychopathology on the part of the patient, as opposed to seeing these unexplained symptoms as being attributable to lack of current medical understanding. Because of the problems associated with the MUS construct, both DSM5 and ICD-11 took the unusual step of deleting the entire somatoform chapter, and reconceptualizing all the conditions contained within them.

Another outdated and ambiguous term is referring to pain as "functional symptom." The term "functional" is ambiguous as it is sometimes used to refer to a state of objectively poor functioning such as that due to deconditioning. Other occasions, the term "functional" is used as a synonym for psychogenic. Overall, the use of the term "functional symptom" is discouraged as is the term psychogenic pain. Further, while the terms somatoform, somatization are still in ICD-10, they have been eliminated from DSM5 and ICD-11 as they are thought to be prejudicial, and malingering has never been a diagnosis. While the use of these terms is discouraged, new terms are believed to more accurately characterize the nature of pain.

Primary vs Secondary Chronic Pain

In contrast to past definitions of pain, the Task Force next conceptualized chronic pain as being subdivided into two diagnostic types, which are primary and secondary pain. Both primary pain and secondary pain are believed to involve biopsychosocial components. While diagnoses of secondary pain are etiologically linked to an identifiable injury or disease process, primary pain is etiologically agnostic, and without clear association with readily identifiable objective pathophysiology. Over time, secondary pain conditions may evolve into primary pain conditions, or vice versa. Primary pain is not theorized to be a "psychogenic" or "somatoform" condition, but rather is currently conceptualized as a disease in its own right. Primary pain is believed to be a disease of the pain sensory system that is associated with both neuroinflammation and psychosocial factors and which produces hyperalgesia.

The ICD-11 diagnosis of chronic secondary pain (CSP) is based on current pain science. It is defined as pain that persists for longer than 3 months and is secondary to an underlying disease or injury. The six CSP diagnostic categories are a) cancer, b) headache / orofacial, c) musculoskeletal, d) neuropathic, e) posttraumatic / postsurgical, and f) visceral. Chronic secondary pain is thought to be most closely associated with nociceptive pain and neuropathic pain mechanisms.

In contrast, the ICD-11 diagnosis of chronic primary pain (CPP) is defined as pain that a) persists for longer than 3 months, b) is associated with significant emotional distress (e.g. anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in ADLs or participation in social roles), and c) the symptoms are not better accounted for as chronic secondary pain or other diagnosis. The five CPP diagnostic *sub*categories are a) headache / orofacial, b) musculoskeletal, c) widespread pain and

fibromyalgia, d) complex regional pain syndrome, and e) visceral. Chronic primary pain is thought to be most closely associated with nociplastic pain mechanisms and is considered to be a disease affecting the pain sensory system. Because all pain has an affective component, both CPP and CSP are thought to be associated with mood and cognition as biopsychosocial conditions.

Nociceptive, Neuropathic, and Nociplastic Pain Mechanisms

The IASP Pain Task Force also concluded that research has identified three different mechanisms that produce pain: (1) nociceptive, (2) neuropathic, and (3) nociplastic mechanisms. While nociceptive and neuropathic pain mechanisms are familiar to clinicians, nociplastic pain is a new conceptualization. Along with neuropathic and nociplastic, nociplastic is one of the three mechanisms of pain now listed in the IASP pain taxonomy, and these concepts are included in the ICD-11 diagnostic system.

Nociceptive pain is pain that is produced by a normally functioning nociceptive sensory system. When functioning normally, nociceptive pain signals actual or potential damage to non-neural tissue. In contrast, neuropathic pain is caused by an injury to or disease of neural tissue. Unlike nociceptive pain, neuropathic pain may not coincide with the site of the nerve injury but may instead be produced by distal pain from radiation down the nerve.

Differing from both nociceptive and neuropathic pain, nociplastic pain is caused by dysfunction of the pain sensory system, producing hyperalgesia with minimal or no nociceptive input. Nociplastic pain is thought to be closely associated with central sensitization, but may also involve peripheral nerve sensitization and other mechanisms. Nociplastic pain is considered to be a disease that is strongly associated with inflammation, cognition and mood, and which dysregulates the pain sensory system, and causes hyperalgesia. Primary pain is thought to be most closely associated with nociplastic pain mechanisms. In its recent update to the definition of chronic pain, the International Association for the Study of Pain recommended that “A person’s report of an experience as pain should be respected."[35] These reports should be considered within the context that some psychological factors (e.g. catastrophizing[36,37] or depression[36,38]) may lead to magnified reports, while other psychological factors (ego stoicism) may lead to minimized reports.

In the occupational medicine setting, a challenge is that verbal reports of pain may be influenced by secondary gain in the form of obtaining monetary reward or more desirable work assignments. This is true though not only of pain complaints, but also of complaints of other subjective symptoms such as fatigue, tinnitus, nausea, or difficulty concentrating. When secondary gain is present, the principle of respect should be balanced with another dictum, “Trust but verify.” While there is no way to directly access a person’s conscious experience, there is a broad consensus that there is value in focusing on function and the patient’s observable behaviors.[39] Although symptoms tend to vary somewhat, feigned symptoms are likely to be associated with gross inconsistencies in behavior, and also with nonadherence in treatment. Methods of verification here include clinical observations, inconsistency in box lifts in therapy, and psychometric measures of validity.[40-42]

Finally, in field tests the ICD-11 diagnostic categories produced substantial interrater reliability, their clinical utility was rated as high, and they were judged to provide more meaningful information than past diagnostic systems.[25,43] Additionally, field tests also found that patients accepted these diagnostic findings. One study concluded that, “These

results show that persons with the lived experience of chronic pain accept and endorse the new diagnoses." [44]

IMPACT

Pain, whether acute or chronic (defined as pain with a duration of more than 3 months), is the most prevalent health condition found among the U.S. workforce and the costliest in terms of lost productivity. Painful conditions are also the leading causes of disability, with arthritic and musculoskeletal disorders resulting in approximately 50% of disability cases [30]. Estimates of chronic pain vary, although 64% of adults over age 30 years were reported to experience chronic pain [17]. A 2022 National Health Interview Survey found that 20.9% of adults experience pain most days or every day, which also was associated with 10.3 days of work lost, compared with 2.8 days lost among those without that definition of chronic pain [31]. An estimated 20% of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more [32].

Health care expenditures for back and neck pain alone have risen to $87.6 billion per year in the United States, while all musculoskeletal disorders annually totaled $183.5 billion; these costs do not include injuries, neurological disorders, and neoplasms causing painful conditions [33]. About 25 million U.S. adults are reporting chronic pain daily at an estimated economic cost of $560-635 billion per year [32,34,35]. The economic burden combines the medical costs of pain care and the economic costs related to disability days, lost wages, and productivity [32]. In addition to the costs of lost productivity, an estimated $64 billion in lost costs is largely invisible to employers because employees are continuing to work with limitations caused by pain, which reduces job performance. This is called "presenteeism," which varies widely by industry and has been estimated to affect 3-45% of some workforces [36-48]. People with chronic pain have the equivalent of 4.9 more days of presenteeism than people without chronic pain [49].

INITIAL ASSESSMENT

The clinician performing an initial evaluation of a patient with chronic pain has the particularly difficult task of ascertaining whether there is (are) other treatable, explanatory condition(s) present. Yet it is also critical to avoid over-testing which may result in increased morbidity (e.g. iatrogenic impairment) through either direct adverse effects of the tests themselves, or more likely through creating and contributing to a mind frame of endless searching for a potential lesion to be "cured." This tends to be most problematic with spine disorders (see e.g., Low Back Disorders Guideline).

Findings of the medical history and physical examination may alert the clinician to other pathology that can present with pain or some of the other constitutional symptoms with which the patient with chronic pain may present. Certain findings, referred to as red flags, raise suspicion of serious underlying medical conditions (see Table 1). Potentially serious disorders include infections, tumors, and systemic rheumatological disorders.

A careful, thorough history is required. The approach generally needs to be comprehensive, exploring all aspects of the physical complaints. A relevant review of symptoms is necessary. It is critical to evaluate psychological and social factors. Equally important is the evaluation

of occupational and environmental functions, with particular emphases on psychological, physical and social barriers that may be addressed to limit the impacts of the condition. Significant efforts to acquire prior test results are preferential to obtaining new studies, as excessive testing tends to maintain foci on symptoms, searches for a "cure," and tends to increase obstacles to achieving a functional recovery. Screening instruments may be helpful especially to screen for psychological disorders.

Absent red flags, most patients with forms of chronic non-malignant pain may be described as having one or more of the following conditions:

- Complex regional pain syndrome (CRPS): Type I and Type II;
- Neuropathic pain: central, peripheral, and radicular;
- Trigger points/myofascial pain (see Shoulder Disorders guideline);
- Tender points/fibromyalgia;
- Degenerative joint disease, including osteoarthrosis (see body part guidelines, specifically Hip and Groin Disorders, and Knee Disorders guidelines);
- Chronic spine pain (see Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines);
- Chronic lower abdominal/pelvic pain;
- Chronic non-specific pain syndrome; and/or
- Psychological disorders (most common are the affective disorders, anxiety, depression; other disorders are also reported risks in some literature).

There also is considerable overlap between many of these chronic pain conditions, and psychosocial factors are considerable [50-55]. A patient with any of the above may also be described as having a chronic pain syndrome, usually with one or more of the following: limited functional status, vocational status, and/or significant psychological features. They may have one or more of several psychological disorders. Depressive disorders are particularly prominent.

EVALUATION AND DIAGNOSTIC ISSUES

- In all cases, the body part that is injured should be carefully evaluated with a history, physical examination, and focused diagnostic testing (see relevant recommendations in other ACOEM guidelines). A complete physical is recommended, since pain can be referred from remote organs or anatomical segments (e.g., gallbladder to shoulder or hip joint to knee pain). The diagnosis should be confirmed, as missed diagnoses are a significant cause of treatment failure.
- Treatment failures can result from many causes: incorrect or missed diagnosis, lack of follow-through on initial recommendations for return to function, mismatch with patient goals (including perception of complete pain elimination) or preferences or expectations, failure to target functional goals with exercises and advancing non/occupational limitations, non-evidence based care or chosen treatments that are not effective at the given time frame, incorrect medication dosing or poor compliance, failure to give treatment a reasonable time to assess efficacy, and failure to tailor pharmacologic with non-pharmacologic interventions for the specific diagnosis. It is important to avoid concluding treatment failures before addressing these issues in search of a "pain cure."
- The first focus of the initial chronic pain examination or consultation of a patient with chronic pain should be the detection of conditions that are readily remediable. This

search also includes “red flags,” “yellow flags,” and searches for potential alternative conditions. Patients with chronic pain also commonly have medical (e.g. CVD, DM, obesity, insomnia, OSA, etc.) and psychologic comorbidities that can impact outcomes, limit treatment options, increase morbidity and mortality, and need to be addressed to achieve better treatment outcomes.

- Judicious use of diagnostic testing for the initial chronic pain examination or consultation to search for a specific, remediable cause may be appropriate.
- Pain is a subjective experience for which there is no unequivocally objective measure. However, verbal reports of pain can be assessed with regard to compatibility with objective medical findings, and the patient’s behavior. This includes consistency of findings with those expected for the condition, consistency of findings during observations within one appointment, and between appointments. It is also important to understand the type of pain and the context of how it affects the patient (e.g. Pain, Enjoyment, General Activity tool; Brief Pain Inventory tool, Chronic pain scale; Neuropathic Pain Questionnaire).[56]
- Repeated diagnostic testing in the absence of indicators for a specifically targeted, remediable cause is not indicated as it focuses the patient on finding an anatomic abnormality, rather than focusing on maintaining and increasing functional outcomes.
- In cases where the chronic pain condition is associated with a substantial functional compromise and the cause is not apparent, a consultation to confirm the diagnosis and management plan is often appropriate and reassuring to the patient and family. Pain medicine specialists, musculoskeletal disorders experts and other experts in the body part injured as well as behavioral health experts (e.g., pain psychologist, psychiatrist) are all potential consultants for these patients, particularly for purposes of diagnostic confirmation.

RED FLAGS

"Flags" are sought on initial evaluation and monitored. As a clinical case progresses, there also should be monitoring for subsequent identification of other flags that are either new and/or were not initially known. Flags are signs, symptoms, attributes, historical findings, or screening/questionnaire test results that are typically correlated with serious conditions, worse prognosis, and/or a need to consider alternate evaluative or treatment approaches, which may be adjunctive. These include red, orange, yellow, blue, and black flags [18]. At least a few flags are present in most patients with chronic pain, and these typically require addressing to achieve an optimal recovery. Evaluations are recommended to be centered on function, while not ignoring pain.

Red flags are the original type of flag described. These are symptoms and/or signs of a serious underlying disorder (e.g., cancer, serious infection, cauda equina syndrome). Physical evidence of an underlying medical problem that correlates with the medical history and test result(s) may suggest a need for immediate consultation. A history of malignancy, infection, endocrinological or systemic disorder may suggest the possibility of an underlying serious condition. A medical history that suggests pathology originating in a location other than that originally injured may require investigations that would not appear to be related to the work injury but would nonetheless need to be performed (e.g., shoulder pain from gall bladder or cervical spine; joint complaints from rheumatological disorders). Table 1 focuses primarily on systemic conditions that may have been missed in a patient with

complaints of chronic pain. However, if the person has no past history, then the clinician should still evaluate, assess, and query about current psychological issues due to the high co-morbidity rate with chronic pain. In the absence of red flags, the evaluation of the patient with chronic pain may progress.

Orange flags are psychosocial flags including symptoms and/or signs of psychological disorders (e.g., depressive, anxiety, personality disorders) Orange flags may also include dangerousness to self or others, acute intoxication, psychosis, and homelessness [57].

Yellow flags are evidence of counterproductive beliefs (e.g., kinesiophobia/fear avoidant beliefs, catastrophization, pain equates to damage), emotional responses (e.g., anxiety, worry, fear, depression), and pain behaviors (e.g., avoidance of work, avoidance of ADLs, undue antalgia). Yellow flags also include poor coping strategies (e.g., overreliance on passive treatments/modalities). Yellow flags are risk factors for delayed recovery [57].

Blue flags are perceptions regarding the relationships between work and health (e.g., belief that work is injurious, coworkers/supervisor is unsupportive).

Black flags are considered to be (relatively) firm limits and/or sometimes considered to include "dark red" flags denoting severe or serious situations. Firm limits include legislative restrictions for return to work, workplace policies of no modified duty, union/contractual issues that block potential performance of a modified/light duty job, conflicts with worker's compensation insurance staff/policies, and interference or over solicitousness of family and/or healthcare providers.

SIGNS AND SYMPTOMS

Pain may or may not be well localized, yet it is frequently compounded by the severity of motivational, affective, cognitive, and behavioral overlay that is often a frustrating aspect of chronic pain.

The signs and symptoms of patients who are at risk for chronic pain include the following:

- More intense pain complaints; Extreme pain
- Widespread pain
- Non-anatomic pain
- Overprotective/fear of exercise and very sedentary (e.g. kinesiophobia or fear avoidance)
- Diffuse symptoms of distress/somatization (e.g. fatigue, anhedonia, appetite disturbance, weight change, poor concentration, nervousness)
- Pain associated with depression, anxiety or anger, or with marked absence of any emotionality (alexithymia)
- Moderate or severe sleep disturbance
- Overreliance on habit-forming medications
- No treatment helps, or only helps a little and for a short period of time. Pain never changes
- Higher disability profiles*
- Dysfunctional pain cognitions
- Moderate to major difficulties with functioning or disability

- Little physical and functional progress
- Catastrophizing; dysfunctional coping strategies
- Emotional characteristics of chronic pain
- Behavioral characteristics of chronic pain
- Dysfunctional movements and patterns contributing to chronicity of pain, including:
    - Antalgic gait
    - Abnormal postures
    - Guarding

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*Disability profile is a term commonly used to project the likelihood of disability. It has little relationship with physical injury or diagnosis. Instead, it is heavily driven by psychosocial health, psychological disorders, coping skills, resilience, etc.

HISTORY

A focus on the potential for a treatable condition is mandatory for an initial evaluation of a patient with chronic pain. Nevertheless, it is recommended that the initial evaluation of patients with chronic pain start with a focus on function, both at work and home. This sets the focus on function that is essential for the vast majority of chronic pain patients, while maintaining a focus on confirmation that prior examiners did not miss a treatable disorder.

Collecting information about occupational history and patterns of daily living and interests assists in understanding patient priorities and targeted outcomes. Examiners should document essential functions and exertional job demand information as part of the examination to develop a return-to-work plan, prognosis and plan of care, and to guide return-to-work decision making. Information sources beyond the patient may include job or ergonomic analysis, company documents, nurse case managers, and supervisors.

Alertness to the patient responses is important, as there may be strong clues to the degree to which preoccupation with somatic complaints instead of a functional focus is present. Unprovoked responses frequently also provide powerful clues to activities the patient is interested in resuming that may ultimately provide the motivational tools to facilitate the patient's functional restoration. The clinician should ask typical questions focused on pain symptoms. Current pain treatments, whether medical or non-medical, should be recorded. Past pain treatments should be reviewed with a careful discernment and documentation of meaningful, lasting functional improvements.

After the function-based and pain histories are obtained, the history should next include a thorough medical history, past medical history, medication history, surgical history, accident history, current psychological history, and past psychological history. Sleep problems should also be identified because they contribute to pain and impair function. Assessments should include psychological disorders, kinesiophobia/fear avoidant beliefs, and symptoms of catastrophization. The patient's education level and cultural background should be considered, including possible language barriers.

The primary treating clinician, other health care professionals, and consultants should approach pain complaints as an integral element of each history and physical examination. Yet the primary focus should be on function, rather than pain to avoid an undue focus on

pain and pain ratings. This includes assessing pain complaints relative to casual patient observations, the physical examination and observation of the patient's functions both while actively examined and ideally outside of the context of the performance of a physical examination. Obtaining a history of functional activities from family members or friends may sometimes be useful.

View Medical History Questionnaire for chronic pain.

PHYSICAL EXAMINATION

A well-performed physical examination is indicated for the evaluation of a patient with chronic pain, both by the treating clinician and a consultant if one is used. Components of the physical examination should follow those of the relevant body part involved and will not be detailed in this section (see other ACOEM Guidelines). The examination of individuals with somatoform disorders is often indistinguishable from that of psychologically normal individuals. The threshold for psychological referral in patients with chronic pain (especially those with functional impairments), including psychometric testing for this and other entities, should be quite low.

Observation of the patient is believed to be the most important aspect of the physical examination. It should begin at the start of the visit—or better still, through a report from the medical assistant who put the patient in an examining room. It should include an evaluation of the patient's ability to rise from a seated position (and other positional changes), gait in the hallway (e.g., for all lower extremity or spine complaints; examination rooms are too small to adequately observe gait), utilization of limbs for tasks, and facial expressions in the course of performing those functions. Synergistic and dys-synergistic history and physical examination findings should be sought and recorded.

Particularly in the setting of chronic pain, signs that are inconsistent with symptoms should be sought. These have been previously referred to as "nonorganic" signs and were developed for the evaluation of low back pain [58,59] (see Table 2). However, similar findings of overreaction and nonanatomic distributions of pain are believed to equally apply to the evaluations of all other body parts. It should be noted that positive results with these maneuvers are sometimes erroneously taken to be definitive of factitious illness and/or malingering. That may or may not be true. "Nonorganic" signs should be assessed in the context of the complete evaluation and more detailed psychologic evaluation is suggested. Patients with "nonorganic" signs may have less optimal outcomes of interventional care [60]. In some cases (e.g., CRPS), varying skin color and temperature is a normal finding. More commonly, it is believed that nonorganic signs may be positive when patients in pain subconsciously exhibit a need for further attention to the painful disorder or sometimes may represent psychological dysfunction. Their presence indicates the likely need for psychosocial evaluation, particularly when multiple signs are present in the context of significant delayed recovery.

In the chronic pain setting, it is frequently helpful to obtain measurements of the patient's capabilities in the clinic to then follow in subsequent clinic visits while the patient is undergoing rehabilitation services. These may include the following:

- Walking distance (observe in the hallway or outdoors and subsequently simultaneously interview the patient about their progress if a longer walking ability is demonstrated)
- Assessment of balance
- Ability to climb stairs (walking to the nearest stairwell with the patient and observing capabilities)
- Dynamometer grip strength measurements
- Pinch strength
- Repeated toe raises (number able to perform)
- Distance of heel walking
- Squats (number)
- Sensory examination findings (e.g., monofilaments)
- Movement inconsistent with pain/injury problem while in exam room

This also moves the examiner from the role of a more passive observer to a more active team leader, including advanced informed decision-making, such as in conjunction with therapists on exercise and other physical activity benchmarks. Active involvement of the clinician is believed to be quite helpful to facilitate the patient's recovery [61]. The use of validated functional assessment tools to follow patient progress is another recommended approach.

TESTING PROCEDURES

Diagnostic testing considerations are defined by the clinical entity and body part being investigated. Testing commonly used for the identification of other disorders is often required to assure that other diagnoses are not present. This should not be considered as justification for ordering tests indiscriminately. Tests should instead, be ordered if there is a reasonable probability that the diagnosis is present. Sometimes, the threshold for ordering a test is lower if the adverse effects from missing the diagnosis are considerable (see other guidelines for guidance on diagnostic testing for specific disorders). Imaging studies can identify abnormalities such as edema, demineralization, or osteoporosis that are consistent with one of the diagnoses associated with chronic pain, but mostly these are non-specific findings. There are different lines of clinical investigation of potentially useful technologies that purportedly assist in objectively diagnosing someone as suffering from, or being limited by pain, or in localizing specific areas of the central nervous system that may influence, or be affected by, a patient's pain. Evaluations of the evidence for the use of many of these are provided in each section of this and the other ACOEM Guidelines (e.g., see Low Back Disorders; Cervical and Thoracic Spine Disorders; Hand, Wrist and Forearm Disorders; and Shoulder Disorders Guidelines).

DIAGNOSTIC CRITERIA

The clinician should determine the diagnosis and criteria presented in Table 3 by following the clinical thought process, from the mechanism of illness or injury, to unique symptoms and signs of a particular disorder and, finally, to test results (if any tests are needed to guide treatment at this stage). The ICD coding system assigns codes based upon pathophysiologic mechanisms. Specific ICD codes are frequently required for reimbursement for medical

services. However, for at least 90% of LBP cases, the ICD codes utilized are overly specific. The pathophysiologic correlates for lumbar sprain and strain, for example, have not been determined. It is also difficult to match specific diagnostic ICD codes to the clinical presentation in many patients with chronic pain, especially initially.

MANAGEMENT APPROACH

Chronic pain is considered by many clinicians to be best evaluated and treated as a disease [62,63,64,65,66,67], although this is disputed by others [68,69]. Pain, defined as an "unpleasant sensory and emotional experience associated with, or resembling that associated with actual, or potential tissue damage" [70], can be a valuable guide to diagnosing and resolving illness or injury. It also can be a problem that interferes with activities of daily living (ADL) and instrumental activities of daily living (IADL). ADLs involve caring for oneself through dressing, grooming, feeding, etc., while IADLs involve functional activities such as using the telephone, shopping, housekeeping, food preparation, transportation outside the home, responsibility for taking medications, and the ability to handle finances.

Nonpharmacological approaches are generally preferable approaches for the management of chronic pain conditions, especially including active exercises and behavioral interventions. Physical activity is increasingly recognized as the cornerstone for chronic pain conditions. The European Pain Federation has recommended that physical activity should be "the primary intervention for individuals living with chronic pain" [71]. See also the ACOEM Work Disability Prevention and Management Guideline.

The "biopsychosocial model" which emphasizes the need to account for the unique interactions between biological, psychological, and social factors in order to better understand health and illness, is now commonly utilized to explain and manage chronic pain since the traditional medical model of acute injury resulting in pain and tissue damage does not explain chronic pain syndromes (see Figure 1).[72-75] Central nervous system (CNS) factors may explain the experience of pain in the absence of tissue damage or after healing has taken place [76,77,78]. Complex genetic factors have been shown to be involved in the perception and responses to chronic pain [79,80,81,82,83]. Psychological and social factors are also involved in the perception and interpretation of pain symptoms and their effects on home and work life [74,81,84]. Psychological factors are prominent in the management of patients with chronic pain, profoundly influence the individual's ability to modulate pain and distress, and are better managed after earlier identification. Alternatively, psychological flexibility has been reported to be a resilience factor [85,86].

Pain occurs in the context of each person's life situation, affecting work and social functioning as well as the ability or willingness to be active. In settings of acute pain (e.g., trauma), brief inactivity may reduce pain. However, in subacute to chronic problems, inactivity results in deconditioning and either results in no improvement or more pain, while delaying functional recovery. Thus, increased activity is indicated for essentially every chronic condition associated with persistent pain. For select, acute pain conditions, reduced activity limitations to facilitate recovery may be appropriate. Yet, in the chronic context, recovery is usually dependent on performing those specific activities that may elicit the pain on a gradually increased basis in order to return to normal function. A substantial clinical difficulty is timing and facilitating the transition from acute pain and activity limitations to chronic pain and graded increases in activities. Determining how soon to recommend

increased activity levels is problematic, although there is increasing consensus to implement increased activity levels earlier and earlier in the acute and subacute phases to prevent delayed recovery and the development of chronic pain syndromes.

Development of chronic pain syndromes may be complicated by the practitioner's lack of a quality curricular background in chronic pain management, a field long underrepresented in educational programs. Clinicians who focus on acute pain management, particularly with reduced activity levels and passive treatments, tend to foster delayed recovery and further development of chronic pain syndromes. Chronic pain differs from acute pain and a different treatment approach is needed.

PALLIATE OR REHABILITATE

A related untoward outcome from the failure of successful restoration of normal function during the initial phases of treatment is the decision to make palliation the main focus of subsequent interventions. To palliate rather than rehabilitate is a profound clinical, ethical, and medico-economic decision that should not be taken lightly or be based on unfounded dogma. While a patient's complaints of pain should be acknowledged, both patient and clinician should instead remain focused on the ultimate goal of rehabilitation leading to optimal functional recovery rather than on continued health care utilization. Early identification and appropriate management of delayed recovery signs is believed to decrease the likelihood that a patient will go on to develop chronic pain. See also the ACOEM Work Disability Prevention and Management Guideline.

This guideline focuses primarily on chronic pain evaluation and treatment. Complete pain relief is clearly a highly desirable endpoint, especially in acute pain states, yet it is usually unattainable in patients with chronic pain. Evidence also suggests that factors other than the nature of the injury are primary determinants of disability. Pain treatment should emphasize functional restoration and pain relief. Emphasizing only pain relief may reinforce negative psychological, environmental, and dependent psychosocial factors that predispose progression to chronic pain states and addiction(s). In chronic pain states, emphasis on functional restoration should focus on improving function while reducing pain or limiting flare-ups to manageable levels. In those settings, the pursuit of an anatomic antecedent pain generator is counter-productive to achieving optimal functional outcomes. Patient education is also an important component to achieve the goals, as without the patient joining the treatment team, progress is typically very slow and the goals may not be achieved.

Pain that cannot be adequately explained by specific physical findings raises many questions: When does acute pain become chronic? Is the diagnosis correct? Is there a second diagnosis? Are changes in the patient's central nervous system creating pain hypersensitivity? What else is going on in the patient's life, either at home or at work, which may be aggravating his or her pain or reinforcing pain or illness behavior? How can such pain problems be articulated to a system that is based on labels and coding? How can that concept of pain be put into a medicolegal context when dealing with workers' compensation issues? Does the current treatment improve function? What role should patients play in promoting optimal function in everyday living and enabling meaningful family, workplace, and social relationships? What is the patient's emotional response to pain? The following discussion sheds light on these questions and suggests an

interdisciplinary model to address the multiple components of the patient's pain problem. It also addresses specific recommendations for several specific, as well as general categories of chronic pain disorders.

PATIENT EDUCATION ISSUES

- Clinicians should reassure the patient that chronic pain is common, has a good prognosis in the absence of specific disorders, and does not cause (or have to cause) serious debility. Clinicians who provide encouragement that chronic pain is common and manageable are believed to have better outcomes with more effective use of resources [87,88,89], including having more satisfied patients and fewer patients on disability. Reassurance should be tailored to the individual's unique perceptions and lifestyle [88,90,91].
- It is helpful for practices to provide affective (creating rapport, showing empathy) and cognitive reassurance (providing explanations and education) to increase a patient's self-management [92].
- Clinicians should address kinesiophobia (fear avoidance), or the fear or anxiety of movement [93,94,95], which may overlap with catastrophization [96]. While activity is feared, it is an important therapeutic target because lack of activity reinforces debility. Patients should be encouraged to work with skilled therapists who can address fear of pain/movement to facilitate recovery and/or functional restoration.
- Patients should be encouraged to maintain as high a level of function at work and resume ADLs and IADLs [97,98,99].
- Rest, bed rest, and disuse of body parts are not recommended for the management of chronic pain conditions as they cause further disability rather than assist in returning the patient to a functional status. The patient may need education to explain these common misconceptions and to address the accompanying fears that are frequently present.
- If the patient has been accurately diagnosed and adequately treated, a continuing focus on pain ratings and symptoms is counterproductive. Treatment must emphasize increasing function and supplementing the functional restoration plan with appropriate, judicious use of medications and other modalities.
- The patient's education level, social situation, and cultural background should be considered, including possible language barriers. Educational session to the patient's preferred learning style (e.g., auditory, visual, print, interactive, kinesthetic), which may also be influenced by education and cultural issues.
- Understanding and retention of key teaching points should be assessed in subsequent appointments.

OCCUPATIONAL ISSUES

1. All patients should be encouraged to return to normal activity or work as soon as possible [99]. Modified duty is most appropriately utilized when the job demands substantially exceed the patient's capabilities. For those patients on modified or light duty, a plan to return to normal job activities should be specified. See also the ACOEM Work Disability Prevention and Management Guideline.
2. Nonphysical factors (such as psychological, psychosocial, workplace, and/or socioeconomic problems) should be particularly addressed in cases of delayed recovery or delayed return to work [100,101].

3. Patients should be encouraged to accept responsibility and learn necessary coping skills for managing their recovery rather than expecting the clinician to supply an easy or complete cure. Taking an active role in the recovery process is paramount if the person with pain is to return to work. This will promote using activity rather than pain as a guide, and it will make the treatment goal of return to occupational and non-occupational activities more obvious.
4. Participatory ergonomics, collaborative problem-solving with the employer, use of recovery and return-to-work inventories [102-106], and return-to-work programs may assist in identifying job attributes that may be perceived barriers to a successful return to work.

APPLIANCES AND SKILLED NONMEDICAL THERAPIES

- Slings, splints, and other appliances are contraindicated in managing chronic pain in the absence of focal neurological or structural deficits as they may reinforce pain and illness behaviors.
- Ice, heat, ultrasound, and other similar modalities are rarely indicated for chronic pain especially in the clinical setting. Heat and ice may be considered as a part of home-based self-care if their use provides the patient with temporary relief of symptoms, though the clinician should be aware that these may also reinforce pain and illness behaviors in persons with chronic nonmalignant pain.
- In the absence of documentation of incremental functional improvements, prolonged and repetitive use of nonmedical therapies (e.g., massage, electrical therapies, manipulation, acupuncture) are not indicated in managing patients with chronic pain. These interventions tend to draw attention towards numbers of appointments and adding or trying more passive modalities, instead of focusing on and benchmarking increases in activity and exercise levels. Their use may be briefly indicated in conjunction with the introduction of an active conditioning program that includes both aerobic and strengthening components for treatment of referred patients found to have significant debility and deconditioning.
- Judicious short-term use of skilled, non-medical therapies may be indicated for significant exacerbations of underlying chronic pain conditions when there has been documented improvement following such treatments. Such exacerbations may be analogous to acute pain episodes; however, in the patient with chronic pain, such exacerbations are also believed to entail risk of sliding into reduced functional status. Clinicians who recommend these therapeutic approaches should be aware that they may detrimentally draw the focus away from increasing function and reinforce pain behavior and disability. A transition back to active treatment modalities and self-care should be reinforced to the patient at that first visit to establish clear expectations.

EXERCISE ISSUES

- Graded exercises to assist in achieving a return to maximal function are indicated. Aerobic and strengthening exercises appear most helpful for the rehabilitation of most chronic pain conditions, with a walking program being the easiest form of aerobic exercise to initiate and progress with benchmarks for most patients. Physical activity is increasingly recognized as the cornerstone for chronic pain conditions. The European Pain Federation

has recommended that physical activity should be "the primary intervention for individuals living with chronic pain" [71].

- Graded exposure is another component to consider in a treatment plan. Graded exposure involves progressive activities that are generally on-the-job (e.g., moving from a 10-pound lifting limit to a 25-pound lifting limit with concomitant job tasks that involve those progressive levels of use). Generally, graded exposure is not exercise, but advancement in both exercise and exposure benchmarks work synergistically to improve function.
- The incorporation of addressing psychosocial risk factors and cognitive behavioral therapy principles into physical and occupational therapy has been termed "psychologically-informed physical therapy" (or "psychologically-informed occupational therapy") and has evidence of being particularly helpful because it provides synergistic reinforcement among the treatments. A related concept of cognitive functional therapy has also been found to be helpful [107].
- Stretching or flexibility exercises may be important components to treat some patient's injuries. They are important when there is a significant reduction in range of motion and where restoration of range of motion is required to enable engagement in strengthening and functional activities. In general, stretching exercises can be taught by therapists, but should be performed by patients, repeatedly with limited numbers of repetitions to achieve most rapid gains in flexibility. However, where there is either minimal or no reduction in range of motion, strengthening and aerobic exercise should be emphasized.
- Combined exercise and CBT has been found to be synergistically helpful.

MEDICATIONS

- Although there is considerable overlap between types of pain and evidence of efficacious medications, the clinician should seek to identify whether chronic non-malignant pain is due to a specific diagnosis and/or thought to be *primarily* nociceptive, neuropathic, or of unclear etiology. Treatment options for these divergent types of commonly encountered pain have some differences. When evidence clearly indicates that specific medications are particularly effective in managing a given diagnosis or type of pain, they should be used preferentially. Ineffective treatments should be discontinued and when the response to a medication has been suboptimal, consideration should also be given to discontinuing it either before or immediately after adding a different agent.
- If an intervention is ineffective, it is better to stop it and try a different intervention (e.g., rather than switch to a different NSAID, consider a change in exercises, and/or a different class of medications).
- Opioid use in the setting of chronic, nonmalignant, or neuropathic pain is controversial and generally not recommended (see Opioids Guideline).

INJECTION AND INFUSION THERAPIES

- While injection and infusion therapies are widely used in the management of patients with chronic pain, there is little high-quality research demonstrating efficacy and no evidence of long-term pain relief or objective functional increases. Hence, while they may

have an occasional role in the management of carefully selected patients, their indiscriminate use is not recommended.

- When the decision is made to employ an indicated injection or infusion therapy as an adjunct to patient care, the goal should be to use the temporary decrease in pain to increase functional activities, increase active exercises, and, if applicable, reduce use of opioids. Documentation of objective, quantifiable benefit as a consequence of their use must be provided, and repeated interventions in the absence of this documentation would not be warranted.

PSYCHOLOGICAL AND BEHAVIORAL ISSUES

- Significant psychological factors are nearly always present as etiologic influences and/or sequelae when pain of nonmalignant origin becomes chronic as per the biopsychosocial model (see Basic Principles). Evaluation and management of these factors by the primary treating clinician is recommended. When recovery is excessively delayed or psychological/psychiatric treatment by the primary clinician is ineffective, there should be strong consideration of obtaining a comprehensive psychological evaluation that includes psychometric testing. Fear of further injury (i.e., fear avoidant belief or "kinesiophobia") or missing a diagnosis also needs to be addressed if the person with pain is to progress. See also the ACOEM Work Disability Prevention and Management Guideline.
- The presence of psychological factors has been significantly associated with the development of pain chronicity in patients with musculoskeletal disorders [57,74,81,84,108,109]. Pre-morbid depression is a particularly notable risk factor for the evolution of chronic back pain complaints, which along with related psychosocial factors, often supersede various mechanical or medical factors [110-134]. However, MDD can and frequently does occur with a pain condition.
- It is often difficult for many clinicians to focus a pain treatment plan primarily on psychological issues, other than mental health professionals. Frequently, a patient may become defensive and deny that there is any psychological component. However, mind and body can be blended together in a comprehensive pain program by ensuring the person with pain understands the connection. Compliance with some of the off-label medications such as antidepressants and anticonvulsants need to be explained to ensure the patient understands the multiple purposes of these treatments.
- Fear-avoidance models are also thought to contribute to explaining chronic pain and kinesiophobia [93,94,95], which may overlap with catastrophization [96,135,136]. There typically are strong fears of further injury and damage. Also, many patients fear having more pain—so addressing pain-related anxiety is important because it impedes rehabilitation. The theoretical premise is that pain-related fear (beliefs that pain is a sign of damage or harm to the body, and activities that might cause pain should be avoided) has a significant impact on disability and adjustment. However, it is the *learned* behavior restrictions which are reinforced by activity avoidance and for which fear is the subjective covariate that are likely etiologic. Rehabilitative strategies which make use of this concept and try to diminish dysfunctional avoidant behaviors that are inconsistent with objectively definable risk of harm tend to be more successful.

OTHER ISSUES

- A second evaluation by another provider is often helpful at some point in the course of the treatment of patients with chronic pain. Purposes include: reassessment/confirmation of the diagnosis, reassurance for the patient, reinforcement of key concepts to the patient, assessment of treatment options, prioritization of treatments, and transfer of care.
- Collaborative care including the patient and all clinicians is often lacking, but it is needed to enhance outcomes [137,138].
- The majority of those with chronic pain do not seek professional health care, and often control symptoms with simple modalities such as over-the-counter medications, a heating pad, exercise and other remedies. Even those who have had complicated courses (e.g., complex treatment, litigation, etc.) may reach a state of self-management and coping with pain. The empowerment of patients to independently manage their pain as early as possible should be strongly encouraged.
- Patients using over-the-counter medications for management of chronic pain should be educated and assessed for potential adverse effects, as those are most likely to occur among chronic medication users, especially with other risk factors such as age. There also are potential interactions between herbal and prescription treatments.
- Self-management, self-efficacy, and coping skills are believed to be important factors to achieve good outcomes.
- Some evidence suggests perceived injustice may be an underlying issue and may need addressing [139].
- A large body of peer-reviewed studies documents that patient involvement in litigation or workers' compensation claims is associated with worse clinical outcomes, including delayed return to work, poorer satisfaction with treatment, and worse surgical outcomes [140-165]. Cohort studies of disc herniation, hip impingement and rotator cuff repair patients have now also shown that the differences between workers compensation and non-workers compensation patients in those studies disappeared in longer-term follow-up studies and/or after cessation of workers compensation benefits [154,155,156]. There are marked differences from state to state with regards to whether patients typically retain attorneys for worker's compensation. Accordingly, whether a patient is involved in litigation over workers' compensation may or may not raise concerns about possible advocagenic* influences on the patient's clinical course and prognosis. It is recommended that these local cultural factors be taken into account when attempting to discern potential influences on pain complaints, treatment responsiveness, and disability.

*An *advocagenic illness* is a response to legal counsel or legal system, induced or magnified by the counsel or system itself; usually used for unfavorable responses.

PSYCHOLOGICAL ISSUES

Pain-related fear is believed to contribute to pain and disability in several ways. While pain avoidance is natural, persons who acknowledge greater pain-related fear tend to avoid more situations than would be normal due to their belief that they may cause pain. Research also suggests that compared with others, these persons tend to focus on the amount of pain experienced during functional activity, leading to greater activity avoidance. In this fashion, pain-related fear and associated avoidance of activity are believed to

contribute to disability independently of pain itself. This may lead to greater physical deconditioning, but also has been shown to be related to musculoskeletal abnormalities such as muscle guarding while bending, which in turn may directly contribute to pain behavior [93,94,95,166,167,168], which may overlap with catastrophization [96].

Pain-related fear is significantly related to greater perceived disability, even when controlling for biomedical factors, demographic variables, and self-reported pain [169,170,171]. Gradually exposing patients to fearful activities as a pathway to reduce or extinguish pain-related fear can be a powerful intervention for chronic pain. A decline in pain-related fear may reduce pain hypervigilance, resulting in a decline in reported pain intensity. Reductions in pain-related fear may be partially responsible for improvement in functional restoration programs as the program duration may be too short for meaningful physiological effects of exercise [172].

The biopsychosocial model (BPS) views health as including optimism, social support, good coping, positive mood, motivation, and work ethic. The model views disorders such as chronic pain as the result of a dynamic interaction among physiologic, psychological, and social factors which perpetuate and may worsen the clinical presentation. Thus, the model explains some patients with severe injuries who have profound perseverance, motivation and superior recovery.

The BPS model focuses on both disease and illness, with disease defined as disruption of specific body structures or organ systems by an objectively definable biological event that leads to anatomical, pathological, or physiological changes. In contrast, illness is generally defined as a subjective experience or self-attribution that a disease is present, thus referring to how a sick individual and members of his or her family live with and respond to symptoms and disability. The BPS model recognizes that each individual experiences pain uniquely, with a range of psychological and socioeconomic factors interacting with physical pathology to modulate a patient's report of symptoms and subsequent disability. The relationship between psychological factors and the development of chronic pain reflects the differences between individuals in both the emotional reactions associated with the perception of pain and the risk of physical harm during the acute phase, as well as the psychological reactions that occur when pain becomes more chronic. The latter reactions take various forms depending upon both premorbid or pre-existing psychosocial characteristics and the patient's socioeconomic and/or environmental milieu. The role of afferent and efferent feedback between biological and psychological systems is emphasized, as the pain due to injury is seen as disrupting the body's homeostatic regulation systems, producing "stress" that ultimately leads to increased activity in the hypothalamopituitary axis (HPA)[,(75)]

These in turn are hypothesized to lead to neurochemical changes at the central level, with the central nervous system altered by chronic pain to increase sensitivity to incoming impulses that amplify pain [76,173]. Activation is believed to lead to further physiological changes, the extent of which are hypothesized to depend on intrinsic (genetic and physiological) and extrinsic factors, which exacerbate and perpetuate a syndrome in which the experience of pain increases despite a lack of objective reasons for this to occur.

The most widely accepted and evidenced model for explicating the biopsychosocial perspective provides a common language for describing and assessing continuing pain complaints [174,175,176]. Pain is defined as a noxious sensory AND emotional experience. Pain

is known to have components designated as nociception, pain, suffering, emotional and pain behavior. The perception of pain may occur in the absence of nociception (or neuropathy) and vice versa. Therefore, the complaint of pain should be considered valid regardless of the assessed tissue pathology. Challenges to the complaint (other than forensic) tend to exacerbate the problem for many patients with chronic pain with resulting increases in pain complaints and pain behaviors.

Suffering is a set of negative affective responses which tends to be associated with the experience of pain. It may be produced by pain, but it may also be influenced by numerous psychosocial factors. These are often manifested by irritability, anger, frustration, personal losses, helplessness, social isolation, and various stress related states. Suffering may occur in the absence of "pain," but it is often described in such terms. In clinical contexts, it is often more necessary to assess how the patient is suffering than to attempt to relieve the pain. *Pain behavior* may be defined as "any response or set of responses which communicates the concept of pain to another person." The concept may be broadened to the notion of *illness behavior,* which involves other health related complaints and responses. Pain behaviors may be considered symptoms in acute pain presentations. However, they are also produced by suffering; and over time they may come under control of various psychosocial or learning influences [177-180]. There is a common misconception that such behaviors may represent consciously "exaggerated" or "magnified" symptoms. This is not possible to assess directly, and such conceptions are often pejorative. Pain or illness behaviors may evolve in persons with chronic pain secondary to a wide range of psychosocial antecedents and learning or conditioning influences. The implication that such behavior indicates a specific psychological etiology or necessitates a psychiatric diagnosis may not be justified. Since there is no known relationship between nociception, pain, and pain behavior when a condition becomes chronic [181], such behavior should be conceptualized as a clinical finding [182]. Pain behavior is also not equivalent to "secondary gain." While the latter is generally based on presumptively seeking reward or other desirable consequences of an injury, pain behavior may be learned or conditioned, shaped, and maintained by subtle reinforcement in persons about whom such psychological inferences may be inappropriate and where significant suffering or antecedent psychosocial problems are not noted. There is evidence that persons with chronic non-malignant pain may be uniquely sensitive to operant and classical (Pavlovian) conditioning in the learning of pain responses [183,184,185]. Still, chronic non-malignant pain may foster psychosocial and behavioral dysfunction, as well as magnify pain. The distinctions between these situations become important in the development of interventions to address them.

In persons with chronic non-malignant pain, many permutations of these concepts are possible. For example, significant and disabling pain and illness behavior may evolve and become a clinical problem, even in the absence of clinically meaningful nociception, pain, or suffering. Pain behavior may be noted in the presence of nociception or neuropathy, but the patient may not be suffering in clinically meaningful ways and may not be disabled. Other persons may be suffering, but their pain complaints may be a minor part of their problems. It is important to view the patient in this context and evaluate and treat these components appropriately, which requires a more complex evaluation and treatment plan than required for the patient with uncomplicated acute pain.

Clinicians should consider referral for further evaluation and perhaps cooperative treatment if any of the following are identified:

- Specific clinical findings suggest previously undetected issues requiring other expertise to adequately address it.
- The clinical course does not follow generally expected patterns.
- Pain distribution is non-anatomic or described in a bizarre or atypical manner. Examples include glove- or stocking-like pain or paresthesias, shock-like pain, pain that radiates up and down the neck and back, burning pain, and pain that is present constantly regardless of position, medication use, or physical treatments.
- Medication use does not decrease as expected, or increases.
- Appropriate active exercises do not appear to be improving function as expected.
- Complaints of pain or dysfunction start to involve other body areas, including instances in which the patient:
    - Ceases to discuss returning to work in a specific time frame but rather in relation to a cure.
    - Fails to benefit from any, or all, rational therapeutic interventions.
    - Experiences increased pain, or at the very least, pain does not decrease, over time.
    - Is unwilling to discuss his or her family situation or expresses comfort with role reversal at home.
    - States that the illness or injury has caused all of his or her problems.
    - Directs excessive anger at the employer or coworkers, the clinician, or an insurer and/or demonstrates an attitude of revenge or wanting to prove an illness.
    - Is less interested in the home therapy program or even in recovery of function.
- There appear to be indications of significant psychosocial dysfunction or psychiatric comorbidity.

Judicious referral may be warranted to corroborate the absence of physical pathology and to assure the patient that increased participation in usual activities will not be detrimental to the patient's overall physical status. This must be a referral to a well-qualified clinician whose practice patterns are consistent with evidence-based evaluations and treatments and focuses on functional recovery, as the potential to do harm by missing a diagnosis, medicalization (e.g., identification and focus on spurious MRI findings), and/or mislabeling a patient is otherwise significant.

INITIAL CARE

This section is a general approach to treatment, not specific to diagnoses covered in other ACOEM Guidelines. The ACOEM guidelines' systematic reviews of treatment literature indicate there are considerable differences in what is effective for treatment of a specific disorder.

The major principle is that chronic pain conditions almost always represent an interaction among some level(s) of physical pathology (current or previous), pain beliefs, pain responses, genetics, prior or concurrent psychological problems, socioenvironmental factors, and work-site issues. To focus on one of these to the exclusion of others in treating patients is usually inappropriate and inadequate. The management of patients with chronic pain, regardless of what is causing their pain, hinges on supporting patient-centered care (including developing self-efficacy). Activities and treatments should improve overall

function, while remaining realistic about timelines and wide variations in reaching a functional recovery. It is important to explain the relevant anatomy and possible pain sources (or lack thereof) and seek to provide the optimal care for the given condition to manage the pain and minimize dysfunction. Kinesiophobia/fear avoidant beliefs and catastrophization require addressing to effect superior functional outcomes. Sleep problems need to be addressed, as they frequently contribute to pain and impaired function. Impairing pharmaceuticals and interventional treatments outside of those used for specific conditions with high probabilities of substantial or complete recovery (or short term exacerbations responsive to treatment) should be avoided. Their use should be seriously questioned in those cases when there are no moderate- to high-level RCTs demonstrating efficacy. This is especially true given the extensive body of literature indicating that the placebo effect, expectation bias, and attention bias may be responsible for a significant amount of the benefit that is seen in conjunction with the use of many new interventions or adaptations of interventions used for other conditions, even those that are clearly of benefit when used to manage the medical problem to which they were initially applied [186,187,188,189,190,191].

The patient should be transitioned to work or from modified work to full work at the earliest date possible. The individual should be supported during that transition, and told of the likelihood of increased symptoms in conjunction with being reassured that pain does not equate to injury in the chronic pain setting. Should it appear unlikely that there will be anything that can be done to cure the patient's pain, they should be informed of that fact, which should be followed with advice that does not equate to disability or hopelessness by stressing that many people have similar conditions yet go to work every day, and take care of their family, leading normal (or nearly normal) lives. The clinicians' "fear-avoidance beliefs" regarding the relationship between pain complaints and patients' ability to return to work have been shown to affect their treatment practices [192] and, as such, could contribute to a relative nocebo effect. It is consequently imperative that the treating clinician be educated regarding exactly what factors are or are not important in developing an appropriate "return-to-work prescription."

Clinicians should consider referral for further evaluation and perhaps cooperative treatment if:

- Specific clinical findings suggest previously undetected clinical pathology requiring other expertise to adequately address it.
- The clinical course does not follow generally expected patterns.
- Pain distribution is non-anatomic or described in a bizarre or atypical manner. Examples include glove- or stocking-like pain or paresthesias, shock-like pain, pain that radiates up and down the neck and back, burning pain, and pain that is present constantly regardless of position, medication use, or physical treatments.
- Medication use does not decrease as expected or increases.
- Appropriate active exercises do not appear to be improving function as expected.
- Complaints of pain or dysfunction start to involve other body areas, including instances in which the patient:
    - Ceases to discuss returning to work in a specific time frame but rather in relation to a cure.
    - Fails to benefit from any, or all, rational therapeutic interventions.

- Experiences increased pain, or at the very least, pain does not decrease, over time.
- Is unwilling to discuss his or her family situation or expresses comfort with role reversal at home.
- States that the illness or injury has caused all of his or her problems.
- Directs excessive anger at the employer or coworkers, the clinician, or an insurer and/or demonstrates an attitude of revenge or wanting to prove illness.
- Is less interested in the home therapy program or even in recovery of function.

- There appear to be indications of significant psychosocial dysfunction or psychiatric comorbidity.

Judicious referral may be warranted to corroborate the absence of physical pathology and to assure the patient that increased participation in usual activities will not be detrimental to his or her overall physical status. This must be a referral to a well-qualified clinician whose practice patterns are consistent with evidence-based medicine, as the potential to do harm by obtaining an MRI or other diagnostic study labeled “abnormal” based upon the presence of anatomic but clinically irrelevant findings is high. Such labeling may further reduce function and increase disability even if there is nothing abnormal for that person’s age group in part by leading to a relative “nocebo effect.”

In general, interventions for treating pain should be time-limited and functional goal-oriented. Persons returning to work and life functions sooner after injury or surgery tend to have the best outcomes. Persons with equivalent diagnoses who are out of work for 3 months have worse return-to-work outcomes than those out 1 month, while those away for 1 year do worse than those out 6 months. Thus, there is a strong basis to return to a functional status sooner than later, including to work.

As noted previously (see Medical History), identification of psychosocial issues should be a major aspect of the initial evaluation or consultation for a new patient with chronic pain. A few of these issues include current or past mental health issues, family, friends, co-workers, supervisor relationships and support, and drug-related issues. The mere denial of problems with (or history of) alcohol, illicit drug usage on initial examination is generally insufficient, as they are of significant prevalence in patients with chronic pain. There should thus be a focus upon approaching and ruling out substance use disorders and psychosocial issues which goes beyond the typical exam questions. Queries should also seek out other "functional disorders" such as chronic fatigue syndrome and irritable bowel syndrome as these disorders are reportedly associated with chronic pain syndromes [193-197] along with numerous other “functional somatic syndromes” and affective disorders [61, 198,199,200].

While there are clinical systems that may elucidate risk factors for delayed recovery [201-203], a comprehensive history and physical will generally identify at-risk individuals, after which referral to a psychologist or pain specialist can be considered if further evaluation and management of risk factors for the development of a chronic pain syndrome is desired. Referral to a psychologist or psychiatrist experienced in pain evaluation is often appropriate, especially when the pain is ill-defined, not well explained by anatomic or physiological abnormalities, associated with disability in excess of what would be expected based upon objective findings, or depression or anxiety are present. An additional consideration in the

initial care of the patient with chronic pain is whether a multidisciplinary approach should be instituted to minimize disability and maximize function. This is described later in this document.

The following is a short outline followed by summaries of each specific disorder that is addressed in this guideline.

- Identify remediable generators of nociception or neuropathy (e.g., aggressive treatment of diabetes for diabetic neuropathy; aggressive rehabilitation exercises for CRPS[,204,205)].
- When there is no *readily resolvable* pain generator, the focus should be on functional restoration.
- Treatments should be individualized, taking into account co-morbidities and preferences.
- Address co-morbid mental health conditions with appropriate behavioral modification or medications.
- Medications or other treatments that have not been of clear benefit with an adequate trial should be discontinued prior to institution of alternative options. Treatments that are of some benefit should be continued while alternatives are weighed and checked to attain a reasonable chronic pain modulation (as a partial control is better than none in this population) to prevent them from seeking potentially detrimental treatment schemes. Medication effectiveness and adverse effects should be reviewed regularly with the patient and well documented in the medical record.
- Interventions with the potential for serious adverse effects should be employed if pain reduction and functional improvement will reasonably outweigh potential harms to the patient. Such interventions should be preceded by an adequate trial of conservative care. However, there are times when judicious interventional or medication therapy may be more appropriate than other strategies with potential to reduce pain and overall costs.

Treatment of most chronic pain conditions consists of a combination of therapies and interventions. Physical and psychosocial aspects should be considered when developing a treatment plan to suit the patient's needs, reduce their pain, and improve their function. Most importantly, the patient must actively participate in the treatment plan. This often requires substantial and continued patient educational efforts. Guidance is available to assist with this approach [(206)].

ACTIVITIES AND ACTIVITY ALTERATION

The overwhelming theme in the management of most patients with chronic pain is to keep them as physically active as possible [(207,208)]. There is no reason to avoid using the affected body part even in severe cases. All patients require advancement of activity levels and education because inactivity is detrimental despite the temporary relief of symptoms. It is ironic that acute pain from an acute injury (not an acute manifestation of disease) may at times be successfully treated through a reduction in activity (e.g., casting a fractured extremity), yet subacute and chronic pain are best treated in exactly the opposite manner. In the late acute phase of subacute and chronic pain, the patient is generally best treated by performing gradually increased or graded activities to incrementally regain a fully functional status (i.e., usually requiring tolerating pain with each graded increase in occupational and non-occupational activity). The inability of some

patients and clinicians to understand this transition and its major implications is believed to be one of the reasons that chronic pain conditions are so costly. Other key factors are the common occurrence (and lack of addressing) of kinesiophobias/fear avoidant beliefs, catastrophization, and self-efficacy.

Because chronic pain conditions are so heterogeneous, it is not possible to give precise activity limitations. In general, patients with mild symptoms should be encouraged to perform all activities as normally as possible. They likely will require education and exercises. Those with moderate symptoms may or may not be able to work. If not, they should be in a therapy program 3 to 5 days a week, including daily home exercises, and gradually advancing activity levels outside of work within a program that targets return to work and meaningful productivity as a main treatment goal. Transition into the workplace is often useful for patients with chronic pain who are not working, particularly those with severe problems. Such transitioning usually requires careful coordination between the patient, treatment team, supervisor and co-workers. It may involve beginning on a modified duty job for 2 hours a day, then gradually advancing job physical requirements and/or length of time on the job until the worker is back to work full time. This process may take many weeks for those more severely affected, but it is usually a highly effective method to both provide treatment and actively rehabilitate the patient with chronic pain.

Precise numbers of physical and occupational therapy appointments (or chiropractic appointments as appropriate) are not possible to specify due to the complexities of diagnosis, severity of the condition, degree of debility and individual factors involving ability to tolerate and exercise through pain. The key questions involve the documentation of ongoing, progressive, objective functional gains (e.g., return to work status, reducing work limitations, more repetitions of a rehabilitative exercise, walking further, etc.). As long as there is meaningful functional progress, additional therapy appointments are warranted until a plateau in function is reached. In general, prescribing therapy appointments for chronic pain patients and post-operative patients in increments of 5-8 appointments and then reassessing for functional gain prior to further prescriptions of additional appointments is recommended. A common approach is to gradually lengthen time between visits. These approaches also allow for the development and implementation of a home exercise program. A similar process for other appointments (e.g., manipulation, acupuncture) is also recommended regarding documentation of functional gain.

In general, activities causing a *significant* increase in symptoms should be reviewed with the patient and modifications advised when appropriate. Home and work activities may require at least temporary modification. It is now believed to be quite important to emphasize that an increase in pain does not represent or document damage. Instead, an increase in short-term pain as a result of increased activity levels in patients with chronic pain is normal and not detrimental to recovery. While the patient is being treated for a chronic pain syndrome, activities that do not aggravate symptoms should nearly always be maintained, and exercises to prevent debilitation due to inactivity should be advised. Aerobic exercise may be beneficial as a part of a therapeutic management technique that includes strengthening exercises as the cornerstone for management of patients with chronic pain (see Exercise). Stretching and flexibility exercises are particularly required where there is a significant limitation in range of motion and sometimes must precede strengthening exercises depending on the severity of the deficits. When range of motion is not significantly reduced, stretching exercises appear to be of much less importance than strengthening and aerobic

exercises; in those settings, stretching exercises may be counterproductive as patients frequently do these easier exercises and then skip or curtail the core rehabilitative exercises. The patient should be informed that activities might temporarily increase symptoms but that such exacerbations are normal.

WORK ACTIVITIES

Work activity modification is an important part of many treatment regimens. Advice on how to avoid substantially aggravating activities that at least temporarily increase pain includes a review of work duties to decide whether or not modifications can be accomplished without employer notification and to determine whether modified duty is appropriate and available. Making every attempt to maintain patients at the maximal levels of activity, including work activities, is strongly recommended as in their best interest, particularly among patients with chronic pain in whom debility is so commonly seen. A corollary from the employment side is disability accommodation, which is the employer's assessment of whether the employer is able to accommodate the work limitations in the current job, another job, or any job at the employer. It is in everyone's best interest for the clinician to help work through what can be an iterative process to achieve return-to-work status in any position initially, and help the advancement of the work status to the original job position whenever possible.

The analysis of work ability requires an assessment of risk, capacity, and tolerance. Risk refers to what a patient can do, but should not do, due to the substantial risk of significant harm, considering probability and severity of potential adverse events. Clinicians impose work restrictions based on estimates of risk. Capacity refers to what a patient is physically capable of doing, as measured by concepts such as range of motion, exercise ability in metabolic equivalents (METs), etc. Tolerance for chronic symptoms such as back pain is the basis for a patient (not a clinician) to decide whether the rewards of work are worth the cost of the symptoms. Details of this assessment methodology have been described [209,210].

The first step in determining whether work activity modifications are required usually involves a discussion with the patient regarding whether the individual has control over the job tasks. In such cases where the worker can, for example, get assistance from someone else to lift a box of parts to assemble, and can alternate sitting and standing as needed, there may be no requirement to write any restrictions even if the pain is limiting. A discussion regarding assessing the patient's beliefs and expectations regarding activity/RTW while symptomatic along with perceptions of supervisor and co-worker support [211] are often helpful, particularly as they provide insights into expectations, perceived support, fear-avoidant beliefs, and catastrophization. Assessment of work activities and potential for modifications may also be facilitated by a worksite visit and analysis by a clinician with appropriate training (e.g., experienced occupational therapist, physical therapist, occupational medicine physician, and/or ergonomist).

Work modifications should be tailored taking into account two main factors:

1. the job physical requirements; and
2. the safety of the tasks, in consideration of the diagnosed condition, age, and relevant biomechanical limitations.

Sometimes it is necessary to write limitations or prescribe activity levels that are above what the patient feels they can do, particularly when the patient feels that complete rest or similar non-activity is advisable. In such cases, the clinician should be careful to not overly restrict the patient, as it is clearly not in his or her best interest, and education about the pain problem and the need to remain active should be provided.

Common limitations involve modifying the weight of objects lifted, degree of stereotypical activity allowed (low, medium, high), frequency of lifts, and posture, all while taking into account the patient's capabilities. As noted above, there are many variables that must be incorporated into prescriptions of physical activities, thus they require individualization. There are not quality studies of restrictions, thus these are clinical judgments.
For *severe* cases of chronic pain syndrome involving an upper extremity, initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- No lifting over 5 pounds; and
- No highly repetitive or high force activities (e.g., push/pull) involving the affected hand.

For severe chronic pain syndrome involving a lower extremity or the spine, initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- No lifting over 10 pounds; and
- Alternate sitting and standing as needed.

These work and home activity guidelines are generally reassessed every week in the early rehabilitation process with graded increases in activity recommended so that patients with a severe chronic pain syndrome evolve off modified duty in generally not more than 16 weeks. The amount of weight handled or force used with the hand can be progressively increased. Clinicians should also be advised that some workplaces provide health care or physical or occupational therapy on-site and this may further facilitate the rehabilitation process.

It is best to communicate early in the treatment that limitations will be progressively reduced as the patient progresses. Experienced clinicians communicate the intended changes in restrictions for the coming week (similar to forecasting increases in exercise program components) at the current visit to reduce the element of surprise and help actively facilitate the patient's most important elements of an active, functional restoration program. Tailoring of restrictions is required in nearly all patients with chronic pain as there is great variability in symptoms and dysfunction. The employer should also be consulted while developing strategies to expedite and support integration of the patient into the workplace.

The clinician can assist patients and employers in explaining that:

- The patients usually have increased pain performing almost any function in the early rehabilitation timeframe, even if "light" duty;
- Increases in pain do not equate to injury for patients with chronic pain;
- Increases in symptoms should be heard with a sympathetic ear and the factors which are associated with significant increases in pain should be addressed;

- Any restrictions are intended to allow for time to build activity tolerance through exercise; and
- Where appropriate, it may be helpful to mention that this rehabilitative plan will also help the patient to regain normal non-occupational life functions.

Every attempt should be made to maintain the patient at maximal levels of activity, including work activities, as it is in the patient's best short term, as well as long term interest. *Work activity limitations should be written whether the employer is perceived to have modified duty available or not. Written activity limitations guidance communicates the status of the patient, and also gives the patient information on what they should or should not do at home.* Table 4 provides recommendations on activity modification and duration of absence from work for CPS. These guidelines are intended for patients without comorbidity or complicating factors, including serious prior injuries. They are targets to provide a guide from the perspective of physiologic recovery.

SPECIFIC TREATMENT INTERVENTIONS

Studies evaluating the efficacy of a variety of treatments in the management of various chronic pain disorders sometimes test interventions, especially medications, in patients with heterogeneous chronic pain disorders. The evidence base for these interventions is discussed in general terms, with individualized indications for use in management of a specific pain state provided when warranted. Treatment of specific disorders is discussed in other guidelines and that specific guidance takes precedent over this guidance.

The emphasis and management of patients with chronic pain is far different than that for acute pain from new physical injuries. For patients with chronic pain rather than acute pain, the concentration on pain treatment with medications and invasive interventions is de-emphasized, while the focus should be on functional restoration. The three most important aspects of functional restoration include active patient engagement through interventions that:

1. change the patient's focus to functional recovery;
2. include aerobic and strengthening exercises; and
3. apply psychological interventions that include enhancing self-modulation of pain and distress.

There are some invasive interventions with efficacy in limited circumstances.

Treatments widely used in the management of chronic pain, regardless of etiology, are behavioral interventions, medications, active exercises, select and judicious use of passive interventions, coordinated multidisciplinary medical and psychological specialty programs, and certain types of injections. The following is the overall discussion of each intervention and information regarding the evidence-basis for recommendations. A summary of the recommendations by chronic pain condition is provided at the beginning of each section.

FOLLOW-UP VISITS

It is recommended that patients seeing a new clinician or while still out of work for a work-related chronic pain disorders should have a follow-up visit every 1 to 2 weeks initially to

evaluate the patient, initiate treatment(s) and/or adjust prior treatment regimen(s). Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. Those initial visits should include further focusing on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals, should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest or appliances. The clinician should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is recommended to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is recommended. However, in the active rehabilitation phase for patients with CRPS, when constant encouragement is required to continue performing exercises, follow-ups weekly for as much as 2 or 3 months is recommended to remain in concert with physical/occupational therapy, as well as to sustain a team-oriented focus on restoration and achievement of functional goals.

PREVENTION OF CHRONIC PAIN SYNDROME

There is an important therapeutic window for preventing chronic non-malignant or non-cancer pain problems from becoming a chronic pain syndrome (e.g., a functioning patient successfully coping with low back pain through exercise and the judicious use of medication vs. a patient seeking treatment after treatment in a protracted quest to eliminate all pain). The timing of the critical window of opportunity to prevent the development of a chronic pain syndrome is unclear, but many experienced clinicians are confident that this window is identifiable in the acute pain phase by recognizing factors for delayed recovery and there is consensus that it should be well recognized no later than the early subacute pain phase. If psychosocial risk factors are not identified and addressed in the subacute phase, there is an increased risk of enduring changes in the central nervous system which contribute to central sensitization and to the transition to a chronic condition. See also the ACOEM Work Disability Prevention and Management Guideline, and consider screening tools (e.g., [106]).

Pain may or may not be well localized, yet it is frequently compounded by the severity of motivational, affective, cognitive, and behavioral overlay that is often a frustrating aspect of chronic pain.

If the focus successfully shifts from pain complaints to function and movement patterns are normalized, symptoms usually diminish and function increases markedly. Normalization is usually achieved through the following:

- Combination of changing emphasis on the desired outcomes (function).

- Reducing emphasis on subjective complaints (pain). However, if a subjective complaint is symptomatic of distress, that should be addressed and treated so the patient acquires and actively uses self-soothing skills.
- Increasing active therapeutic interventions.
- Normalizing movement patterns.
- Reducing passive interventions.
- Addressing psychosocial factors sympathetically.
- Acknowledging that psychological conditions occur frequently with pain disorders.

The patient's level of education, cultural background, literacy, health literacy, and language background should be considered for their potential as barriers to progress. Reducing barriers to effective treatment may also help prevent the development of a chronic pain syndrome.

The keys are to promptly recognize this transitional period (when the patient begins to deviate from the expected recovery trajectory for his or her complaint, illness, or injury) and to institute rehabilitative or appropriate pain management techniques (e.g., institution of active therapies with fear avoidance belief training). Inability to make progress on these issues necessitates an early referral (e.g., experienced secondary or tertiary pain clinician and psychologist) as the patient with chronic pain requires significantly different interventions than does the acute pain patient. While this sometimes places a strain on the time and skill of the treating clinician, the clinician is usually the most influential person in the patient's recovery, and his or her appreciation of and attending to these factors as valid and important clinical issues, is often key to successful resolution of delayed recovery and prevention of a chronic pain syndrome in an acute or subacute patient.

Before pain becomes chronic, there is an important therapeutic window for preventive interventions. During this transitional period, patients may present with some or all of the emotional and behavioral characteristics that are seen with chronic pain, but their pain is still potentially explainable with reference to tissue damage. It is important to recognize when the patient begins to deviate from the expected recovery trajectory for his or her complaint, illness, or injury, and to institute rehabilitative or appropriate pain management techniques or make a timely referral. For many patients, psychological or multidisciplinary evaluations may help, but the treating clinician is still the most influential practitioner involved in the patient's recovery. The treater's understanding of these issues, directly addressing them, and attending to them as valid and important clinical issues during frequent supportive follow-up appointments, is often key to successful resolution of either delayed recovery in a "pre-chronic patient" or effective treatment of a chronic pain syndrome.

WORK-RELATEDNESS

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. Each disorder-specific ACOEM guideline has detailed discussions and evidence citations regarding specific occupational disorders. Thus, this guideline will only briefly review a few additional chronic pain-specific issues.

Aside from a significant, discrete traumatic event (e.g., laceration; substantial slips, trips, or falls), much of what is classified as acute pain in the occupational setting is best modeled as

a relatively sudden onset of pain, such as low back pain, in the context of a multifactorial disorder. The minority who sustain a significant traumatic event have workers' compensation claims that are largely noncontroversial. This applies to many cases of complex regional pain syndrome if the onset was due to a specific, discrete event at work.

Work-relatedness of specific disorders are discussed in those modules, including Complex Regional Pain Syndrome, Fibromyalgia, and Neuropathic Pain.

Chronic pain associated only with psychological disorders may be occupational, although most cases are not work-related. Factitious illness, malingering, conversion disorder, somatization disorder, hypochondriasis, and body dysmorphic disorder are all non-occupational conditions. Pain disorder, which also falls into the somatoform disorders category, may or may not be associated with a medical condition; thus, it may or may not be occupational depending on whether there is a clear occupational inciting event that caused the medical disorder.

COMPLEX REGIONAL PAIN SYNDROME

INTRODUCTION

Complex regional pain syndrome (CRPS) is a generally painful condition that is most often associated with recent trauma, surgery, or injury. It has been variously defined by the International Association for the Study of Pain (IASP),[212] and the "Budapest Criteria" as generally including the presence of diffuse moderate to severe spontaneous or stimulus-evoked, non-dermatomal regional pain, usually with allodynia [213,214,215]. The exact pathophysiological mechanism(s) remain unclear. There is some evidence of inflammatory components, autoimmunity, vasomotor dysfunction, psychological distress, and central sensitization [216].

Multiple studies of brain activity in patients with CRPS have observed changes that include reorganization of brain circuits involving cognition, pain, fear, and movement [217-220], atrophy of specific brain regions [217,221-223], and specific cognitive deficits [219,221,224,225]. This suggests that although CRPS may be precipitated by a peripheral injury, in time central nervous system involvement may contribute to or maintain the condition.

CRPS has a reported prevalence of 20.6 to 113.5 per 100,000 adults [226,227]. There are only two population-based studies that report incidence of CRPS; however, it is noteworthy that the reported incidence rates varied between those studies by approximately four-fold. The first reported from Mayo Clinic found an incidence rate of 5.46 per 100,000 person years in Rochester County, MN [228]. Another study reported an annual incidence in the Netherlands at 26.2 per 100,000 person years (95% CI 23.0-29.7)[226]. Females are diagnosed with CRPS 3.4 times more frequently than males, and incidence is highest among the 50- to 70-year age range [226]. Upper extremity injuries are more commonly associated with CRPS as compared to lower extremities, and a fracture is the most common injury type associated with CRPS (44%). The risk of CRPS has been estimated at 1% among patients after a distal radius fracture [229].

CRPS has been variously categorized into different subtypes and stages, including type 1 and type 2, depending on whether there is an associated peripheral nerve injury (i.e., type 2,[212]. Other classifications used involve describing CRPS as warm or cold [230], and other subtypes

classify based on course and intensity of the condition. Another approach classifies CRPS into three distinct CRPS subtypes [231]: (1) a relatively limited syndrome with vasomotor signs predominating, (2) a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating, and (3) a CRPS syndrome similar to "classic RSD" descriptions. Subtype 3 showed the highest levels of motor/trophic signs and possible disuse-related changes (osteopenia) on bone scan, despite having directionally the briefest pain duration of the three groups . Three stages of CRPS have also been described based largely on time: Stage I (Acute stage: 0-3 months); Stage II (Dystrophic stage: 3-9 months); Stage III (Atrophic stage: 9-18 months[215,232].

While theorized, it is important to note that there is, as best, very limited quality evidence for any specific treatment to define treatment approaches that differ based on the various subtypes and/or stages that have been proven.

RISK AND CAUSATION

WORK-RELATEDNESS

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. The work-relatedness of specific disorders is discussed in guidelines such as Hand, Wrist and Forearm Disorders, Ankle and Foot Disorders, and Knee Disorders. Thus, aspects of work-relatedness regarding sequelae of acute injuries that may be relevant for some patients are not duplicated here.

CRPS is reported most frequently after a peripheral traumatic insult [233-237], central nervous system insults including strokes [238], myocardial infarction, or other major system insult [239]. There is controversy regarding work-relatedness for some cases. This is due to: limited insight into the pathophysiology of the syndrome, use of this diagnosis without objective evidence, reported advocagenic influences* and apparent lack of a dose-response relationship between injury severity and probability of the disease. There are also some reported associations with psychosocial factors, including anxiety and depression [240,241]. Among patients who have unequivocal evidence of the diagnosis and an overt traumatic occupational injury, work-relatedness of this condition is usually relatively non-controversial as the setting of the trauma determines the causal conclusion and those cases arising from an occupational trauma are usually considered occupational injuries and diseases [242]. CRPS Type II involves an overt nerve lesion [243], thus the cause of the overt nerve lesion determines the work-relatedness of CRPS Type II. There are some occasions where the cause is unknown (approximately 5 to 15%). In such cases, a determination of work-relatedness is necessarily speculative. As well, when there is either controversy over the diagnosis or there is lack of an overt, significant occupational injury, work-relatedness of CRPS is controversial and speculative.

(See Impact and Basic Principles and Definitions for more information.)

*Advocagenic influences include responses to legal counsel or legal system, induced or magnified by the counsel or system itself; usually used for unfavorable responses.

INITIAL ASSESSMENT

The initial assessment requires a thorough history and physical examination with somewhat different emphases compared with most chronic pain patient evaluations. This includes a history of symptoms, trauma, purported cause of the symptoms, treatments attempted, and exercises performed. The history and physical examination require particular attention to differences in use of the limb, pain, strength, color, and temperature [(244)]. Selective testing is needed to confirm the clinical impression. The most important point is to comprehensively develop and address a differential diagnosis, as well as to exclude other potential explanatory conditions.

For more information, please see Initial Assessment in the Chronic Pain Introduction.

SIGNS AND SYMPTOMS

Symptoms typically develop within a few days to weeks after an acute injury, including fractures and surgery, and can include the following [(245,246,247)]:

- Constant severe burning or throbbing pain, typically isolated to one limb
- Trauma or surgery that precedes symptoms
- Pain that is disproportionate to the trauma or tissue injury
- Nonradiating pain
- Spontaneous pain at rest without any provoking stimuli
- Significantly worsening pain with activity
- Unusual sensitivity to touch; pain with minor pressure or palpation, including feeling pain from a stimulus that would not normally be painful
- Sensitivity to cold and/or heat
- Skin coloration changes, including blanching/pale, mottling, reddish or purplish
- Changes in skin temperature, which may fluctuate
- Swelling of the affected limb
- Sweating changes
- Skin texture changes, developing shininess and thinness
- Changes in hair and nails
- Decreased function of the limb
- May also have numbness, stiffness, and sensitivity to other dermal stimuli, such as capsaicin [(248)]

There is limited evidence that some signs and symptoms may be more important for the diagnosis [(249)].

HISTORY

The vast majority of the literature addresses chronic and/or well-established CRPS. Yet, the onset of CRPS is believed to be critical in thwarting the trajectory towards fully-established CRPS. A growing body of evidence indicates that CRPS most commonly starts with symptom onset at few days to weeks after an injury, surgery or event. Although the diagnosis may be

missed initially, a careful patient history and medical records may provide historical evidence to support an earlier onset. Thus, the medical history naturally starts with the details of that event [250-255]. This includes the subsequent clinical course with attention to deviation(s) from the typically expected course for similar injuries or surgeries. A 5+ pain rating in the first week after trauma and fracture has been suggested to be a red flag for the potential to develop CRPS [254,255].

A focus on the potential for a treatable condition is also mandatory for the initial evaluation of a patient with possible CRPS. Nevertheless, it is recommended that the initial evaluation of patients with potential CRPS start with a focus on function, both at work and home. This sets the focus on function that is essential for the vast majority of patients with chronic pain, including patients with CRPS, while maintaining a focus on confirmation that prior examiners did not miss another treatable disorder.

CLINICAL COURSE

Characteristics of pain are then elicited that are unusual and disproportionate compared with the degree of the injury and narrowed to that injured limb [249]. Pain is typically described as severe, non-radiating, and worse with user or activity. Excessive sensitivity to normally nonpainful stimuli, such as touch or pressure on the skin typically develops. Unusual and asymmetric temperature differences between the limbs occur frequently. Cold intolerance is common. Edema, sweating, and skin color changes may occur. Disuse and limb weakness occur, especially if the condition is not recognized early and strengthening and conditioning exercises applied. Late changes that may occur include skin thinness and shiny skin development; hair and nail changes also occur later in the course of more severe cases and/or those without prior emphases on functional restoration. The clinical course has been described by some to progress through three distinct phases: Stage 1 (acute), Stage 2 (dystrophic), and Stage 3 (atrophic).

Stage I (acute stage: 0-3 months), which is characterized primarily by pain/sensory abnormalities (e.g. hyperalgesia, allodynia), signs of vasomotor dysfunction, and prominent edema and sudomotor disturbance; Stage II (dystrophic stage: 3-9 months), which is characterized by more marked pain/sensory dysfunction, continued evidence of vasomotor dysfunction, with development of significant motor/trophic changes; and Stage III (atrophic stage: 9-18 months), which is characterized by decreased pain/sensory disturbance, continued vasomotor disturbance, and markedly increased motor/trophic changes [232,244]. While these stages have been defined, there are many patients who do not follow these stages, including, e.g., those with early resolution, milder cases, those treated to avoid the disuse findings, those treated with early functional restoration, and some with asymptomatic presentations [215,244,256].

Collecting information about occupational history and activities of daily living and interests assists in understanding patient priorities and targeted outcomes. Alertness to the patient responses is important, as there may be strong clues to the degree to which preoccupation with somatic complaints instead of a functional focus is present. Unprovoked responses frequently also provide powerful clues to activities the patient is interested in resuming that may ultimately provide the motivational tools to facilitate the patient's functional restoration. The clinician should ask typical questions focused on pain symptoms. Current CRPS treatments, whether medical or non-medical, should be recorded. Past treatments

should be reviewed with careful discernment and documentation of meaningful, lasting functional improvements.

After the function-based and pain histories are obtained, the history should next include a thorough medical history, past medical history, medication history, surgical history, accident history, and current/past psychological history. There should be a low threshold for a thorough psychological assessment for those who have an atypical presentation, do not respond to treatments as is expected, fail to follow an expected clinical course and/or have a history of prior mental health disorder(s).

The primary treating clinician, other health care professionals, and consultants should approach CRPS symptoms as an integral element of each history and physical examination. Yet the primary focus should be on function, rather than pain, to promote recovery and to avoid an undue focus on pain and pain ratings. This includes assessing pain complaints relative to casual patient observations, the physical examination, and observation of the patient's functions both while actively examined and ideally outside of the context of the performance of a physical examination. Obtaining a history of functional activities from family members or friends may sometimes be useful.

PHYSICAL EXAMINATION

The physical examination of a patient with well-established signs of CRPS is generally straightforward, particularly for the examiner familiar with CRPS [214]. However, early findings are often clinically subtle and the diagnosis may be more tentative. Still the primary intervention is the same: education and directed specialized therapies with primary emphasis on strengthening, functional active use, and aerobic components to prevent dysfunction. Early psychological interventions may benefit selected individuals as well, particularly if there is concomitant catastrophization, post-traumatic stress disorder and/or poor coping [257]. Often the patient will be observed limiting use of the extremity, including protecting and avoiding use of the limb. This can include not shaking hands or avoiding weight bearing on the affected limb.

A key feature of this condition is that objective findings in the affected extremity contrast significantly with those of the unaffected extremity. The skin temperature may differ, usually being cooler in the affected extremity, although it can be warmer (an infrared thermometer should usually be used, as simple touch may miss a temperature difference). If advanced, the skin may have a smooth, thinned, atrophic appearance [249,258]. Skin coloration changes are also generally present, including mottling, reddish or purplish appearance. Livido reticularis (a mottled purplish discoloration of the skin) may be present. The extremity may become edematous. With passage of time, the nails may also become atrophic. A distinguishing characteristic is allodynia, or the experience of pain with something that normal individuals would not consider painful. Examples include pain with light touch, shaking hands, or even the weight of the clothing on the extremity. Hyperalgesia, or abnormally high pain experienced from a normally painful stimulus, is also common. Circumferences of the affected extremity may differ. They may be increased in edematous states (generally earlier and reduced if there is disuse dystrophy in chronic states. Range of motion may be reduced. Tremor and weakness may occur. Water displacement volumes may be measured to attempt to ascertain degrees of swelling, although the baseline measures will not be comparable with the pre-morbid state, which is

unknown. Additional findings reported include misperceiving the correct finger that is being touched, inability to identify an object solely with tactile input (astereognosis), and hand laterality identification with motor imagery [259]. While occasional measurements may be acceptable, there may be a tendency towards preoccupation with those measures by some, which has the potential to draw attention away from active therapy, towards symptoms and signs, and may inadvertently promote delayed recovery. Also, the examiner should be alert for changes such as skin color, swelling, and temperature changes with activity.

For more information, please see Physical Examination in the Chronic Pain Introduction.

DIAGNOSTIC CRITERIA

Most of the diagnostic criteria reported include common characteristics for the diagnosis of CRPS [249,260-265]. However, there have been some differences in case definition criteria [266, 267]. Table 5 presents frequently used and supportable criteria [249].

The criteria in Table 5 are recommended for diagnosing CRPS but may be challenging as objective measurements and equipment such as temperature probes, volumetry, goniometers, and pain scales are required [268]. For patients not meeting the diagnostic criteria, or if CRPS either continues or progresses, the diagnosis of CRPS should be confirmed via a completely independent and competent medical examination (i.e., an exam by someone other than the treating physician). Such an examination should particularly focus on the absence of another explanatory diagnosis, the presence of a temporal inciting event, the historical information particularly from a credible patient, objective evidence (e.g., bone scan), presence of a known nerve injury (CRPS II), responsiveness to prior evidence-based treatments to which CRPS responds, and application and comparisons with the diagnostic criteria (copies of which could be sent to the examiner at the time of an independent medical examination). The threshold for concomitant psychological consultation and psychometric testing in such circumstances should be quite low, especially if there are unusual symptoms, the physical examination reveals unusual findings, there are prior mental health disorder(s), there is deviation from an expected clinical course and/or the patient does not respond to treatments as expected.

An additional major issue is that the diagnosis may previously have been made on purely subjective grounds, without objective evidence [269, 270]. Thus, the original IASP criteria has been modified many times (see Table 5) [214,247,258,271-273]. However, even these significant advancements may be insufficient as the inter-rater reliability scores among physician examiners were reported as adequate, but the numeric data suggest otherwise [268]. Another study also showed evidence that range of motion measurement differences were not inconsequential [274].

The sensitivity of the CRPS diagnostic criteria has been estimated at 85-99%, with a specificity of 68-69% [245,247]. Additional subsets of patients have been recognized; however, the clinical implications have not been well defined in quality studies [214].

Classification

Complex regional pain syndrome is traditionally classified as either Type I or Type II. Type I

is associated with a specific event, such as a fracture or crush injury. Type II is associated with a defined nerve lesion.

MANAGEMENT APPROACH

This section is a general approach to treatment of CRPS (see also Algorithm 2). In general, early CRPS cases, especially in the first few weeks, usually and naturally fail to meet all of the diagnostic criteria. Limited research data are available on the evaluation and treatment of these patients. Nevertheless, early cases must exist; otherwise, it would be impossible to develop chronic CRPS. The early timeframe and presentation are believed to afford an excellent opportunity to intervene aggressively, especially with strengthening exercises, to speed recovery and effect an excellent clinical outcome. The treatment approach to these patients generally follows that for the chronic cases, while being vigilant for the potential of an inexplicable clinical course and/or a different diagnosis to be present that becomes apparent with time.

Interventions for treating CRPS should be time-limited and function-focused, rather than primarily medication-focused. Persons returning to work and life functions sooner after the identification of CRPS tend to have the best outcomes. Persons with CRPS who are out of work for 3 months have worse return-to-work outcomes than those out 1 month, while those away for 1 year do worse than those out 6 months. Thus, there is a strong basis to return to a functional status sooner than later, including to work. For those unable to return to full, unrestricted work, restricted work is the next best option, with careful supportive monitoring and advancement of the work activities over time.

As noted previously (see History), the early identification of psychosocial issues should be a major aspect of the initial evaluation or consultation for a new patient with either potential or confirmed CRPS. Future psychosocial challenges and prior mental health disorder(s) should also be identified as part of an evaluation if there is failure to respond to treatment as expected, deviation from the expected clinical course, and/or mental health disorders that may interfere with recovery (e.g., catastrophization). A few of the issues that suggest an earlier need for psychosocial evaluation include anxiety disorders, catastrophization (e.g., often first signaled by high pain ratings, high self-rated disability), current or past mental health issues, fear avoidant beliefs, poor and/or troubled interpersonal support and relationships (e.g., family, friends, co-workers, supervisor), drug-related issues [275], failure to comply with progressive strengthening exercises, failure to comply with other treatments, failure to respond to evidence-based treatments for CRPS, involvement in litigation, especially early and or seemingly inexplicable deviations from the expected clinical course. There should thus be a focus upon approaching and ruling out substance use disorders and psychosocial issues which go beyond the typical exam questions. Queries should also seek out chronic fatigue syndrome, irritable bowel syndrome, and other "functional disorders" as these disorders are reportedly associated with chronic pain syndromes [193-197] along with numerous other “functional somatic syndromes” [61].

While there are clinical systems that may elucidate risk factors for delayed recovery [201,202,203,206], a comprehensive history and physical will generally identify at-risk individuals, after which referral to a psychologist or pain specialist should be considered for further evaluation and management of risk factors for the development of, and often drivers of,

chronic pain syndromes (see above). An additional consideration in the initial care of the patient with CRPS is whether, and at what point, a multidisciplinary approach should be instituted to minimize disability and maximize function. This is described later in this guideline.

The following is a short outline followed by summary of prioritized/hierarchical CRPS treatments.

- The singular focus should be on functional restoration (i.e., strengthening exercises, aerobic exercises, cognitive behavioral therapy and return to work and function).
- Identify remediable generators of nociception or neuropathy that may be contributing (e.g., aggressive treatment of diabetic neuropathy).
- Treatments beyond functional restorative treatments above should be individualized, be evidence-based, and consider co-morbidities and patient preferences when there are plausible alternatives (there are no plausible alternatives to strengthening exercises, despite many patients avoiding them).
- Address co-morbid mental health conditions with appropriate behavioral modification or medications.
- Medications or other treatments that have not been of clear benefit with an adequate trial should be discontinued prior to institution of alternative options. Treatments that are of some benefit should be continued while alternatives are weighed and checked to attain a reasonable modulation of CRPS symptoms (as a partial control is better than none) and to prevent them from seeking potentially detrimental treatment schemes. Medication effectiveness and adverse effects should be reviewed regularly with the patient and well documented in the medical record.
- Interventions with the potential for serious adverse effects should be employed after treatments with less morbidity have been trialed with insufficient results and/or pain reduction and functional improvement will reasonably outweigh potential harms to the patient. However, there are times when judicious interventional or medication therapy may be more appropriate than other strategies with potential to reduce pain and overall costs.

Treatment of most patients with CRPS consists of a combination of exercises, CBT, therapies and interventions. Physical and psychosocial aspects should be considered when developing a treatment plan to suit the patient's needs, reduce their symptoms, and improve their function. Most importantly, the patient must actively participate and follow the treatment plan. This often requires substantial and continued patient educational efforts, especially with the strengthening exercise component, which is essential but can be painful to initiate.

ACTIVITIES AND ACTIVITY ALTERATION

The overwhelming theme in the management of patients with CRPS is to institute and advance strengthening exercises as the treatment cornerstone. Advancement of these exercises should also be based on achievement of benchmarks, and not symptom-limited. The patient should also be as physically active as possible [71,207,249]. There is no reason to avoid using the affected body part even in severe cases. All patients require advancement of activity levels and education as inactivity is detrimental to the clinical course of CRPS despite the temporary relief of symptoms that often accompanies disuse. It is ironic that acute pain from an acute injury (not an acute manifestation of disease) may at times be successfully treated through a reduction in activity (e.g., casting a fractured extremity), yet subacute and chronic pain due to CRPS is best treated in the opposite manner. Patients with CRPS are best

treated by performing gradually increased or graded activities to incrementally regain a fully functional status (i.e., usually requiring tolerating pain with each graded increase in occupational and non-occupational activity). The inability of some patients and clinicians to understand this transition and its major implications is believed to be one of the reasons that CRPS is identified late it its course, resulting in increased morbidity, healthcare costs, and indemnity costs.

Because CRPS is so heterogeneous, it is not possible to give precise activity limitations. In general, patients with mild symptoms should be encouraged to perform all activities as normally as possible. They usually require education and exercises. Those with moderate CRPS symptoms may or may not be able to work depending on job physical requirements. If not, the patient should be in a therapy program 3 to 5 days a week, that prominently includes daily home strengthening exercises, aerobic exercises, and gradually advancing activity levels outside of work within a program that targets return to work and meaningful productivity as the main treatment goals. Transition into the workplace is often useful for patients with CRPS who are not working, particularly those with severe problems combined with the setting of whether there is an ability of the workplace to accommodate severe limitations. Such transitioning usually requires careful coordination between the patient, treatment team, supervisor and co-workers. It may involve beginning on a modified duty job for 2 hours a day, then gradually advancing job physical requirements and/or length of time on the job until the worker is back to work full time. This process may take many weeks for those more severely affected, but is usually a highly effective method to both provide treatment and actively rehabilitate the patient with CRPS.

Precise numbers of therapy appointments are not possible to specify due to the complexities of diagnosis, severity of the condition, degree of debility and individual factors involving ability to tolerate and exercise through pain. The key questions involve the documentation of ongoing, progressive, objective functional gains (e.g., return to work status, reducing work limitations, more repetitions of a rehabilitative exercise, walking further, etc.). As long as there is meaningful functional progress, additional therapy appointments are warranted until a plateau in function is reached. In general, prescribing therapy appointments for chronic pain patients and post-operative patients in increments of 5-8 appointments and then reassessing for functional gain prior to further prescriptions of additional appointments is recommended. A common approach is to gradually length time between visits. These approaches also allow for the development and implementation of a home exercise program. A similar process for other appointments (e.g., manipulation, acupuncture) is also recommended regarding documentation of functional gain.

In general, activities causing a *significant* increase in symptoms should be reviewed with the patient and modifications advised when appropriate. Home and work activities may require at least temporary modification. It is now believed to be quite important to emphasize that an increase in pain does not represent or document physiological damage. Instead, an increase in short-term pain as a result of increased activity levels in patients with chronic pain is actually believed to be normal and not detrimental to recovery. While the patient is being treated for a chronic pain syndrome, activities that do not aggravate symptoms should nearly always be maintained, and exercises to prevent debilitation due to inactivity should be advised. Aerobic exercise may be beneficial as a part of a therapeutic management technique that includes strengthening exercises as the cornerstone for management of patients with chronic pain (see Exercise). Stretching and flexibility exercises

are particularly required where there is a significant limitation in range of motion and rarely must precede strengthening exercises depending on the severity of the deficits; in severe cases, stretching exercises may be combined with some strengthening exercises. When range of motion is not significantly reduced, stretching exercises appear to be of much less importance than strengthening and aerobic exercises; in those settings, stretching exercises may be counterproductive as patients frequently do these 'easier' exercises and then skip or curtail the core rehabilitative exercises, especially among patients with CRPS. The patient should be informed that activities might temporarily increase symptoms but that such exacerbations are normal.

WORK ACTIVITIES

Work activity modification is an important part of many treatment regimens. Advice on how to avoid substantially aggravating activities that at least temporarily increase pain includes a review of work duties to decide whether or not modifications can be accomplished without employer notification and to determine whether modified duty is appropriate and available. Making every attempt to maintain patients at the maximal levels of activity, including work activities, is strongly recommended as in their best interest, particularly among patients with chronic pain in whom debility is so commonly seen.

The analysis of work ability requires an assessment of "risk," "capacity," and "tolerance." Risk refers to what a patient can do, but should not do, due to the substantial risk of significant harm, considering probability and severity of potential adverse events. Clinicians impose work restrictions based on estimates of risk. Capacity refers to what a patient is physically capable of doing, as measured by concepts such as range of motion, exercise ability in metabolic equivalents (METs), etc. Tolerance for chronic symptoms like back pain is the basis for a patient (not a clinician) to decide whether the rewards of work are worth the cost of the symptoms. Details of this assessment method have been described [209].

The first step in determining whether work activity modifications are required usually involves a discussion with the patient regarding whether the patient has control over the job tasks. In such cases where the worker can, for example, get assistance from someone else to lift a box of parts to assemble, and can alternate sitting and standing as needed, there may be no requirement to write any restrictions even if the pain is limiting. Assessment of work activities and potential for modifications may also be facilitated by a worksite visit and analysis by a clinician with appropriate training (e.g., experienced occupational therapist, physical therapist, occupational medicine physician, and/or ergonomist).

Work modifications should be tailored taking into account two main factors:

1. the job physical requirements; and
2. the safety of the tasks, in consideration of the diagnosed condition, age, and relevant biomechanical limitations.

Sometimes it is necessary to write limitations or prescribe activity levels that are above what the patient feels they can do, particularly when the patient feels that complete rest or similar non-activity is advisable. In such cases, the clinician should be careful to not overly restrict the patient, as it is clearly not in his or her best interest, and education about the pain problem and the need to remain active should be provided.

Common limitations involve modifying the weight of objects lifted, degree of stereotypical activity allowed (low, medium, high), frequency of lifts, and posture, all while taking into account the patient's capabilities. As noted above, there are many variables that must be incorporated into prescriptions of physical activities, thus they require individualization. There are not quality studies of restrictions, thus these are clinical judgments.
For *severe* cases of upper extremity CRPS, frequent initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- No lifting over 5 pounds; and
- No highly repetitive or high force activities (e.g., push/pull) involving the affected hand.

For severe lower extremity CRPS, frequent initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- Walking limit of 5 minutes; and
- Alternate sitting and standing as needed.

These work and home activity guidelines are generally reassessed every week in the early rehabilitation process with graded increases in activity recommended so that patients with a severe CRPS evolve off modified duty in generally not more than 16 weeks. The amount of weight handled or force used with the hand can be progressively increased. Clinicians should also be advised that some workplaces provide health care or physical or occupational therapy on-site and this may further facilitate the rehabilitation process.

It is best to communicate early in the treatment that limitations will be progressively reduced as the patient progresses. Experienced clinicians communicate the intended changes in restrictions for the coming week (similar to forecasting increases in exercise program components) at the current visit to reduce the element of surprise and help actively facilitate the patient's most important elements of an active, functional restoration program. Tailoring of restrictions is required in nearly all patients with CRPS as there is great variability in symptoms and dysfunction. The employer should also be consulted while developing strategies to expedite and support integration of the patient into the workplace.

The clinicians can assist patients and employers in explaining that:

- The patients usually have increased pain performing almost any function in the early rehabilitation timeframe, even if "light" duty;
- Increases in pain do not equate to injury for patients with CRPS;
- Increases in symptoms should be heard with a sympathetic ear and the factors which are associated with significant increases in pain should be addressed;
- Any restrictions are intended to allow for time to build activity tolerance through exercise; and
- Where appropriate, it may be helpful to mention that this rehabilitative plan will also help the patient to regain normal non-occupational life functions.

Every attempt should be made to maintain the patient at maximal levels of activity, including work activities, as it is in the patient's best short term, as well as long term interest. *Work activity limitations should be written whether the employer is perceived to have modified duty available or not. Written activity limitations guidance communicates the status of the patient, and also gives the patient information on what the patient should or should not do at home.* Table 4 provides recommendations on activity modification and duration of absence from work for CRPS. These guidelines are intended for patients without comorbidity or complicating factors, including serious prior injuries. They are targets to provide a guide from the perspective of physiologic recovery.

PROGNOSIS

The prognosis of CRPS ranges from excellent to guarded. Quality literature to quantify the prognosis is highly limited. A population-based study from Olmsted County over a 10-year period found CRPS spontaneously resolved in 74% of cases [(228)]. A systematic review found the following six factors for poor prognosis have moderate supportive evidence: higher pain intensity, self-rated disability, anxiety, pain-related fear, being female, and high-energy triggering event [(275)]. A large database analysis found that those diagnosed with CRPS incurred higher healthcare costs in the year ***prior*** to diagnosis, higher total healthcare costs during their CRPS diagnostic period that were 2.17 times their baseline and prescription costs which were 2.56 times their baseline prescription costs [(276)].

The outcome is believed to be heavily dependent on the rate of, institution of, and compliance with functional restoration that primarily relies on strengthening and aerobic exercises. Fear avoidant belief training, cognitive behavioral therapy, quality multidisciplinary rehabilitation programs, selective medications, and other interventions all help produce better outcomes. Lack of focus on these interventions and lack of focus on active exercise worsens prognoses. Earlier use and earlier return to work all help improve outcomes. Earlier treatment with evidence-based approaches are also believed to improve outcomes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CRPS is diverse. Below are some of the more common alternate diagnoses, rather than a complete list.

- Diabetic neuropathy
- Alcoholic neuropathy
- Autoimmune neuropathies
- Rheumatological disorders
- Vasculitis
- Cerebrovascular accident
- Multiple sclerosis
- Trauma
- Peripheral nerve injuries
- Posttraumatic neuralgia
- Nerve entrapment syndromes
- Fibromyalgia
- Neoplasia

- Radiculopathy
- Radiculitis
- Plexopathy
- Chronic inflammatory demyelinating polyneuropathy
- Monomelic amyotrophy
- Herpes zoster/Shingles
- HIV/AIDS
- Guillain-Barre Syndrome
- Intracranial aneurysm
- CNS tumor
- Cellulitis
- Erythromelalgia
- Peripheral arterial disease
- Deep venous thromboses
- Lymphedema
- Anxiety disorders
- Somatic symptom disorder (formerly, somatoform disorder)
- Munchausen syndrome
- Conversion disorder
- Malingering
- Idiopathic

DIAGNOSTIC RECOMMENDATIONS

OVERVIEW

Diagnostic testing considerations are defined by the potential diagnosis of CRPS and body part being investigated [(249)]. Testing commonly used for the identification of other disorders is often required to assure that other diagnoses are not present, potentially including psychological evaluation with psychometric testing. This should not be considered as justification for ordering tests indiscriminately. Tests should be ordered if there is a reasonable probability that an alternate diagnosis is present. Sometimes, the threshold for ordering a test is lower if the adverse effects from missing a potential diagnosis are considerable (see other guidelines for guidance on diagnostic testing for specific disorders). Imaging studies can identify abnormalities such as edema, demineralization, or osteoporosis that are consistent with CRPS, but mostly these are non-specific findings. There are different lines of clinical investigation of potentially useful technologies that purportedly assist in objectively diagnosing someone as suffering from, or being limited by "pain," or in localizing specific areas of the central nervous system that may influence, or be affected by, a patient's pain. Evaluations of the evidence for the use of many of these are provided in each section of this and the other ACOEM Guidelines (e.g., see Ankle and Foot Disorders; Low Back Disorders; Cervical and Thoracic Spine Disorders; Hand, Wrist and Forearm Disorders; Knee Disorders; and Shoulder Disorders).

ANTIBODY TESTING

ANTIBODIES FOR DIAGNOSING CHRONIC PAIN WITH SUSPICION OF RHEUMATOLOGICAL DISORDER

Recommended

Antibody levels are recommended as a screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) and for assessing patients with suspicion for rheumatological disorder.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Undiagnosed patients with either systemic arthropathies and/or peripheral neuropathies, or patients who have had incomplete evaluations. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin in presence of peripheral neuropathy) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete. Unfocused batteries of tests are not advised.

Benefits

Diagnosing an unknown condition. Providing opportunity to prevent destruction of joints.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated with a significant change in symptoms It is also reasonable to repeat testing after a period of 1-2 years as initial testing is known to occasionally become positive with the passage of time.

Rationale

Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false-positive results, especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antibodies, Antibody Testing, Rheumatic Disorder, Rheumatology, Rheumatologic Disorder; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 3 articles, 3 in CINAHL, 0 in Cochrane Library, 2,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANSAR TESTING

AUTONOMIC NERVOUS SYSTEM TESTING (ANSAR) FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Autonomic nervous system testing (ANSAR) is not recommended to assist in diagnosing complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Autonomic nervous system abnormalities have been reported in patients with CRPS. However, available evidence does not show that ANSAR testing alters the clinical management of patients with CRPS (Lee, 2021)(Scheuren, 2023). ANSAR is noninvasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. In the absence of quality evidence of utility, ANSAR is not recommended for evaluation of patients with CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ANSAR Testing, Autonomic Nervous System Testing; complex regional pain syndrome, CRPS;

diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 3 articles, 0 in CINAHL, 3 in Cochrane Library, 139 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BONE SCANNING

BONE SCANNING FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Bone scanning is selectively recommended to confirm the diagnosis of complex regional pain syndrome (CRPS) with a duration greater than 6 months.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Symptoms of possible CRPS generally for at least 3-6 months, with an uncertain diagnosis.

Benefits

Identification of significantly asymmetric findings consistent with disuse of a limb.

Harms

Radiation exposure, minor adverse effects associated with venipuncture.

Frequency/Dose/Duration

One evaluation. A second evaluation would be rarely indicated, except in certain cases (e.g., concerns about occult fracture).

Rationale

Bone scanning has been used for treatment of complex regional pain syndrome (Held et al., 2015). Quality studies have evaluated the utility of bone scans for the diagnosis of patients with CRPS. Bone scanning has quality evidence of utility as a good diagnostic test to evaluate suspected metastases, infected bone (osteomyelitis), inflammatory arthropathies, and trauma (e.g., occult fractures). It is believed to be reasonably effective for evaluating patients with moderate to severe CRPS (Cheon et al., 2021,Pendon et al., 2016, Held et al., 2015, Sampath et al., 2013, AlSharif et al., 2012), as bone metabolic changes occur over time. The sensitivity and specificity have been estimated in a meta-analysis of studies with clearly defined diagnostic criteria, at 80% and 73% respectively. Although bone scans do not provide direct evidence to support the diagnosis of CRPS, they may reveal osteopenia or osteoporosis, which if unequivocally asymmetric, would presumably be secondary to relative disuse of the body part tested as a result of the disease. In patients for whom the diagnosis is felt to be secure, there is not an indication for bone scanning as it does not alter the treatment or management. Bone scanning has modest risks associated with radiation, is high cost, has likely efficacy for limited use, and is thus selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bone Scans, Skeletal Scintigraphy; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 30 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 18 articles, 7 in CINAHL, 0 in Cochrane Library, 3910 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 19 diagnostic studies and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CYTOKINE TESTING

CYTOKINE TESTS FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME AND CHRONIC PAIN

Not Recommended

Routine use of cytokine testing is not recommended to diagnose complex regional pain syndrome (CRPS) or chronic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Cytokines purportedly determine whether a patient is experiencing pain or has suffered a toxicological insult. However, there are no quality studies that address this premise, especially in patients with CRPS. Available studies suggest that these markers may be elevated in chronic pain conditions, but these studies did not have adequate control groups and did not control for potential confounders. The range of disorders in which cytokines may be elevated also needs definition, as the current range of conditions appears large (Taaffe et al., 2000, Martelletti et al., 1999, Covelli et al., 1991, Gratt et al., 2005, Alexander et al., 1998, Chen et al., 2004, Gur et al., 2002, Madson et al., 1994), suggesting they are not specifically isolated to patients with chronic pain, and thus the specificity of these tests seems likely to be quite low. A high-quality, 7-year study of 880 elderly subjects evaluated impacts of IL-6 and CRP on both cross-sectional associations with morbidity and long-term mortality (Taaffe et al., 2000). CRP and IL-6 were higher among smokers at baseline and those with higher body mass indexes (BMIs). IL-6 and CRP were also higher among those with hypertension, myocardial infarction, stroke, elevated glycosylated hemoglobin levels, HDL, and number of chronic conditions. Both IL-6 and CRP were inversely related to quartiles of moderate and strenuous physical activity. CRP and/or IL-6 were associated with incidence of hypertension, myocardial infarction, diabetes, and incident cases of chronic conditions. Physical performance measures of changes in grip strength, signature time, chair-rise and 6-m fast walk all were not significant for IL-6 or CRP. A nested case-control within a cohort found a lack of correlation between post-fracture cytokines and subsequent development of CRPS (Parkitny L, 2022).

Cytokines need to be rigorously studied to ascertain if there is a place for them in the evaluation and/or management of chronic pain conditions, including stratification for occupationally-relevant diseases. Documentation that the discovery of elevated cytokine levels results in changes in evaluation and/or clinical management would also be necessary. Alternatively, this testing may be useful if the absence of elevated cytokine levels would warrant concluding that a patient does not have a remediable physical cause of pain. While cytokine testing is minimally invasive, and has a low risk of adverse effects, these tests are high cost, with no evidence that they alter the clinical management of patients with chronic pain. Their place in the evaluation of patients with chronic pain is yet to be determined and cytokine testing is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Cytokine, Cytokine testing; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value

of tests, efficacy, and efficiency. We found and reviewed 22 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 22 articles, 2 in CINAHL, 0 in Cochrane Library, 17,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ELECTROMYOGRAPHY

SURFACE ELECTROMYOGRAPHY FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME AND CHRONIC PAIN

Not Recommended

Surface electromyography (EMG) is not recommended for the differential diagnosis of complex regional pain syndrome (CRPS) and chronic pain. There are selective indications for use with biofeedback.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality trials of surface EMG, and thus it has no demonstrated value in the clinical evaluation or treatment of CRPS with resultant altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training and gait analysis for musculoskeletal and/or neurologic disorders, but it has no clearly established use in the management of CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Surface EMG, Surface Electromyography; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 1 article in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 1 article, 501 in CINAHL, 483 in Cochrane Library, 1,680 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from

CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL ELECTROMYOGRAPHY (EMG) FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Functional electromyography (EMG) is not recommended for the evaluation of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies assessing the utility of functional EMG in the evaluation of CRPS. Because there is no quality evidence and the testing is costly, functional EMG is not recommended for the evaluation of patients with CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Functional EMG, Functional Electromyography; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 10 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 10 articles, 1 in CINAHL, 3 in Cochrane Library, 24 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL MRI

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Functional magnetic resonance imaging (fMRI) is not recommended for diagnosing complex regional pain syndrome (CRPS). There are other indications for the use of MRI.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one quality study indicating that the findings on MRI were not helpful for diagnosis of CRPS (Agten et al., 2020). One study of only seven patients suggested differences are identifiable in uptake of fluorodeoxyglucose PET (Yoon et al., 2022). Functional MRI and MRI are minimally invasive and have low adverse effects, but are high cost; in the absence of quality evidence of efficacy, they are not recommended for the diagnosis of CRPS. There are other indications for MRI.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: MRI, magnetic resonance imaging; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 70 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 70 articles, 199 in CINAHL, 3 in Cochrane Library, 17000 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOCAL ANESTHETIC INJECTIONS

LOCAL ANESTHETIC INJECTIONS FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Local anesthetic injections are selectively recommended for evaluations in patients with possible complex regional pain syndrome (CRPS). (See also the recommendation for lidocaine infusions.)

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Patients with possible CRPS in whom there may be a specific nerve distribution that is otherwise unexplained by other investigations, including imaging, electromyography, and nerve conduction studies.

Benefits

Potential to identify a potentially treatable lesion

Harms

Medicalization, nerve trauma, and continuing a search for a fixable lesion if one is not to be found.

Frequency/Dose/Duration

Once

Rationale

Local anesthetics have been used for treatment of complex regional pain syndrome (O'Connell et al., 2016). Local injections have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes, although they may assist with diagnosis and consideration of potential treatment options and are thus selectively recommended. (See also the separate recommendation regarding lidocaine infusions.) However, corticosteroid or neuroablative injections/procedures for localized pain are not recommended because the risk of increased pain, local tissue reaction, and neuroma outweigh any documented benefits.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Local Anesthesia, Local Anesthetic; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 37 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 37 articles, 1,000 in CINAHL, 5 in Cochrane Library, 6,180 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from

Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 diagnostic studies and 1 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NONSPECIFIC INFLAMMATORY MARKERS

NONSPECIFIC INFLAMMATORY MARKERS TO SCREEN FOR INFLAMMATORY DISORDERS

Sometimes Recommended

Erythrocyte sedimentation rate and other inflammatory markers are selectively recommended for screening for signs of systemic inflammation, particularly when assessing patients with ill-defined pain conditions.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Undiagnosed patients with symptoms consistent with either systemic rheumatological diseases and/or patients have had incomplete evaluations. Subsequent tests may be needed, including rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another treatable contributing factor, especially if explanation of the symptoms is incomplete. However, indiscriminate ordering of tests is not advised.

Benefits

Diagnosing an unknown condition. Opportunity to prevent joint destruction.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated with a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale

There are no quality studies evaluating the utility of C-reactive protein, erythrocyte sedimentation rate, and other non-specific inflammatory markers for the diagnosis of patients with CRPS.

Erythrocyte sedimentation rate is the most commonly used systemic marker for nonspecific inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein is a marker of systemic inflammation that has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with chronic pain without clear definition of a diagnosis or those with myofascial pain syndrome, although the specificity is not high. However, ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Non-specific inflammatory markers; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 0 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 0 articles, 0 in CINAHL, 0 in Cochrane Library, 12,100 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

QUANTITATIVE SUDOMOTOR AXON REFLEX TESTING (QSART) TESTING

QUANTITATIVE SUDOMOTOR AXON REFLEX TESTING (QSART) FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of quantitative sudomotor axon reflex testing (QSART) to assist in the diagnostic confirmation of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are few quality studies of QSART that evaluated patients with CRPS. One study of 174 CRPS patients reported QSART had a sensitivity of 68% and specificity of 41% (Lee et al., 2019). A few small-scale studies evaluating QSART to detect abnormal responses in CRPS patients suggested it may be successful (Chemali et al., 2001,Kim et al., 2023).Thus, the reported results of sensitivity and specificity do not clearly support the use of QSART for the diagnosis of CRPS. QSART is not invasive, does not have significant adverse effects, but is costly. As bone scans have evidence of efficacy and may demonstrate osteopenia or osteoporosis (which may develop in patients with CRPS) bone scans are preferable to QSART.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: QSART; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 3 articles, 0 in CINAHL, 1 in Cochrane Library, 214 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET) FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Single-photon emission computed tomography (SPECT) is not recommended to evaluate patients with complex regional pain syndrome (CRPS), aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests. The use of positron emission tomography (PET) is also not recommended to evaluate patients with CRPS.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

SPECT and PET scanning have no quality, sizable evidence of efficacy in evaluation of patients with CRPS (Yoon et al., 2022). SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions; however, aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with CRPS. PET scanning is expensive and SPECT scanning is moderately costly. Both are mildly invasive. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. There is no quality evidence of efficacy to support the use of SPECT or PET scanning for diagnosing CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: positron emission tomography computed tomography, PET, SPECT, Single Photon Emission Computed Tomography; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 14 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 14 articles, 44 in CINAHL, 4 in Cochrane Library, 5040 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SWEAT PRODUCTION TESTING

SWEAT PRODUCTION TESTING FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Sweat production testing is not recommended for the evaluation of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies assessing the utility of sweat production in the evaluation of patients with CRPS. A small comparative study found no differences in sweat output between patients with CRPS-I and a control group (Poudel A, 2015). Because there is no quality evidence and the testing is costly, sweat production testing is not recommended for the evaluation of CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Sweat Production Testing; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 1 article in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 1 article, 2 in CINAHL, 0 in Cochrane Library, 16,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

THERMOGRAPHY

THERMOGRAPHY FOR DIAGNOSING COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against thermography for diagnosing complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Thermography has been evaluated in a few moderate-quality studies of patients with CRPS, which reported conflicting results. The two largest studies suggested some efficacy (Packham et al., 2018), with bone scanning outperforming thermography (Cheon et al., 2021). Other studies were small in size, with controls frequently outnumbering cases (Niehof et al., 2006, Niehof SP, 2008, Krumova EK, 2008). Thermography has been demonstrated to be able to quantify temperature differences. However, more than a large proportion (often greater than 50%) of patients do not have significant temperature differences. Thus, provoking temperature differences through heating or cooling the extremity has been tried. Thermography has no quality evidence of benefits over various inexpensive devices (non-contact infrared thermometer) may also be effectively utilized to easily measure limb temperature differentials. Thermography is not invasive, has no adverse effects, is moderately costly but does not have clear evidence of efficacy and is thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: thermography; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 5 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 5 articles, 3 in CINAHL, 4 in Cochrane Library, 2030 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 5 diagnostic studies and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

X-RAYS

X-RAYS FOR DIAGNOSIS OF COMPLEX REGIONAL PAIN SYNDROME

Recommended

X-rays are recommended for the evaluation of patients with suspected complex regional pain syndrome (CRPS). If used, both extremities should be included for comparative purposes. X-rays are often used prior to bone scanning.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Patients with suspected CRPS.

Benefits

May show osteopenia and asymmetry; may also show other findings of another disorder.

Harms

Negligible.

Rationale

There are no quality studies of x-rays for the diagnosis of CRPS. X-rays are not invasive, have no significant adverse effects, and are low to moderate cost. They are recommended for patients with suspected CRPS to help with identification of osteopenia and other disorders, and are frequently used as a study prior to bone scanning.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: X-Rays, Radiography; complex regional pain syndrome, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 27 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 27 articles, 240 in CINAHL, 1 in Cochrane Library, 17300 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TREATMENT RECOMMENDATIONS

ACTIVITY MODIFICATION AND EXERCISE

REDUCED ACTIVITY OR BED REST FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Reduced activity and bed rest are not recommended for complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

There is no evidence that reduced activity or bed rest is helpful for patients with CRPS. Reduced activity is the antithesis of a functional restoration program and is believed to be quite detrimental to patients with CRPS. Reduced activity has been found to be unhelpful for low back pain and other disorders. Potential adverse effects reportedly have included pulmonary emboli (see Low Back Disorders guideline) and debility. Although noninvasive, reduced activity or bed rest is costly, has no documented benefits, and is associated with higher morbidity and delayed recovery; thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: bed rest, immobilization, bedridden; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 13 in CINAHL, 0 in Cochrane Library, 17,800 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AEROBIC EXERCISE FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Aerobic exercise is recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

All phases of CRPS. Consider aquatic therapy if largely or completely non-weight bearing status (see below). Those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 11th ed. (Liguori G, 2020), in regards to health screening and risk stratification.

Benefits

Improved function, improved endurance, improved return to work status.

Harms

Negligible. Intolerance of weight bearing in severe lower extremity CRPS cases, however that may nevertheless be beneficial. Other musculoskeletal disorders possible (e.g., plantar heel pain).

Frequency/Dose/Duration

Start with 3 to 4 visits a week to also include other exercises; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Simultaneous home exercise prescription. Transition to home-based exercise program. Target minimum of 30-45 minutes/day in one session. When at 30-45 minutes, increase pace. Prolonged supervised therapy may be required for CRPS cases due to the necessity to assure compliance and ongoing encouragement of progressive use.

Indications for discontinuation

Short of developing a severe non-CRPS disorder (e.g., myocardial infarction), there is no reason to discontinue an aerobic exercise prescription. Consider altering the method(s) for non-tolerance, failure to progress, or reaching a 4- to 6-week timeframe.

Rationale

There is no quality evidence that aerobic exercise is helpful for treatment of injury-related CRPS; however, there is one low quality trial suggesting aerobic exercise is of additive benefit (i.e., assessed by pain, hyperalgesia, tenderness) to a standardized physiotherapy program (i.e., TENS analgesic current, cold-packs, retrograde massage, contrast baths) for treatment of stroke patients with CRPS (Topcuoglu et al., 2015). Yet, weight-bearing exercise is believed to be the single best therapy for lower extremity CRPS. Weight-bearing exercise generally involves arm swing as well as conditioning/endurance, thus likely helpful for upper extremity CRPS. Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong rationale for treatment of CRPS patients, and thus is recommended. Pain-exposure therapy may be advisable to be incorporated in an aerobic exercise prescription (den Hollander et al., 2016). First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates

(see algorithm). First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, which include mirror therapy, pain exposure therapy, virtual reality, desensitization, antidepressants (TCAs, SNRIs), gabapentin, and DMSO.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: aerobic exercise; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 19 articles in PubMed, 37 in CINAHL, 3 in Cochrane Library, 17,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STRENGTHENING EXERCISES FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Strengthening exercise is recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

All patients with CRPS.

Benefits

Resolution of CRPS, improved function, reduced pain, improved strength, improved ability to perform strength-demanding job tasks

Harms

Negligible. Increased pain complaints as the strength demands are increased, yet the increased strength capacity is usable to document progress for the patient.

Frequency/Dose/Duration

Typically start with 3 to 5 visits a week, with more visits for those more severely affected. Many severe CRPS patients will require daily treatments at first to encourage increased activity, progress exercises and address fear avoidant beliefs ("kinesiophobia"). Mild to moderate cases may be reasonably treated twice to three times weekly. Should have demonstrable evidence of functional improvement within first 2 weeks to justify additional visits; if not, then changes in therapeutic approach are advised (e.g., mirror therapy if not already instituted).

Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. The patient should transition to in-home exercises. Even in severe cases, active treatment regimens are recommended to be initiated at the first appointment (sometimes termed "stress loading"), then merely supplemented with passive modalities as indicated (Harden, 2005,Harden et al., 2022). Those initiating treatment may well have increased symptoms for the first few days of treatment; however, pain and edema should decrease within a few days. It is believed to be critical for the entire treatment team as well as the family to be aware of this and to continue to encourage the patient to continue to progress, rather than decrease or eliminate active program elements.

There are many potential strengthening exercises and these are believed to be the most important programmatic elements in the treatment of a CRPS patient (Harden, 2006,Harden et al., 2022). A few examples of these activities include scrubbing, repeated forceful grasp, carrying of progressively heavier objects, distance walked, and repeated toe raises.

Patients should be instructed that strengthening exercises are the most important aspects of the treatment program (Harden, 2006,Harden et al., 2022), such exercises should be initiated at the first appointment, and home exercises should be strongly encouraged. It may be particularly helpful to monitor and graph the patient's progress through treatment sessions to demonstrate graphically that the endurance of pain is having meaningful benefits and used for motivational benefit. Activities that can be graphed include grip strength, amount and time of weight carried, time of scrubbing activity, numbers of repeated toe raises, and/or distance walked.

Indications for discontinuation

Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4- to 6-week timeframe.

Rationale

There is no quality evidence that strengthening exercises as a stand-alone intervention are helpful for treatment of CRPS, although strengthening exercises are believed to be the most important therapeutic intervention for CRPS (Harden et al., 2022,Rho RH, 2002). One moderate-quality trial suggested graded exercise is effective for CRPS (de Jong JR, 2005). Another trial found mostly comparable results between graded exercise and intentional exposures to painful stimuli that included forced, progressive use (Barnhoorn et al., 2015). There is evidence that progressive exercises are beneficial for CRPS, and graded exposure to feared activities is beneficial for individuals with pain-related fear (de Jong JR, 2005).

Despite the absence of quality evidence, the widespread acknowledgement of the criticality of exercise regimens is underscored by the inclusion of exercises in the treatment arms of many RCTs of CRPS (Sanders et al., 2005, Harden, 2006), as well as in the review articles and published guidance (Harden et al., 2022,Rho RH, 2002). Thus, exercise and therapeutic modalities are believed to be highly important and the cornerstone of CRPS treatment.

The single most important method to manage edema is believed to be mobilization, rather than passive therapeutic modalities. The sooner the patient begins to use the extremity normally, the sooner the edema will resolve. There is no evidence that manual techniques and appliances to reduce edema are effective. Instead, they may take the focus away from the self-efficacy and active treatment program, instead spending precious time on passive treatment. Edema management should be utilized in rare circumstances where there is a functional deficit or secondary vascular changes directly from the edema (see below). Otherwise, the focus and time in therapy should be spent on active therapies dealing with progressive active range-of-motion and strengthening exercises, which indirectly treat the edema as well. Pain-exposure therapy may be advisable to be incorporated in a strengthening exercise prescription (den Hollander et al., 2016).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, which include mirror therapy, pain exposure therapy, virtual reality, desensitization, antidepressants (TCAs, SNRIs), gabapentin, and DMSO.

Strengthening exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for select indications, and thus are recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Strength training, resistance training, conditioning; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 7 articles in

PubMed, 54 in CINAHL, 2 in Cochrane Library, 17,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 5 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STRETCHING EXERCISES FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Stretching exercises are selectively recommended for the treatment of complex regional pain syndrome (CRPS), in conjunction with functional exercises (e.g., strengthening, aerobic, image/mirror therapy).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Severe, chronic CRPS with significant reductions in range of motion. May be indicated especially if the patient avoids all use of the extremity as a co-prescription with progressive strengthening, aerobic exercises and image/mirror therapy; in such cases, pain-exposure therapy is advisable to be incorporated (den Hollander et al., 2016). Aquatic therapy should be considered if the patient is largely or completely not bearing weight (see below).

Benefits

Improved function, improved endurance, improved return-to-work status.

Harms

Stretching is often used as a poor substitute for functional strengthening and aerobic exercises in CRPS patients. Strengthening is believed to be far superior; therefore, excessive time spent on flexibility may inadvertently delay recovery. Careful supervision of the course toward functional recovery is essential in all patients with CRPS, but it is of critical importance to avoid stretching as the sole or major exercise prescribed and instituted.

Frequency/Dose/Duration

Start with 3 to 4 visits a week; advance exercises and demonstrate evidence of functional improvement. Should concomitantly include strengthening exercises, aerobic exercises, and image/mirror therapy or other functional exercise. Simultaneous home exercise prescription. Transition to home-based exercise program.

Indications for discontinuation

Consider altering the method(s) for non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe. Lack of improvement may suggest the need to discontinue stretching and solely rely on strengthening exercises, aerobic exercises, and/or image/mirror therapy, other functional-active exercises.

Rationale

Although widely used, there are no quality studies indicating that stretching exercises are helpful for the treatment of CRPS. Strengthening exercises are instead believed to be the essential cornerstone of CRPS treatment (Harden et al., 2022, Rho RH, 2002).

Among patients with severe pain and disuse of the extremity, flexibility exercises may be helpful to co-transition to other exercises (e.g., strengthening, image/mirror therapy, aerobic, yoga), although this should generally be co-prescribed with pain-exposure therapy (den Hollander et al., 2016). Most patients with non-severe CRPS do not have meaningful reductions in range of motion. Therefore, an emphasis on range of motion is usually to the detriment of advancing more functionally important and essential exercises, such as strengthening and aerobic or conditioning. Stretching exercises are mainly indicated for select patients with CRPS who have meaningful reductions in range of motion. However, stretching exercises should not be the sole exercise prescription for such patients.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, which include mirror therapy, pain exposure therapy, virtual reality, desensitization, antidepressants (TCAs, SNRIs), gabapentin, and DMSO. There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Stretching exercises are not invasive, have negligible adverse effects, and may be low cost when self-administered to moderate cost in aggregate. However stretching exercises do not have quality evidence for efficacy in patients with CRPS. Because they may be helpful in select patients with reduced range of motion, stretching exercises are selectively recommended to be co-prescribed with other functional exercises.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms:

stretching exercises; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 4 in CINAHL, 2 in Cochrane Library, 18,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MIRROR THERAPY AND GUIDED IMAGERY FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Mirror therapy is recommended for patients with complex regional pain syndrome (CRPS). Other components of guided imagery may be utilized.

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

All patients with CRPS. May be particularly helpful for those having difficulty complying with progressive strengthening exercises.

Benefits

Accelerated progressive exercises and progressive use, with reduced need for medications

Harms

Negligible

Frequency/Dose/Duration

Home exercises requiring an estimated 10 minutes of each waking hour for 6 weeks. Best results are obtained from viewing the unaffected limb and performing activities as fast and accurately as possible with the affected limb. Clinic appointments are needed and are estimated at least 3 times a week for 6 weeks in addition to home exercises. In the event of ongoing improvements and need for additional appointments, additional treatments to

continue the therapy would be indicated in 2- to 3-week increments provided there was continuing objective evidence of ongoing improvement after each additional increment.

Indications for discontinuation

Resolution or sustained noncompliance. In the event of noncompliance, an evaluation is needed to assess motivational factors, secondary gain, and related issues.

Rationale

Mirror therapy has been used for treatment of complex regional pain syndrome (Méndez-Rebolledo G, 2017). There are three moderate-quality studies suggesting efficacy of mirror therapy, which have been performed by the same research group (Moseley, 2004, Moseley, 2005, Moseley, 2006). One research group has also suggested efficacy for treatment of stroke patients with CRPS (Vural et al., 2016). The intensity and type of involvement by the experimental group brings into question whether they were completely blinded. As well, reproducibility is a little unclear as most of the literature is from one research group; thus, the strength of evidence rating was downgraded from "B" to "C" level evidence. These studies demonstrated a decrease in pain rating and improvement in numerical task rating scale. The benefits include evidence of subsequent reduction in need for health care treatment (Moseley, 2006).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Mirror therapy is not invasive, has no adverse effects, is not costly, and has quality evidence of efficacy; thus, it is recommended. The main difficulty is the requirement to comply with the exercise frequency of 10 minutes of each waking hour.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Mirror movement therapy, mirror therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 14 articles in PubMed, 5 in CINAHL, 0 in Cochrane Library, 17,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 6 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AQUATIC THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Aquatic therapy is recommended for patients with complex regional pain syndrome (CRPS) to develop increasing tolerance to graded activities.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Patients with moderate to severe CRPS, especially those with lower-extremity CRPS who have severe difficulties with weight bearing, underlying morbidity with weight-bearing problems (e.g., severe lower extremity degenerative joint disease), or those who previously exercised by swimming. May also include those with severe upper-extremity CRPS when there is inclusion of upper extremity exercises in the aquatic therapy prescription. Co-prescription with pain-exposure therapy is generally advisable (den Hollander et al., 2016).

Benefits

Improved function, reduced pain, resolution of the symptoms and signs of CRPS

Harms

Initially increased pain while increasing strength; however, this typically reduces with further progressive use. Water temperature may have to be fairly high for some of the more severely affected patients with CRPS.

Frequency/Dose/Duration

Appointments may be initially 3 times a week, but up to 5 times a week if the CRPS is severe. Home exercises should be simultaneously prescribed.

Indications for discontinuation

Resolution, ability to maintain progressive increases without supervision.

Rationale

There are no quality studies of aquatic therapy for the treatment of CRPS. However, there is a strong rationale for increasing active exercises as the primary treatment of CRPS and

strengthening is the cornerstone of patient treatment (Rho RH, 2002, Harden et al., 2022). For some patients with CRPS, weight bearing is especially challenging and aquatic therapy may be a bridge to increase weight-bearing tolerance.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Aquatic therapy is not invasive, has low adverse effects, is moderate to high cost in aggregate, and is selectively recommended. A co-prescription with pain-exposure therapy may be advisable (den Hollander et al., 2016).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: aquatic therapy, hydrotherapy, aquatic exercise, water exercise; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 8 in CINAHL, 0 in Cochrane Library, 14,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DESENSITIZATION TECHNIQUES FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Desensitization techniques are selectively recommended for patients with moderate to severe complex regional pain syndrome (CRPS). Patients should have significant hyperalgesia and be engaged in a core program of graded strengthening exercises and pain exposure therapy, or have a plan to implement such exercises shortly after or in conjunction with desensitization techniques. (Desensitization techniques are unlikely to be successful for functional restoration and are not recommended as a sole exercise or therapy intervention.)

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Moderate to severe CRPS patients with significant hyperalgesia. Should be primarily engaged in a core program of graded strengthening exercises or for whom there is a plan to implement such exercises shortly after or in conjunction with desensitization techniques. (Desensitization techniques are unlikely to be successful for functional restoration and are not recommended as a sole exercise or therapy intervention.)

Benefits

Improved function, reduced pain, resolution of the symptoms and signs of CRPS .

Harms

Emphasis on passive treatment instead of active exercises, which may result in increased pain with limited gain. Susceptibility to view desensitization as the primary treatment instead of progressive strengthening.

Frequency/Dose/Duration

Appointments initially 3 times a week, but 5 times a week if severe CRPS. At-therapy and home-based strengthening exercises and activities should be simultaneously prescribed as the cornerstone for treatment.

Indications for discontinuation

Resolution, sufficient improvement to no longer require desensitization, ability to maintain progressive increases without supervision.

Rationale

There are no quality trials of desensitization techniques. Desensitization techniques are thought to be helpful for severe cases of CRPS where there are significant problems with allodynic pain. Such techniques may include rubbing the extremity with progressively more textured materials and/or with more force. Contrast baths is a related therapy, however, exacerbation by cold water is common and this intervention is generally thought to not be particularly effective. Contrast baths are not indicated for nearly all CRPS patients; however, there may be a limited role in some patients.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. Desensitization techniques are not invasive, have low adverse effects,

are cumulatively moderate to high cost and have limited evidence suggesting potential efficacy. Thus, desensitization techniques are selectively recommended; however there are many other interventions thought to be far more important for recovery, including progressive strengthening, aerobic exercises, pain-exposure therapy, and mirror therapy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Desensitization; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 4 in CINAHL, 1 in Cochrane Library, 8760 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

YOGA FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Yoga is selectively recommended for the treatment of complex regional pain syndrome (CRPS), but should not be a substitute for progressive strengthening and aerobic exercises.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Particularly indicated for those patients with CRPS who are motivated and interested in yoga. Should not be used as a substitute for progressive strengthening and aerobic exercises.

Benefits

Improved function, reduced pain, resolution of the symptoms, and signs of CRPS

Harms

Yoga could be used as a substitute for strengthening exercises and conditioning and thus delay recovery.

Frequency/Dose/Duration

Appointments initially 3 times a week, but 5 times a week if CRPS is severe. Daily home exercises should be simultaneously prescribed.

Indications for discontinuation

Resolution, ability to maintain progressive increases without supervision.

Rationale

There is no quality evidence for yoga to treat patients with CRPS. There is moderate-quality evidence of the effectiveness of yoga for the treatment of chronic LBP (Galantino et al., 2004, Sherman et al., 2005, Williams et al., 2005), although there are many different types of yoga and no study results have been replicated. Evidence also suggests that patient motivation must be high, and there is much self-selection in the reviewed studies, as compliance and adherence reportedly are not good.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Yoga is not invasive, has low potential for adverse effects, is low cost, has no evidence of efficacy, but a few highly motivated patients may engage in and increase activity with yoga; thus, it is selectively recommended. Yoga should not be a substitute for progressive strengthening exercises, which are the cornerstone of CRPS treatment (Rho RH, 2002, Harden et al., 2022).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: yoga; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 8 in CINAHL, 1 in Cochrane Library, 9750 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TAI CHI FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Tai chi is selectively recommended for the treatment of complex regional pain syndrome (CRPS), but it should not be a substitute for progressive strengthening exercises.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Particularly indicated for patients with CRPS who are motivated and interested in tai chi. Should not be used as a substitute for progressive strengthening exercises.

Benefits

Improved function, reduced pain, resolution of the symptoms of CRPS.

Harms

Tai chi could be used as a substitute for using and increasing strengthening exercises and conditioning and thus delay recovery.

Frequency/Dose/Duration

Appointments may be initially 3 times a week, but up to 5 times a week if CRPS is severe. Daily home exercises should be simultaneously prescribed.

Indications for discontinuation

Resolution, ability to maintain progressive increases without supervision.

Rationale

There is no quality evidence on tai chi for the treatment of CRPS. Evidence for a potentially analogous intervention, yoga, also suggests that patient motivation must be high and there is much self-selection, as compliance and adherence reportedly are not good.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be a low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Tai chi is not invasive, has low potential for adverse effects, is low cost, and has no evidence of efficacy. However, a few highly motivated patients may engage in and increase activity with tai chi. Thus, it is selectively recommended. Tai chi should not be a substitute for progressive strengthening exercises, which are the cornerstone of CRPS treatment (Rho RH, 2002, Harden et al., 2022).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Tai Ji, Tai Chi; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 5420 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PAIN EXPOSURE PHYSICAL THERAPY FOR TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME

Recommended

Pain exposure physical therapy is recommended for the treatment of patients with complex regional pain syndrome (CRPS), including elements of cognitive behavioral therapy (CBT).

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Patients with CRPS, especially those demonstrating kinesiophobia, voicing threatening tasks/exposures/activities, fear-avoidant beliefs, or failure to engage in or comply with progressive strengthening exercises.

Benefits

Markedly improved engagement in exercises and activities of daily living, along with reductions in pain and disability (den Hollander et al., 2016).

Harms

Negligible

Frequency/Dose/Duration

The sole quality trial used 1-hour weekly sessions for 17 weeks. Particularly addresses and implements treatments that are perceived as "threatening."

Indications for discontinuation

Resolution of CRPS, completion of a course of treatment with demonstrated independence and exercise compliance with a trajectory towards resolution.

Rationale

Pain exposure physical therapy has been used for treatment of complex regional pain syndrome (Kavka, 2023). One moderate-quality RCT reported strikingly superior outcomes (i.e., disability ratings, catastrophizing, perceived harmfulness of activities, health-related quality of life, pain intensity), both post-treatment and at 6 months compared with pain-contingent therapy (den Hollander et al., 2016).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first-line therapy.

Pain exposure physical therapy that includes CBT has evidence of efficacy, has negligible adverse effects, is moderate cost, and is recommended for the treatment of patients with CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: pain exposure, pain contingent physical therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 16 articles in PubMed, 6 in CINAHL, 16 in Cochrane Library, 12,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane

Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GRADED MOTOR IMAGERY FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Graded motor imagery is selectively recommended for treatment of patients with severe complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Treatment of patients with severe CRPS, generally after trials of progressive strengthening, aerobic exercises, pain-exposure therapy, mirror therapy, and medications shown to be effective (e.g., bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressants and gabapentinoids).

Benefits

Reduced pain with movement and increased function

Harms

Negligible, other than delayed healing if there is no progressive strengthening exercise component

Frequency/Dose/Duration

Three stages are recommended: recognition of hand laterality 3 times every waking hour for 10 minutes; imagined hand movements 3 times every waking hour for 15 minutes; and mirror movements 10 times a day.

Indications for discontinuation

Resolution, sufficient improvement, noncompliance

Rationale

One moderate-quality randomized crossover trial found efficacy of graded motor imagery for treatment of CRPS (Moseley GL, 2004). One trial used graded motor imagery in both arms of the trial as its active exercise to test the additive value of a passive modality (Lagueux et al., 2018). A low-quality study also suggested efficacy (Strauss et al., 2021).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Graded motor imagery is generally indicated after trials of first-line treatments with proven efficacy. Guided motor imagery is not invasive, has low adverse effects, is low to moderate cost, has some evidence of efficacy, and is thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Graded motor imagery; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 17 articles in PubMed, 8 in CINAHL, 14 in Cochrane Library, 17,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VIRTUAL REALITY THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Virtual reality therapy is selectively recommended for the treatment of patients with moderate to severe complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients with moderate to severe CRPS, generally after trials of progressive strengthening exercises, aerobic exercise, pain exposure therapy, and mirror therapy.

Benefits

Improvements in pain and function.

Harms

Negligible.

Frequency/Dose/Duration

1-2 appointments per week for 4 weeks. Successive sets of appointments based on progressive functional gain. Another option is rental of a headset, allowing more intensive daily use.

Indications for discontinuation

Resolution, sufficient improvement, non-compliance.

Rationale

Virtual reality has been used for treatment of complex regional pain syndrome. One short, moderate-quality RCT found evidence of efficacy for treatment of CRPS (Lewis et al., 2021). First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, which include mirror therapy, pain exposure therapy, virtual reality, desensitization, antidepressants (TCAs, SNRIs), gabapentin, and DMSO.

Virtual reality is not invasive, has negligible adverse effects, is cumulatively moderate to high cost, has evidence of efficacy, and is thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Virtual Reality Exposure Therapy, virtual reality therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 4 in CINAHL, 1 in Cochrane Library, 17,100 in Google Scholar, and 0 from other

sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VISUAL ILLUSIONS FOR CRPS

No Recommendation

There is no recommendation for visual illusions for treatment of CRPS.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One trial with two publications has suggested some very short-term benefit of visual illusions (Lewis et al., 2021, Lewis et al., 2020). Further trials with longer follow-up timelines than 2 weeks are needed to develop evidence-based guidance, particularly when there are numerous other proven effective exercise-based treatments available.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Illusion, Visual Illusions; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 1 in CINAHL, 1 in Cochrane Library, 4,160 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MEDICATIONS

ORAL NSAIDS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Oral NSAIDs are selectively recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS that is sufficiently severe to require medication. NSAIDs are recommended as a second- or third-line adjunct to strengthening, conditioning and aerobic exercises, however there is evidence that glucocorticosteroids may be superior (Kalita et al., 2006) among stroke patients with CRPS. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence for treatment of multiple other disorders suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers, although for CRPS, other medications are typically co-prescribed as some other medications appear to be superior to NSAIDS (e.g., glucocorticosteroids, bisphosphonates).

Harms

Gastrointestinal adverse effects are especially prominent in those with past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Those elderly, with diabetes mellitus and rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the more Cox-2 selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders). It appears that despite widespread usage, diclofenac does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events (McGettigan et al., 2006).

Frequency/Dose/Duration

For most patients, scheduled dosage, rather than as needed, is preferred especially for those with worse symptoms, but prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities may require more frequent monitoring. Use of an adjunctive cytoprotective agent may also be warranted.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There is no quality evidence of efficacy of NSAIDs compared with placebo for CRPS. There is evidence that a COX-2 inhibitor (parecoxib) is superior to placebo as part of an intravenous regional blockade that includes clonidine and lidocaine (Frade et al., 2005). There also is evidence that piroxicam is inferior to prednisolone for post-stroke CRPS Type I (Kalita et al., 2006). However, those results might not apply to other causes of CRPS.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first line therapy. NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, are effective for treatment of many painful conditions, and are thus selectively recommended generally with or after other medications with better evidence of efficacy are prescribed. However, diclofenac is not recommended due to apparent increased adverse cardiovascular events; thus, other NSAIDs are recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: nsaids or non-steroidal anti-inflammatory drug; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 40 in CINAHL, 5 in Cochrane Library, 17,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TOPICAL NSAIDS FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Topical NSAIDs are selectively recommended for treatment of patients with complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS sufficiently severe to require medication. NSAIDs including topical NSAIDs are recommended as a second-line or third-line adjunct to strengthening, conditioning and aerobic exercises, however there is evidence that glucocorticosteroids may be superior to oral NSAIDs (Kalita et al., 2006) among stroke patients with CRPS.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers, although for CRPS, other medications are typically prescribed as some other medications appear to be superior to NSAIDS (e.g., glucocorticosteroids, bisphosphonates).

Harms

Negligible

Frequency/Dose/Duration

Per manufacturer instructions.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

One placebo-controlled trial among heterogenous patients (including post-herpetic neuralgia and an unclear proportion with CRPS) comparing topical diclofenac with placebo reported evidence of efficacy (Ahmed et al., 2015); however, it is limited by the patient heterogeneity.

There are some trials of oral NSAIDs to consider. There is no quality evidence of efficacy of oral NSAIDs compared with placebo for CRPS. There is evidence that a COX-2 inhibitor (parecoxib) is superior to placebo as part of an intravenous regional blockade that includes clonidine and lidocaine (Frade et al., 2005). There also is evidence that oral piroxicam is inferior to prednisolone for post-stroke CRPS Type I (Kalita et al., 2006). However, those results might not apply to other causes of CRPS.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first line therapy. Topical NSAIDs are not invasive, have low adverse effects, are low to high cost depending on treatment duration, are effective for treatment of many painful conditions, and are thus selectively recommended generally with or after other medications with better evidence of efficacy are prescribed.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Topical NSAIDs; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 article in PubMed, 262,614 in CINAHL, 3 in Cochrane Library, 534 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACETAMINOPHEN FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Acetaminophen is recommended for treatment of complex regional pain syndrome (CRPS), particularly if NSAIDs are contraindicated.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS sufficiently severe to require medication. Acetaminophen is recommended as an adjunct to strengthening, conditioning and aerobic exercises. Generally, generic ibuprofen, naproxen, or other older-generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.

Harms

Negligible if used as prescribed. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.

Frequency/Dose/Duration

Generally prescribed up to 3.5g/day in divided doses, usually QID dosing

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There are no quality trials of acetaminophen for treatment of CRPS. First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy as part of first line therapy. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of some musculoskeletal disorders, and is thought to have modest efficacy; thus, it is recommended for treatment of CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Acetaminophen, Paracetamol; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 9 in CINAHL, 4 in Cochrane Library, 17600 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTIDEPRESSANTS FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Antidepressants are recommended for the treatment of complex regional pain syndrome (CRPS), including tricyclic antidepressants, tetracyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS that is sufficiently severe to require medication. While there are no quality trials demonstrating efficacy for treatment of CRPS, antidepressants are considered among the first-line agents to treat neuropathic pain. Several of the anti-depressants may also be used to take advantage of the sedating properties for nocturnal sleep disturbance due the neuropathic or CRPS pain. One trial for neuropathic pain suggested superiority of combination therapy of nortriptyline with gabapentin compared to each drug alone , while another suggested superiority of combining amitriptyline 25mg/day with pregabalin 75mg BID .

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities; thus, especially in those cases, these medications are inappropriate for safety-sensitive jobs. Dry mouth, constipation, suicide risk, urinary retention, glaucoma, QT prolongation, sinus tachycardia, dizziness, weight gain, and cardiotoxicity.

Frequency/Dose/Duration

Prescribe at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until a sub-maximal or maximal dose is achieved, sufficient effects are achieved, or adverse effects occur. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program. One reportedly efficacious combination was nortriptyline 100 mg with gabapentin 3600 mg per day , while another was amitriptyline 25mg/day with pregabalin 75mg BID . Regimens also used in the quality trials for neuropathic pain treatment include escitalopram 20mg/day (Otto M, 2008, Brasch-Andersen C, 2011), bupropion SR 150mg/day (Semenchuk MR, 2001), and up to 60mg/day of fluoxetine. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There is one quality trial for treatment of CRPS, which found citalopram superior to placebo and stronger results if the citalopram was combined with 5 lidocaine nerve blocks over a 50-day period (Fallico et al., 2022). Another trial of amitriptyline and gabapentin suggested comparable efficacy (Brown et al., 2016). There are multiple moderate-quality trials for treatment of neuropathic pain with tricyclic/tetracyclic, and SNRI antidepressants that included desipramine, amitriptyline, nortriptyline, clomipramine, duloxetine, venlafaxine (Bowsher D, 1997)(Watson CP, 1982, Watson PNC, 1992)(Hall et al., 2010, Kajdasz et al., 2007, Sindrup et al., 2003). All quality data suggest efficacy. Comparable efficacy was been shown between amitriptyline and duloxetine, as well as between amitriptyline and nortriptyline . One trial suggested combination therapy of nortriptyline with gabapentin was superior to single drug arms and another trial suggested superiority of a combination of amitriptyline and pregabalin . One study involving maprotiline did not show efficacy when compared to amitriptyline .

There are five moderate-quality studies evaluating selective serotonin reuptake inhibitors for neuropathic pain. Data suggest modest efficacy. As SSRI antidepressants have evidence of efficacy for treatment of fibromyalgia, but have evidence of lack of efficacy for treatment of some presumed nociceptive chronic pain conditions (see Low Back Disorders Guideline), the mechanism of potential efficacy for neuropathic pain is unclear. As one trial suggested potentially superior results with desipramine, and evidence is more robust for the other anti-depressants, treatment with tricyclics and SNRIs as initial prescriptions is generally recommended before SSRIs.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, which include mirror therapy, pain exposure therapy, virtual reality, desensitization, antidepressants (TCAs, SNRIs), gabapentin, and DMSO.

Tricyclic, tetracyclic, SNRI, and SSRI antidepressants are not invasive, have adverse effects that range from modest to intolerable, are low cost, and have evidence of efficacy for treatment of neuropathic pain. Thus, they are recommended for treatment of CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: antidepressants, antidepressant medication, ssri, selective serotonin reuptake inhibitors; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 18 articles in PubMed, 24 in CINAHL, 3 in Cochrane Library, 10,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTICONVULSANT AGENTS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

The use of anticonvulsant agents for treatment of severe complex regional pain syndrome (CRPS) is selectively recommended after attempted management with progressive exercises, image/mirror therapy, glucocorticosteroids, bisphosphonates, NSAIDs, other medications with documented efficacy.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Generally not indicated, but may be a consideration for severe chronic CRPS as a fourth- or fifth-line agent, and initiated by clinicians familiar with their use and able to monitor patients closely for adverse effects. Treatments that should be attempted first include progressive strengthening and aerobic exercises that should be continued. Other prior treatment considerations include other exercises, glucocorticosteroids, bisphosphonates, NSAIDs and anti-depressants (TCA and SNRI).

Benefits

Theoretical potential to improve pain.

Harms

Caution is warranted for prescribing such agents in patients employed in safety-sensitive positions as such medications cause sedating effects. These medications also may inadvertently raise concerns about fitness for duty due to the possibility of a seizure disorder. Carbamazepine may cause fluid and electrolyte abnormalities. Topiramate may cause renal stones and ocular toxicity.

Frequency/Dose/Duration

Frequency and dosing per manufacturer. Duration for patients with CRPS may be prolonged, although most of these patients do not require indefinite treatment as the condition usually improves or resolves spontaneously.

Indications for discontinuation

Resolution of pain, lack of efficacy, development of adverse effects.

Rationale

There are no quality studies evaluating these medications for CRPS. Anti-convulsants have long been thought to be effective for treatment of neuropathic pain (see Neuropathic pain section). However, that may not be correct (Backonja et al., 1998). There now appears to be no clear pattern to allow a single conclusion of efficacy for these medications for a group of disorders. Instead, treatments appear to require specification or individualization. There is some evidence for efficacy against neuropathic pain and there is quality evidence that

topiramate is effective for the treatment of chronic LBP (Muehlbacher et al., 2006, see Low Back Disorders guideline). The most commonly used anti-convulsant is carbamazepine. However, it has not been studied in large, moderate- or high-quality studies for purposes of treating chronic pain including CRPS.

There is evidence suggesting efficacy from an experimental design utilizing carbamazepine for the management of peripheral neuropathic pain (Harke H, 2001). Moderate-quality RCTs conflict regarding whether a related compound, oxcarbazepine, is effective in treating diabetic neuropathy (Grosskopf et al., 2006, Beydoun S, 2007). Thus, it is unclear whether that related compound or even carbamazepine is useful for treating neuropathic pain (or CRPS). This suggests that other options should be attempted first. Lamotrigine has also been studied and has been found to be effective for treating diabetic neuropathy, although the magnitude of benefits is not large (Vinik et al., 2007, Eisenberg E, 2001). Lamotrigine was not found useful as an adjunct to treatment with other agents such as tricyclic anti-depressants (Silver et al., 2007). There is quality evidence that topiramate is not effective for treating painful diabetic neuropathy (Thienel et al., 2004), although a small quality study showed weak benefits (Raskin et al., 2004). Dropout rates are high with topiramate (37 to 62%), which suggests that the medication is not well tolerated.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. These drugs are not invasive, have some adverse effects, and may be moderately costly. Because they are beneficial for some forms of neuropathic pain, anti-convulsants conceivably could be of benefit for CRPS. These agents are generally used for neuropathic pain and thus may be reasonable options for CRPS after more efficacious treatment strategies are implemented.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Anticonvulsants, Hydantoins, Barbiturates; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 10 articles in PubMed, 4in CINAHL, 2 in Cochrane Library, 10,600 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GABAPENTIN OR PREGABALIN FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Short-term use of gabapentin or pregabalin is recommended for the treatment of moderate to severe complex regional pain syndrome (CRPS), after attempted management with more effective treatments.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

CRPS in whom other methods to control symptoms have been proven to be unsuccessful, including strengthening exercises, aerobic exercises, other exercises, image/mirror therapy, glucocorticosteroids, bisphosphonates, NSAIDs, clonidine, and tricyclic anti-depressants. Should be used as an adjunct to a functional restoration program to facilitate the program advancement for the 4 weeks that the medication shows some evidence of efficacy. There is no recommendation for ongoing treatment beyond one course.

Benefits

Improved pain control, may include reduced sleep disturbance. Improved ability to tolerate and engage in progressive exercise program.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness.

Frequency/Dose/Duration

One trial utilized gabapentin 600mg QD x 2 days, then 600mg BID x 2 days, then 600mg TID for Days 5 to 21. Duration of use for CRPS patients is usually limited as most of these patients do not require indefinite treatment. The condition usually improves or resolves spontaneously. However, the efficacy of gabapentin has been labeled as “mild” for CRPS and quality evidence suggests that benefits are short-term (van de Vusse et al., 2004).

Indications for discontinuation

Resolution, intolerance, adverse effects, or failure to objectively improve during a trial period of medication initiation. Discontinue after 4 weeks unless clearly objective evidence of ongoing, continuing improvement as evidence suggests loss of efficacy with no demonstrable benefits from a second 3-week course (van de Vusse et al., 2004).

Rationale

There is one moderate-quality placebo-controlled trial suggesting gabapentin is mildly effective for a short-term trial for treatment of CRPS (van de Vusse et al., 2004). Another trial of amitriptyline and gabapentin suggested comparable efficacy (Brown et al., 2016).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO.

Gabapentin and pregabalin are not invasive, have significant adverse effects in some patients, are low to moderate cost, have evidence of modest efficacy, and thus are recommended for a short-term course as an adjunct to more effective treatments.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: gabapentin, pregabalin; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 5 in CINAHL, 22 in Cochrane Library, 14,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BISPHOSPHONATES FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

. ƛăLJK2ăLJK2yl·űŜă l·NŜ ăűN2yƎfè NŜŎ2Y ΥŜyŘŜŘ ₮2N LJl·űƛŜyűă ǿƛűK Ŏ2ΥLJfŜÈ NŜƎƛ2yl·f LJl·ƛ˝ ăèyŘN2Y ΥŜ ó/wt{ú l·₮űŜN2 2N ƛ˝ l·ŘŘƛűƛ2˝ű2Σ LJN2ƎNŜăăƛØŜ ŜÈŜNŎƛăŜăƛ . 2űK 2Nl·f l·yŘ ƛyűNl·ØŜy2dză ōƛăLJK2ăLJK2yl·űŜă KI·ØŜ ōŜŜ˝dzăŜŘΣ l·fűK2dzƎK űKŜ 2yfè Ijdzl·fƛűè ŜØƛŘŜyŎŜ ƛyØ2fØŜă 2Nl·ffè l·ŘY˝ƛyƛăűŜNŜŘ ΥŜŘƛŎl·ûƛ2yΦ

Strength of evidence {űN2yƎfè wŜŎ2Y ΥŜyŘŜŘΣ 9ØƛŘŜyŎŜ ó ! ú
Level of confidence l ƛƎK

Indications

a 2ŘŜNl·ûŜ 2N ăŜØŜNŜ /wt{Σ ƛyŎftdzŘƛyƎ ƛ˝ l·ŎdzűŜ û2 ădzōl·ŎdzűŜ l·ă ǿŜff l·ă ŎKN2yƛŎ LJKl·ăŜăΦ {K2dzfŘ ōŜ ƛyŎftdzŘŜŘ l·ă LJl·Nű 2₮ ₮dzyŎűƛ2yl·f NŜăű2NJl·ûƛ2˝LJfl·˝ ǿKŜNŜ ăűNŜyƎűKŜyƛyƎΣ l·ŜN2ōƛŎ l·yŘ 2ûKŜN ₮dzyŎűƛ2yl·f ŜÈŜNŎƛăŜă l·NŜ ŎŜyűNJl·f ₮2Ŏƛ 2₮ LJNŜăŎNƛLJűƛ2yãΦ l 2ǿŜØŜNΣ ōl·ăŜŘ 2˝ŜØƛŘŜyŎŜ 2₮ Ŝ₮₮ƛŎl·Ŏè Σ ōƛăLJK2ăLJK2yl·ûŜă l·NŜ 2yŜ 2₮ ûKŜ Ŝl·NfŁŜN ΥŜŘƛŎl·ûƛ2yã NŜŎ2Y ΥŜyŘŜŘ û2 ōŜ úNƛl·fŜŘ ₮2N /wt{Φ hyŜ f2ǿπljdzl·fŁűè Ŏl·ăŜ ăŜNƛŜă ădzƎƎŜăűŜŘ 2ØŜNJl·ff Ŝ₮₮ƛŎl·Ŏè 2₮ τ₹ ǿƛűK ōŜűűŜN Ŝ₮₮ƛŎl·Ŏè ₮2N Ŏl·ăŜă úNŜl·ûŜŘ 2˝l·ØŜNJl·ƎŜ l·ú o Y2yűKăΣ ₮Nl·ŎűdzNŜ l·ă ûKŜ Ŝűƛ2f2ƎèΣ l·yŘ ƀǿl·NY ƀ ŘƛăŜl·ăŜ ădzōűèLJŜ ó±l·NŜyƴl· Ŝű l·fΦΣ нлмтúΣ ǿKƛfŜ l·y2ûKŜN ăűdzŘè ădzƎƎŜăűŜŘ ŘƛăŜl·ăŜ ŘdzNl·ûƛ2˝ōŜűǿŜŜy˝oπc Y2yűKă ǿl·ă l·ăă2ŎƛI·ûŜŘ ǿƛűK ōŜűűŜN Ŝ₮₮ƛŎl·Ŏè óCl·ƎƎƛl·y^ Ŝű l·fΦΣ нлнмúΦ

Benefits

LY˝LJNN2ØŜŘ LJl·ƛ˝Ŏ2yűN2f l·yŘ l·ōƛfŁűè û2 ű2fŜNJl·ûŜ ƛyŎNŜl·ăŜŘ ŜÈŜNŎƛăŜ NŜƎƛY ŜyΦ LY˝LJNN2ØŜY ŜyűăKl·ØŜ NŜLJ2NűŜŘfè ōŜŜy˝Yl·ƛyűl·ƛyŜŘ 2ØŜN мн Y2yűKă Ŏ2Y˝LJl·NŜŘ ǿƛűK LJfl·ŎŜō2 ó±l·NŜyƴl· Ŝű l·fΦΣ нлннúΦ

Harms

9ă2LJKl·Ǝƛűƛă Σ KèLJ2Ŏl·fŎŜY˝ƛl·Σ Řƛl·NNNKŜl·Σ Ŏ2yăűƛLJl·ûƛ2yΣ ō2yŜ LJl·ƛyΣ ₮l·ûƛƎdzŜΣ NŜyl·f ƛyãdz₮₮ƛŎƛŜyŎèΣ ƨl·ǿ 2ăűŜ2yŜŎN2ăƛăΦ

Frequency/Dose/Duration

¢l·ʃŜy˝ƛy˝2Nl·f 2N LJl·NŜyűŜNJl·f ₮2NY˝dzfl·ûƛ2yãΦ ¢NŜl·ûY˝Ŝyűă dzăŜŘ ƛy˝ûKŜ Ijdzl·fƛűè úNƛl·fă ƛyŎftdzŘŜŘY ! fŜyŘN2yl·ûŜ плY˝Ǝ v5 ₮2N y ǿŜŜʃăT /f2ŘN2yl·ûŜ оллY˝Ǝ L± v5 ₮2N мл Řl·èăT ! fŜyŘN2yl·ûŜ тΦpY˝Ǝ L± v5 ₮2N o Řl·èăT t l·Y˝ƛŘN2yl·ûŜ слY˝Ǝ L± ₮2N 2yŜ Ř2ăŜT bŜNƛŘN2yl·ûŜ мллπY˝Ǝ L± v мл Řl·èă ₮2N пл Řl·èăΦ 5dzNJl·ûƛ2Y˝₮2N 2NJl·f úNŜl·ûY˝Ŝyű 2₮ /wt{ LJl·ûƛŜyűă Y˝l·è ōŜ ƛyŘŜ₮ƛyƛűŜΣ l·fűK2dzƎK Y˝2ăű Ř2 y2ű NŜIjdzƛNŜ ƛyŘŜ₮ƛyƛűŜ úNŜl·ûY˝Ŝyű l·ă ûKŜ Ŏ2yŘƛûƛ2˝dzădzl·ffè ƎNJl·Řdzl·ffè ƛY˝LJNN2ØŜă 2N ƛ˝ ă2Y˝Ŝ Ŏl·ăŜă NŜă2fØŜă ălJ2yűl·yŜ2dzăfèΦ

Indications for discontinuation

wŜă2fdzűƛ2yΣ l·ŘØŜNăŜ Ŝ₮₮ŜŎűăΣ ƛyű2fŜNJl·yŎŜΦ

Rationale

There are many high- and moderate-quality studies of bisphosphonates for CRPS. These studies show consistent, generally substantial benefits (Adami et al., 1997, Manicourt et al., 2004, Varenna et al., 2000, Robinson et al., 2004, Varenna et al., 2013), including durable results over 12 months of follow-up (Varenna et al., 2022). A comparative trial of IV pamidronate with oral glucocorticoids found comparable efficacy (Young et al., 2016). Patients with either early or established CRPS have both been shown to respond favorably to bisphosphonates.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second line treatments are: mirror therapy, pain exposure therapy, virtual reality (VR), desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO.

Bisphosphonates are not invasive in oral formulations and minimally invasive in parenteral administrations, have adverse effects, are moderate to high cost, have evidence of significant efficacy, and are thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: diphosphonates, bisphosphonates; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 22 articles in PubMed, 13 in CINAHL, 7 in Cochrane Library, 4,420 in Google Scholar, and 0 from other sources†. We considered for inclusion 9 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 7 randomized trials and 5 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MYCOPHENOLATE FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against mycophenolate for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one small trial of mycophenolate with limited outcomes data that reported potential benefits (Goebel et al., 2018). Complete outcomes data in a larger trial are needed before a recommendation is able to be formulated.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Mycophenolate, CellCept; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 article in PubMed, 2 in CINAHL, 1 in Cochrane Library, 4140 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CALCITONIN FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Calcitonin is recommended as a treatment option for patients with complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe CRPS with inadequate symptom relief with strengthening, aerobic exercise, NSAIDs, corticosteroids, active physical and/or occupational therapy, and bisphosphonates.

Benefits

Improved pain control and ability to tolerate progressive exercises.

Harms

Muscle cramps, fever, chills, dizziness, joint pain, nausea, vomiting, seizures.

Frequency/Dose/Duration

Dosing in the quality trials were intranasal calcitonin: 100IU TID for 3 weeks (Gobelet et al., 1992), 400IU QD for 4 weeks (Bickerstaff et al., 1991), and 200 IU QD plus calcium 500mg a day (Sahin et al., 2006). Duration of use for CRPS patients may be indefinite, although most do not require this as the condition usually improves or resolves spontaneously.

Indications for discontinuation

Recovery, intolerance, adverse effects, failure to improve, reaching the end of a 2-month period without objective evidence of ongoing improvement.

Rationale

There are a few heterogeneous studies assessing the efficacy of calcitonin for CRPS. The studies do not agree, as more indicate a benefit (Gobelet et al., 1986, Gobelet et al., 1992, Hamamci et al., 1996) and some do not (Bickerstaff et al., 1991, Sahin et al., 2006). There is no clear pattern elucidated from the studies rated as higher quality. Due to data heterogeneity, it is also questionable to combine these data in a meta-analysis. Both studies using parenteral calcitonin were positive (Gobelet et al., 1986, Hamamci et al., 1996), possibly indicating a problem with dose and route of administration. There also are conflicts regarding the ideal timing of administration, whether after significant osteopenia, immobility, and trophic changes, or whether early in the disease process (Gobelet et al., 1992). This literature contrasts with that for bisphosphonates, which have much better evidence for efficacy. Calcitonin is non- to minimally invasive, has relatively few adverse effects, and is moderately costly. The mechanism of action in CRPS is unknown.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. Calcitonin is selectively recommended for patients who do not have adequate symptom relief with first-line treatments.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Calcitonin; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*,

randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 145 in CINAHL, 0 in Cochrane Library, 8640 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 4 article considered for inclusion, 4 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CLONIDINE FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Clonidine (administered orally or by regional blockade) is recommended for treatment of moderately severe complex regional pain syndrome (CRPS) that is not responsive to rehabilitative therapy, NSAIDs, or glucocorticosteroids.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe CRPS that is not responsive to strengthening exercises, aerobic exercise, other exercise, NSAIDs, bisphosphonates, and glucocorticosteroids.

Benefits

Improved pain control and ability to progress with functional exercises.

Harms

Adverse effects related to either clonidine, lidocaine and/or NSAID. Includes hypotension, dysrhythmias.

Frequency/Dose/Duration

Three injections at weekly intervals. The single quality study used: 30 µg clonidine plus 1 mg/kg lidocaine plus 0.9% saline solution plus 5 mg parecoxib (Frade et al., 2005). Because parecoxib is not available in the United States, other NSAIDs should be considered.

Indications for discontinuation

Resolution, intolerance, adverse effects, failure to improve. For IV administrations, reaching the end of the series of 3 injections.

Rationale

There is one moderate-quality trial suggesting that an intravenous regional blockade that includes clonidine, parecoxib and lidocaine is superior to placebo (Frade et al., 2005). Another crossover trial comparing intrathecal clonidine with adenosine found decoupling between reductions in pain scores compared with reductions in hyperalgesia (Rauck et al., 2015). Intravenous regional blockades are invasive, have adverse effects, are moderate to high cost, have some evidence of efficacy, and thus are selectively recommended.

However, although there are no direct comparative studies, overall results suggest that the magnitude of benefits may be greater for bisphosphonates; therefore, some physicians may opt to use them preferentially before resorting to clonidine if needed. There are no quality studies of oral clonidine treatment, but efficacy is suggested by the results from interventional routes of administration.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Clonidine; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 article in PubMed, 0 in CINAHL, 1 in Cochrane Library, 7320 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 5 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ORAL GLUCOCORTICOSTEROIDS FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Oral glucocorticosteroids are moderately recommended for the short-term treatment of complex regional pain syndrome (CRPS).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Moderate to severe CRPS with symptoms insufficiently controlled with progressive strengthening, aerobic and other active exercises, and NSAIDs. Bisphosphonates are another reasonable option at this stage. Few patients with mild CRPS may be candidates, especially if there is a lack of progress or worsening of symptoms.

Benefits

Improved pain and improved function with better tolerance of exercises.

Harms

Agitation, worsening diabetes or glucose intolerance, weight gain, hypertension or worsened blood pressure control, infection. Generally relatively limited for a short-term treatment such as for CRPS; while longer term treatment has significantly greater adverse effects.

Frequency/Dose/Duration

One regimen used was Prednisolone 40mg PO QD for 14 days and then 10 mg/week taper (Kalita et al., 2006). A second regimen was prednisone 10mg PO TID for up to 12 weeks (Christensen et al., 1982). There is no comparative evidence to suggest which regimen is superior. If there is significant improvement in objective findings and an additional treatment is felt to be indicated, it appears reasonable to continue treatment for an additional two months. Subsequent treatment should be individualized based on ongoing improvements, and inadequacy of progressive exercises.

Indications for discontinuation

Completion of a course of treatment, sufficient clinical response to provide for progressive exercise program compliance, non-tolerance or adverse effects.

Rationale

Treatment of CRPS with glucocorticosteroids have been assessed in multiple quality studies, all of which suggest considerable efficacy. Two trials have strongly positive results compared with placebo and NSAID (Christensen et al., 1982, Kalita et al., 2006), and another that compared an oral steroid with a proven effective medication, a bisphosphonate (IV pamidronate), found comparable efficacy (Young et al., 2016). Another low-quality placebo-controlled trial also suggested efficacy (Braus et al., 1994). Thus, all placebo-controlled trials and trials against a proven effective therapy show positive results. A trial of prednisolone 20mg vs. 40 mg found comparable efficacy (Kalita et al., 2023), suggesting higher doses may not help, although the overall highly favorable results may limit the ability to detect differences. Intrathecal glucocorticosteroid has been shown to be ineffective (Munts et al., 2010).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). Oral glucocorticosteroids are not invasive, have adverse effects, are low cost, but have significant evidence of efficacy and are thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Oral Glucocorticosteroids; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 20 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 article considered for inclusion, 4 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

KETANSERIN FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of ketanserin for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies reported evaluating ketanserin to treat CRPS. Thus, there is no recommendation for or against its use to treat CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ketanserin; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials,

randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 358 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MAGNESIUM SULFATE FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Magnesium sulfate is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate quality study evaluating magnesium sulfate to treat CRPS (Fischer et al., 2013), which found no meaningful differences between groups for any outcomes at 12 weeks. Magnesium sulfate is invasive, has some adverse effects, is low to moderate cost, but has quality evidence of a lack of efficacy and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: magnesium sulfate; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 4 in CINAHL, 0 in Cochrane Library, 2,640 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

THALIDOMIDE AND LENALIDOMIDE FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Thalidomide is not recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

A moderate quality trial found lack of efficacy of lenalidomide for treatment of CRPS (Manning et al., 2014). Lenalidomide has fewer adverse effects than thalidomide. Regardless, these medications are not invasive, have modest to high adverse effects, have no evidence of efficacy and thus are not recommended for treatment of CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: thalidomide, lenalidomide; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 3,450 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CAPSICUM CREAMS FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of capsicum creams for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of capsicum for treatment of CRPS. Capsicum is not invasive, has modest adverse effects, is low to moderate cost in aggregate, has no evidence of efficacy for treatment of CRPS, and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: **Capsicum, Capsicum cream**; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 725 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DIMETHYL SULFOXIDE (DMSO) FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Dimethyl sulfoxide (DMSO) is selectively recommended for treatment of complex regional pain syndrome (CRPS), after trials of progressive strengthening exercises, image/mirror therapy, bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressants, and gabapentinoids.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS that is sufficient to require medication. Generally should also have failed multiple other modalities including progressive strengthening exercise, aerobic exercise, NSAIDs, tricyclic anti-depressants, bisphosphonates, and anti-convulsant agents.

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

May have dermatological effects, dry skin, breathing difficulties, garlic taste, headache, dizziness, drowsiness, diarrhea, constipation.

Frequency/Dose/Duration

DMSO applied 50% 5 times a day to affected extremity. Duration in the highest quality study was 17 weeks (Perez et al., 2003). Some patients do not require lengthy treatment, particularly if they are compliant with a functional restoration program which should be the key focus of the treatment program.

Indications for discontinuation

Resolution, development of adverse effects, failure to adhere to a restoration program.

Rationale

There is one low quality, placebo-controlled study suggesting some modest efficacy of DMSO. One high-quality trial had no placebo control and found comparable efficacy with N-Acetylcysteine (Perez et al., 2003). Adverse effects (skin reactions) occur in approximately 4% of patients (Perez et al., 2003). Although two studies suggest benefit, flaws in their design preclude drawing robust conclusions regarding DMSO's efficacy.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second-line treatments include mirror therapy, pain exposure therapy, VR, desensitization, antidepressants (TCA, SNRI), gabapentin, and DMSO. DMSO is not invasive, has generally low adverse effects, is moderately costly in aggregate, and has some evidence suggesting efficacy; thus, it is selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: dmso, dimethyl sulfoxide; complex regional pain syndrome, CRPS; controlled clinical trial,

controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 4 in CINAHL, 6 in Cochrane Library, 3,270 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

N-ACETYLCYSTEINE (NAC) FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

N-acetylcysteine (NAC) is selectively recommended for treatment of patients with complex regional pain syndrome (CRPS) who have had insufficient results from treatment with progressive strengthening exercises, bisphosphonates, glucocorticosteroids, NSAIDs, antidepressants, and gabapentinoids.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS that is sufficient to require medication. Generally should also have failed multiple other modalities including progressive strengthening exercise, aerobic exercise, bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressants, and gabapentinoids.

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

GI adverse effects often sufficient to require discontinuation.

Frequency/Dose/Duration

N-Acetylcysteine 600mg PO TID. Duration in the quality trial was 17 weeks (Perez et al., 2003). Some patients do not require lengthy treatment, particularly if they are compliant with a functional restoration program which should be the key focus of the treatment program.

Indications for discontinuation

Resolution, intolerance, development of adverse effects, failure to respond.

Rationale

NAC has some evidence suggesting comparable efficacy with DMSO (Perez et al., 2003), but no quality placebo-controlled evidence that is available.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, and DMSO.

NAC is not invasive, but has severe GI adverse effects (resulting in discontinuation of treatment in 6.8% of patients (Perez et al., 2003)), is moderately costly in aggregate, and has evidence somewhat suggestive of efficacy. Thus, NAC is selectively recommended for treatment of patients with CRPS who have failed multiple other modalities, including progressive strengthening exercise, aerobic exercise, bisphosphonates, glucocorticosteroids, NSAIDs, antidepressants, and gabapentinoids.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: N-acetylcysteine, Acetylcysteine; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 3 in CINAHL, 0 in Cochrane Library, 2980 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 1 randomized trials and 1 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

EMLA CREAM FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of EMLA cream for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

EMLA cream was used in one RCT but rather than testing its efficacy, the trial had endpoints such as cortical inhibition; there are no quality studies directly assessing the efficacy of EMLA. EMLA is not invasive, has low adverse effects, and is moderately costly in aggregate. In the absence of evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: EMLA Cream, Lidocaine, Prilocaine Drug Combination; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 486 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LIDOCAINE PATCHES FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for lidocaine patches for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of lidocaine patches. Patches are also unable to cover most areas of patients' symptoms, and patches are cumulatively costly and so they are generally not indicated. Thus, there is no recommendation. for lidocaine patches, and there are numerous other effective treatments to prescribe.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Lidocaine plaster, Lidocaine Medicated Plaster; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 633 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VITAMIN C FOR PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME

Recommended

Vitamin C is moderately recommended for preventing complex regional pain syndrome (CRPS) in patients with fractures and, by analogy, other extremity trauma. It is also moderately recommended for patients at high risk for CRPS (i.e., from surgical release for Dupuytren’s contracture).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

All patients thought to be at increased risk of CRPS, especially those with prior CRPS and those sustaining distal upper and lower extremity fractures.

Benefits

Nearly all trials suggest >50% reduction in the risk of developing CRPS.

Harms

Negligible.

Frequency/Dose/Duration

Trials have mostly used 500mg-1gm/day for 40-50 days.

Indications for discontinuation

Complete course of treatment

Rationale

There are multiple moderate- and high-quality trials, with all but one trial showing considerable efficacy of vitamin C for the prevention of CRPS (Zollinger et al., 1999, Zollinger et al., 2007, Besse et al., 2009, Hernigou J, 2021, Hernigou et al., 2021, Alimian et al., 2021). Two studies by the same author suggested vitamin C of at least 500mg/day is effective compared with placebo for prevention of CRPS in wrist facture patients (Zollinger et al., 1999, Zollinger et al., 2007). There was no incremental benefit of 1.5 g over 500 mg/day (Zollinger et al., 2007). More recently, other trials have also shown efficacy among patients with upper/lower extremity fractures (Hernigou et al., 2021), and after total knee arthroplasty (Hernigou J, 2021). A low-quality experimental trial also suggested efficacy for foot and ankle surgery (Besse et al., 2009). One trial suggested lack of efficacy among patients with wrist fractures (Ekrol I, 2014).

Vitamin C is not invasive, has negligible adverse effects, and is low cost. Because there is mostly strong evidence of efficacy for prevention of CRPS, it is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: vitamin c, ascorbic acid; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 20 articles in PubMed, 48 in CINAHL, 14 in Cochrane Library, 17,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 11 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 6 randomized trials and 7 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OPIOIDS FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

See the ACOEM Opioids Guideline. Others have noted that the prescription of a drug known to cause hyperalgesia (opioids) for a condition with hyperalgesia "is questionable" (Harden et al., 2022).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Opioid, Opiate, Narcotic; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 25 articles in PubMed, 35 in CINAHL, 7 in Cochrane Library, 18,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HYPERBARIC OXYGEN FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of hyperbaric oxygen for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one moderate-quality study of HBO of 45-day duration without follow-up that suggested potential efficacy for treatment of CRPS (Kiralp et al., 2004), but these results have not since been replicated. HBO is not invasive, has generally low adverse effects, is

high cost, and has one study that is somewhat suggestive of efficacy. However, there is no recommendation for or against its use for CRPS until results from the single available study have been independently shown to be reliable and valid with sufficient follow-up. There are combinations of active exercises and medications that are shown to be effective and are thus recommended prior to consideration of this intervention.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: hyperbaric oxygen therapy, hbot, hyperbaric oxygen; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 6 in CINAHL, 1 in Cochrane Library, 4,160 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HOT AND COLD THERAPIES

CRYOTHERAPIES FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Cryotherapies are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of cryotherapies alone for treatment of CRPS. One trial compared a heterogenous set of interventions (NSAID, exercise, cryotherapy) with polarized low-energy radiation for the prevention of CRPS in post-fracture patients, finding better results with the polarized low-energy radiation (Zlatkovic-Svenda et al., 2019); however, the lack of an isolated intervention precludes formulation of an evidence-based recommendation. Cryotherapies are not invasive, have negligible adverse effects, are low

cost when self-applied, but are generally not well tolerated by patients with CRPS. Therefore, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: cryotherapy, ice therapy, cold therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 3,550 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SELF-APPLICATION OF HEAT THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Self-application of low-tech heat therapy is recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

CRPS sufficient to require treatments beyond exercises and potentially medication. Applications should be home-based as there is no evidence for efficacy of clinician-based heat treatments. Primary emphasis should generally be on compliance with progressive strengthening, aerobic exercises, image/mirror therapy and pain-exposure therapy as part of a functional restoration program elements, rather than on passive treatments in patients with chronic pain which could be detrimental.

Benefits

Mild improvements in symptoms

Harms

Misplaced focus on passive modalities instead of active exercises, which may hinder progress.

Frequency/Dose/Duration

Self-applications may be periodic, generally up to a few times a day. Education regarding home heat application should be part of the treatment plan if heat has been effective for reducing pain.

Indications for discontinuation

Intolerance, increased pain, development of a burn, other adverse event.

Rationale

There are no quality studies of heat therapies for treatment of CRPS. First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see Algorithm). There should be a low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO.

Heat therapies are not invasive, have negligible adverse effects, are low cost when self-applied, seem to be helpful for some patients, and thus are selectively recommended. The main hazard is a misplaced focus on passive modalities instead of active, progressive exercises. Clinician-administered heat therapies are generally not indicated.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Heat Therapy, Heat Treatment, Hot Therapy, Thermal Therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 article in PubMed, 0 in CINAHL, 0 in Cochrane Library, 384 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we

review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DIATHERMY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Diathermy is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of diathermy for treatment of CRPS. It has not been shown to be more effective than placebo diathermy in studies of the spine (see Low Back Disorders). Diathermy is not invasive, has negligible adverse effects, is moderately costly, has no quality evidence of efficacy for CRPS, and additionally also likely removes the focus from active exercise to passive modalities, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: diathermy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 2 in Cochrane Library, 1,750 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ALLIED HEALTH INTERVENTIONS

FLUIDOTHERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

Fluidotherapy (which has features of desensitization techniques and heat) is recommended for patients with moderate to severe complex regional pain syndrome (CRPS) and significant hyperalgesia.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Moderate to severe CRPS with significant hyperalgesia. Patients should be currently engaged in a core program of graded strengthening exercises or have a plan to implement such exercises shortly after or in conjunction with fluidotherapy/desensitization techniques. Fluidotherapy and desensitization techniques are unlikely to be successful for functional restoration and are not recommended as a sole exercise or therapy intervention.

Benefits

Improved function, reduced pain, resolution of the symptoms and signs of CRPS

Harms

Negligible

Frequency/Dose/Duration

Appointments initially 3 times a week, but 5 times a week if severe CRPS. Home exercises should be simultaneously prescribed.

Indications for discontinuation

Resolution, sufficient improvement to no longer require desensitization, ability to maintain progressive increases without supervision.

Rationale

Two small, moderate-quality trials both suggest fluidotherapy is effective for treatment of CRPS (Ozcan et al., 2019, Sethy et al., 2017).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Second-line treatments are: mirror therapy, pain exposure therapy, VR, desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO.

Fluidotherapy is not invasive, has negligible adverse effects (provided strengthening exercises are also performed, thus not delaying recovery), is low to high cost depending on the number of treatments, has some evidence of efficacy, and thus is recommended for treatment of CRPS. However, there are many other interventions thought to be more important, including progressive strengthening, aerobic exercises, pain-exposure therapy, and mirror therapy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Fluidotherapy, Fluidized therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 2 in CINAHL, 3 in Cochrane Library, 399 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MAGNETS AND MAGNETIC STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Magnets and magnetic stimulation are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Magnets or magnetic stimulation has been used for treatment of complex regional pain syndrome. There is no quality evidence suggesting efficacy of magnets to treat CRPS. Thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: transcranial magnetic stimulation, tms, rtms, magnets, magnetic stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 17 articles in PubMed, 6 in CINAHL, 1 in Cochrane Library, 10,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OCCLUSAL SPLINT FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Occlusal splints are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate quality trial reported a lack of efficacy for nocturnal occlusal splinting for treatment of CRPS who also had temporomandibular joint issues (Fischer et al., 2008). These interventions are not invasive, have minimal adverse effects, are moderately costly, but in the absence of evidence of efficacy are not indicated for the treatment of CRPS. Occlusal splints may have other uses for which they are indicated (temporomandibular joint problems).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: occlusal splint; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 3 in

CINAHL, 1 in Cochrane Library, 5,110 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACUPUNCTURE FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against acupuncture for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality trials evaluating acupuncture for treatment of CRPS. (One small study found no differences between sham and classic Chinese acupuncture (Korpan et al., 1999).) The majority of quality trials on various chronic pain disorders have demonstrated that there is no benefit of traditional Chinese acupuncture over other types of acupuncture (see other guidelines, e.g., Low Back, Cervical Spine). When performed by experienced professionals, acupuncture is minimally invasive, has minimal adverse effects, and is moderately costly. However, because it lacks evidence of efficacy for treatment of CRPS, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: acupuncture, electroacupuncture; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 46 in CINAHL, 2 in Cochrane Library, 14,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MYOFASCIAL RELEASE FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Myofascial release is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of myofascial release for treatment of CRPS. Myofascial release is not invasive, has low adverse effects, and is moderate to high cost in aggregate. In the absence of quality evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: myofascial release; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 13,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REFLEXOLOGY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Reflexology is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of reflexology for treatment of CRPS. Reflexology is not invasive, has negligible adverse effects, is moderate cost in aggregate, has no quality evidence of efficacy for CRPS, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Reflexology, Musculoskeletal Manipulations; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 3 in Cochrane Library, 824 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ELECTRICAL THERAPIES

EXTERNAL RADIATION FOR SYMPATHETIC BLOCKADE FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

External radiation for sympathetic blockade is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

While external radiation has been used to treat CRPS, available quality studies suggest it is not effective (Basford et al., 2003). External radiation is not invasive, has adverse effects, is

moderate to high cost, but has no evidence of efficacy for CRPS and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: external radiation, external beam therapy, proton therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 3 in CINAHL, 0 in Cochrane Library, 9,560 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INFRARED THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Infrared therapy is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of infrared therapy for treatment of CRPS. It has not been shown to be more effective than placebo in studies of other disorders. Infrared therapy is not invasive, has negligible adverse effects, is moderately costly, has no quality evidence of efficacy for CRPS, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: infrared therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled

trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 1 in CINAHL, 10 in Cochrane Library, 17,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOW-LEVEL LASER THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation regarding low-level laser therapy (LLLT) for treatment of complex regional pain syndrome (CRPS). Patients should have generally trialed progressive strengthening exercises, aerobic exercises, mirror therapy, bisphosphonates, glucocorticosteroids, antidepressants, and gabapentinoids previously.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no sham-controlled trial of LLLT for treatment of CRPS. There also is no comparative trial with a treatment of known efficacy. There is one moderate-quality study of LLLT for treatment of CRPS that compared additive LLLT with additive inferential; however, it included an intensive treatment of daily use, making its utility challenging for many patients despite efficacy (Dimitrijevic et al., 2014). LLLT is not invasive, has negligible adverse effects, is moderately to high cost in aggregate, and does not have any sham-controlled trial or a trial with an intervention of known efficacy. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Low-Level Light Therapy, LLLT, Laser Biostimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 6 in CINAHL, 3 in Cochrane Library, 135 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane

Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HIGH-VOLTAGE GALVANIC THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

High-voltage galvanic therapy is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of high-voltage galvanic for treatment of CRPS. High-voltage galvanic is not invasive, has low adverse effects, and is moderately costly. In the absence of evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: high-voltage pulsed galvanic stimulation, high-voltage galvanic stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 8050 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTERFERENTIAL THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Interferential therapy is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no sham-controlled trial of inferential for treatment of CRPS. There also is no comparative trial with a treatment of known efficacy. There is one moderate-quality study that compared additive LLLT with additive inferential and included an intensive treatment of daily use, making its utility challenging for many patients irrespective of efficacy (Dimitrijevic et al., 2014). It suggested the inferential therapy underperformed the LLLT. Inferential therapy is not invasive, has negligible adverse effects, is moderately to high cost in aggregate, and does not have any sham-controlled trial or a trial with an intervention of known efficacy. Also, the comparative trial suggested inferiority to LLLT. Thus, inferential therapy is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Interferential therapy, IFT, Electric Stimulation Therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 91 articles in PubMed, 2 in CINAHL, 2 in Cochrane Library, 531 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

IONTOPHORESIS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Iontophoresis is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of iontophoresis for treatment of CRPS. Iontophoresis is not invasive, has low adverse effects, and is moderately costly. In the absence of evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: iontophoresis, electrophoresis; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 9 in CINAHL, 1 in Cochrane Library, 1340 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MICROCURRENT ELECTRICAL STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Microcurrent electrical simulation is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of microcurrent electrical stimulation for treatment of CRPS. Microcurrent electrical stimulation is not invasive, has low adverse effects, and is moderately costly. In the absence of evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Microcurrent electrical stimulation, electrical stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 26 in CINAHL, 3 in Cochrane Library, 169 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Percutaneous electrical nerve stimulation (PENS) is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

PENS has been evaluated in small-scale, short-term studies of patients with chronic pain, but no quality studies are available for CRPS. PENS is minimally invasive, has low adverse effects, and is moderately costly. In the absence of evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Percutaneous electrical nerve stimulation, PENS; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 17 in CINAHL, 2 in Cochrane Library, 6,310 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SYMPATHETIC ELECTROTHERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Sympathetic electrotherapy is not recommended for treatment of complex regional pain syndrome (CRPS) or other chronic pain conditions.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies identified and there is no quality evidence of efficacy. Other modalities have been shown to be effective in the treatment of CRPS and other patients with chronic pain. Sympathetic electrotherapy is not invasive, likely has relatively minor adverse effects, and is costly. In the absence of quality evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Sympathetic Electrotherapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 17 articles in PubMed, 7 in CINAHL, 2 in Cochrane Library, 466 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Transcutaneous electrical nerve stimulation (TENS) is selectively recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients with severe CRPS. Should generally have trialed progressive strengthening exercises, aerobic exercises, mirror therapy, bisphosphonates, glucocorticosteroids, antidepressants, and gabapentinoids prior to TENS. There is no quality evidence that more complex TENS units beyond the single or dual channel models are more efficacious; thus, those models are not recommended.

Benefits

Potentially modestly accelerated improvements in pain and range of motion (Bilgili et al., 2016).

Rationale

There is one moderate-quality study of TENS for treatment of CRPS with poorly described patients that suggests improvements with TENS compared with sham (Bilgili et al., 2016). The patients improved considerably with sham as well as TENS (e.g., VAS pain decreasing from 47 to 14 vs. 35 to 23 over 15 sessions) raising questions about the patient population and generalizability of results. TENS is not invasive, has low adverse effects, and is moderately costly. With evidence of modest efficacy, TENS is selectively recommended. Patients should generally have trialed progressive strengthening exercises, aerobic exercises, mirror therapy, bisphosphonates, glucocorticosteroids, antidepressants, and gabapentinoids prior to TENS. There is no quality evidence that more complex TENS units beyond the single or dual channel models are more efficacious; thus, those models are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TENS, transcutaneous electrical nerve stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 807 in CINAHL, 3 in Cochrane Library, 14,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

POLARIZED POLYCHROMATIC LIGHT THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of polarized polychromatic light therapy for complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no sham-controlled trials and no trials with a comparator of known efficacy. One moderate-quality trial including multiple co-interventions suggested polarized polychromatic as a co-intervention was effective; however, the comparator group included cryotherapy, which is not generally tolerated by patients with CRPS (Zlatkovic-Svenda et al., 2019). Because there is no clear evidence of efficacy, there is no recommendation for polarized polychromatic light therapy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Polarized Polychromatic Light Therapy, Bioptron Light Therapy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 77 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DIRECT CURRENT STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for transcranial or trans-spinal direct current stimulation for treatment of complex regional pain syndrome (CRPS)

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Moderate-quality RCTs conflict regarding efficacy (Lagueux et al., 2018, Hodaj H, 2023). Thus, there is no recommendation regarding direct current stimulation for CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TENS, transcutaneous electrical nerve stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 3 in CINAHL, 1 in Cochrane Library, 7,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PULSED ELECTROMAGNETIC FIELD THERAPY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Pulsed electromagnetic field therapy is not recommended for treatment of complex regional pain syndrome (CRPS)

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial suggested that pulsed electromagnetic field therapy provides no additive benefit when added to conventional therapy (Cömertoğlu et al., 2022). Pulsed electromagnetic field therapy is not invasive, has low adverse effects, and is moderately costly. With evidence of a lack of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Pulsed electromagnetic field therapy, PEMF; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 1 in CINAHL, 2 in Cochrane Library, 16,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INJECTION THERAPIES

ADENOSINE FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against adenosine for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One very short-term experimental crossover trial with clonidine and adenosine has been reported (Rauck et al., 2015). Without a longer trial that is needed to potentially formulate a recommendation, there is no recommendation for or against adenosine.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms:

Adenosine; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 8 in CINAHL, 1 in Cochrane Library, 16,300 in Google Scholar, and 0 from other sources†. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRATHECAL GLUCOCORTICOSTEROIDS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Intrathecal glucocorticosteroids are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Oral glucocorticosteroids have evidence of efficacy in the treatment of CRPS (Christensen et al., 1982, Kalita et al., 2006). However, a moderate-quality study of intrathecal administration of methylprednisolone (Munts et al., 2010) showed evidence of a lack of efficacy. Intrathecal glucocorticosteroids are invasive, have adverse effects, are moderate to high cost, and have evidence of a lack of efficacy. Thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: intrathecal glucocorticosteroids; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 2 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

KETOROLAC INJECTIONS FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for ketorolac injections for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

A small crossover trial of intravenous regional blocks with lidocaine and varying doses of ketorolac showed no durable benefits (Eckmann et al., 2011). Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ketorolac; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 6 in CINAHL, 1 in Cochrane Library, 3,430 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRATHECAL BACLOFEN FOR COMPLEX REGIONAL PAIN SYNDROME

Recommended

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Strength of evidence wŜŎ2ΥΥŜyŘŜŘΣ LyãdzŦŦλŎλŜyű 9ØλŘŜyŎŜ óLú
Level of confidence [2Ø

Indications

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Harms

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Frequency/Dose/Duration

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Indications for discontinuation

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Rationale

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Evidence

! Ŏ2ΥLJNJŜKŜyãλØŜ fλűŜNJI·ûdzNJŜ ăŜI·NJŎK ØI·ă Ŏ2yŘdzŎűŜŘ dzăλyƎ tdzō a ŜŘΣ /Lb ! I [Σ /2ŎKNJI·yŜ [λōNJI·NJèΣ I·yŘ D2Ǝ2ƎfŜ {ŎK2fI·NJ ØλűK ŘI·ûŜ fλΥλűă 2Ŧ нлмр û2 ûKŜ LJNJŜăŜyű dzăλyƎ ûKŜ Ŧ2ff2ØλyƎ ûŜNJΥăY λyűNJI·úKŜŎI·f ōI·Ŏf2ŦŜyΣ ōI·Ŏf2ŦŜyT Ŏ2ΥLJfŜÈ NJŜƎλ2yI·f LJI·λyΎăèyŘNJ2ΥŜΣ /wt{T Ŏ2yűNJ2ffŜŘ ŎfλyΎŎI·f úNJλI·fΣ Ŏ2yűNJ2ffŜŘ úNJλI·făΣ NJI·yŘ2YλÎŜŘ Ŏ2yűNJ2ffŜŘ úNJλI·fΣ NJI·yŘ2YλÎŜŘ Ŏ2yűNJ2ffŜŘ úNJλI·făΣ NJI·yŘ2Y I·ff2ŎI·úλ2yΣ NJI·yŘ2Y ƑΣ NJI·yŘ2YλÎŜŘΣ NJI·yŘ2YλÎI·úλ2yΣ NJI·yŘ2YfèΣ äèăűŜYI·ûλŎΣ äèăűŜYI·úλŎ NJŜØλŜØΣ NJŜűNJ2ăLJŜŎűλØŜΣ LJNJ2ăLJŜŎűλØŜ ăűdzŘλŜăφ ² Ŝ Ŧ2dzyŘ I·yŘ NJŜØλŜØŜŘ π I·NJűλŎfŜă λyΎtdzō a ŜŘΣ м λyΎ /Lb ! I [Σ т λyΎ /2ŎKNJI·yŜ [λōNJI·NJèΣ мΣтфл λyΎD2Ǝ2ƎfŜ {ŎK2fI·NJΣ I·yŘ л ŦNJ2Y 2ûKŜNJ ă2dzNJŎŜăϟφ hŦ ûKŜ н

articles considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

KETAMINE INFUSION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Ketamine infusion is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies on efficacy of ketamine for CRPS. One low-quality study suggested lack of efficacy at 12 weeks (Schilder et al., 2013). In a nonrandomized study, bone scans predicted responsiveness to ketamine (Sorel et al., 2018). Ketamine is invasive, has adverse effects (e.g., respiratory depression and hallucinations), is moderately costly, and has no quality evidence of efficacy. Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ketamine, ketamine infusion; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 14 articles in PubMed, 12 in CINAHL, 13 in Cochrane Library, 14,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MANNITOL FOR TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Mannitol is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Mannitol has been evaluated in one moderate-quality trial and found to be ineffective (Rowbotham, 1998). Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: mannitol; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 4580 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRAPLEURAL BUPIVACAINE INFUSIONS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Intrapleural bupivacaine infusions are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Intrapleural bupivacaine infusions have not been evaluated in sizable quality studies for diagnostic, prognostic, or treatment purposes for patients with CRPS. These infusions are invasive, have potential adverse effects, and are costly. In the absence of quality evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: intrapleural bupivacaine, bupivacaine; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 2 in CINAHL, 5 in Cochrane Library, 396 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TUMOR NECROSIS FACTOR-ALPHA BLOCKERS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Tumor necrosis factor (TNF)-alpha blockers are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

TNF-alpha blockers have not been evaluated in quality studies for CRPS (Korhonen et al., 2006, Korhonen et al., 2005). There is one low quality trial that was prematurely terminated (Dirckx et al., 2013). These agents are minimally invasive, have significant adverse effects, and are high cost. In the absence of quality evidence of efficacy, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TNF-alpha blockers, tumor necrosis factor inhibitors; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic,

systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 10 in CINAHL, 0 in Cochrane Library, 4770 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LIDOCAINE INFUSION FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of lidocaine infusions for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One low-quality study suggests short-term improvements in some measures (Wallace et al., 2000). However, there is no quality evidence of efficacy for treatment of patients with CRPS. There is no evidence that these infusions result in a sustained decrease in pain medication requirements, reported pain, or an increase in overall function. Lidocaine infusions may be reasonable for select patients (e.g., CRPS) for diagnostic purposes. Repeated infusions without objective evidence of prolonged efficacy and functional improvement are not recommended. Some centers reportedly are using multi-day inpatient infusions of lidocaine for patients with CRPS. There are no large, quality studies evaluating the safety and effectiveness of this treatment. Lidocaine infusions have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes. Lidocaine infusions are invasive, have adverse effects (Viola et al., 2006, Tremont-Lukats et al., 2006, Kvarnstrom et al., 2003), and are moderate to high cost. In the absence of quality evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: lidocaine infusion, lidocaine); complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 3 in

CINAHL, 17 in Cochrane Library, 16,100 in Google Scholar, and 0 from other sources†. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Intravenous immunoglobulins are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Rationale

Intravenous Immunoglobulin (IVIG) has been evaluated in two RCTs for CRPS. Although the initial small trial suggested efficacy (Goebel, 2010), the much larger trial was negative (Goebel et al., 2017). Thus, intravenous immunoglobulin is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: immunoglobulins; intravenous; IVIG; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 23 in CINAHL, 1 in Cochrane Library, 8900 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.
† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STELLATE AND LUMBAR GANGLION BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Stellate and lumbar ganglion blocks are selectively recommended for acute complex regional pain syndrome (CRPS) or an acute flare-up of CRPS that has not responded or is inadequately controlled with progressive strengthening, graded exercise, physical therapy/occupational therapy, and medications. Stellate and lumbar ganglion blocks should be integrated into a comprehensive treatment program emphasizing functional restoration.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Acute CRPS or an acute flare-up of CRPS that has not responded or is inadequately controlled with progressive strengthening, graded exercise, physical therapy/occupational therapy and medications. Should be performed when it is integrated into a comprehensive treatment program emphasizing functional restoration.

Benefits

Potential improved ability to tolerate and accomplish progressive exercise.

Harms

Complications of the procedure, medicalization, externalization away from a focus on active exercise.

Frequency/Dose/Duration

Blocks with anesthetics are typically performed, although one RCT suggested injection with Botulinum A resulted in superior outcomes at 1 and 3 months compared with anesthetic (Yoo et al., 2022). Additional blocks if clear objective evidence of functional improvement.

Indications for discontinuation

Resolution, adverse effects, intolerance, failure to improve or non-compliance with treatment recommendations.

Rationale

There are small studies that have evaluated the efficacy of stellate ganglion blocks (Price et al., 1998), suggesting that duration of pain relief is related to success of a block. There are no quality trials of lumbar sympathetic blocks, but they are included under the presumption of being a similar intervention with presumed similar efficacy. A comparison between anesthetic and botulinum A found better results at 1 and 3 months post-procedure with botulinum A (Yoo et al., 2022). One trial compared adjunctive clonidine with

methylprednisolone and found comparable results; however, without a placebo comparator, the utility of this approach is unclear (Naskar et al., 2023). There is no sizeable study of high-grade evidence. A small trial found no differences between blocks under fluoroscopy compared with ultrasound (Imani et al., 2016).

The available evidence suggests that, at best, there is a modest degree of improvement assuming larger studies are able to detect any improvement at all. These injections also are unlikely to provide long-term benefits unless promptly coupled with graded exercises.

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. Second line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line-treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments. Third-line treatments are stellate ganglion blocks and bretylium blocks.

Sympathetic blocks are invasive and have some complications. One block is moderately costly, but repeated blocks are high cost. A sympathetic block is recommended for highly select patients who may benefit from blockade to facilitate involvement and advancement in a functional restoration approach.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: stellate ganglion block; stellate ganglion; complex regional pain syndrome; CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 21 articles in PubMed, 9 in CINAHL, 25 in Cochrane Library, 3500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 4 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Recommended

Bier blocks using bretylium are recommended for treatment of severe cases of complex regional pain syndrome (CRPS).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe CRPS that has not responded or is inadequately controlled with progressive exercise, bisphosphonates, glucocorticosteroids, NSAIDs, active exercise, physical therapy/occupational therapy, and potentially mirror therapy. It may be reasonable to attempt control with clonidine, anti-convulsants, tricyclic anti-depressants, or hyperbaric oxygen prior to consideration of bretylium. Should be performed as an adjunct to improve physical capabilities through a functional restoration program.

Benefits

Theoretical potential to tolerate an advanced progressive exercise program.

Harms

Elevated blood pressure, hypotension, dizziness, nausea, vomiting, dysrhythmia, rare risk of fatality

Frequency/Dose/Duration

Lidocaine 40ml with bretylium 1.5mg/kg. (Hord et al., 1992). Additional blockades should be based on objective evidence of progressive improvement.

Indications for discontinuation

Resolution, adverse effects, intolerance, failure to improve, non-compliance.

Rationale

There is one moderate-quality trial of bretylium bier blocks suggesting efficacy for CRPS (Hord et al., 1992).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with

documented compliance and outcomes prior to trials of third line treatments. Third-line treatments are stellate ganglion blocks and bretylium blocks.

Bretylium blocks are invasive, have adverse effects, are at least moderate cost, and have some evidence of efficacy. Thus, they are selectively recommended for CRPS.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bier block; intravenous regional anesthesia; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 1 in CINAHL, 3 in Cochrane Library, 879 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GUANETHIDINE BIER BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Bier blocks using guanethidine are strongly not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Strongly Not Recommended, Evidence (A)
Level of confidence High

Rationale

All of the highest-quality trials suggest that guanethidine bier blocks lack efficacy for CRPS (Livingstone et al., 2002, Jadad et al., 1995, Ramamurthy et al., 1995, Blanchard et al., 1990). The lowest-quality study reported no differences between guanethidine and reserpine (Rocco et al., 1989). Guanethidine blocks are invasive, have adverse effects, are at least moderate cost, and have strong evidence of lacking efficacy; thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Guanethidine bier block; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 57 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 article considered for inclusion, 5 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PHENTOLAMINE BIER BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for or against the use of bier blocks using phentolamine for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality trials of phentolamine bier blocks for CRPS. Phentolamine blocks are invasive, have adverse effects, are at least moderate cost, and have no evidence of efficacy. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Phentolamine bier block, phentolamine; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 2 in CINAHL, 179 in Cochrane Library, 300 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

METHYLPREDNISOLONE BIER BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Bier blocks using glucocorticosteroids are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial of methylprednisolone bier blocks suggesting lack of efficacy for CRPS (Taskaynatan et al., 2004). Glucocorticoid blocks are invasive, have adverse effects, are at least moderate cost, and have evidence of lacking efficacy; thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: methylprednisolone bier blocks; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 226 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

RESERPINE BIER BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Bier blocks using reserpine are not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one comparative trial suggesting comparable results between guanethidine and reserpine (Rocco et al., 1989). Because there is evidence guanethidine is not superior to placebo, there is therefore evidence suggesting reserpine is not likely effective. Reserpine blocks are invasive, have adverse effects, are at least moderate cost, and have indirect evidence suggesting lack of efficacy. Thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: reserpine bier block; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 1 in CINAHL, 1 in Cochrane Library, 30 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BRACHIAL PLEXUS BLOCKS AND INFUSIONS FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for brachial plexus blocks and infusions for treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one pilot RCT of brachial plexus blocks compared with stellate ganglion blocks (Toshniwal et al., 2012), but it lacked a placebo control. The study suggests a need for a larger trial. Thus, there is no quality evidence that brachial plexus/neuraxial blocks and infusions alter the course of CRPS. Brachial plexus/neuraxial blocks have been reported in

conjunction with active rehabilitation services in recalcitrant cases of CRPS. Brachial plexus/neuraxial blocks are invasive, require inpatient hospitalization, have significant adverse effects, and are costly. However, they are sometimes utilized in more severe cases where treatment options may be difficult and limited. Thus, there is no recommendation either for or against the use of these blocks and infusions.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Brachial plexus block, brachial plexus; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 16 articles in PubMed, 6 in CINAHL, 0 in Cochrane Library, 9,280 in Google Scholar, and 0 from other sources†. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REGIONAL NERVE BLOCKS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Lidocaine nerve blocks are selectively recommended for management of complex regional pain syndrome (CRPS) after strengthening exercises, image/motor therapy, bisphosphonates, glucocorticosteroids, NSAIDs, antidepressants, and gabapentinoids are trialed with inadequate results.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Moderate to severe CRPS cases after trials of strengthening exercises, image/motor therapy, bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressants and gabapentinoids are trialed with inadequate results.

Benefits

Reduction in pain, edema, temperature differences and grip strength (Fallico et al., 2022).

Harms

Adverse effects are either typical for injections (residual injection pain, bleeding, infection) or are complications of technique (e.g., laceration).

Frequency/Dose/Duration

Five nerve blocks with 5mL of lidocaine given as a regional nerve block in the affected nerve distribution every 10 days (Fallico et al., 2022). As other injectable anesthetics have longer durability, injection with a longer-lasting agent may be advisable, although there is no quality literature to address this question.

Indications for discontinuation

Resolution of symptoms, completion of a course, intolerance, non-compliance, and/or adverse effects.

Rationale

One quality trial found superior results with a combination of 5 regional nerve blocks of lidocaine plus oral citalopram to be superior to lidocaine regional nerve blocks alone, which was superior to placebo blocks; and the combination therapy was associated with the best clinical improvements (Fallico et al., 2022).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments. Third-line treatments are stellate ganglion blocks and bretylium blocks.

Nerve blocks are minimally invasive, have modest adverse effects in experienced hands, are cumulatively high cost, and have evidence of significant efficacy. Thus, nerve blocks are selectively recommended for management of CRPS after trials of strengthening exercises, image/motor therapy, bisphosphonates, glucocorticosteroids, NSAIDs, antidepressants, and gabapentinoids are trialed with inadequate results.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Nerve block; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective,

prospective studies. We found and reviewed 33 articles in PubMed, 61 in CINAHL, 16 in Cochrane Library, 13,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRAVENOUS NSAIDS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

NSAIDs are recommended for the treatment of complex regional pain syndrome (CRPS) as intravenous adjuncts to regional blockades that also include lidocaine and clonidine.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe CRPS that has responded insufficiently to progressive strengthening exercises, aerobic exercises and oral medications, generally including bisphosphonates.

Benefits

Improved pain control with ability to sustain progressive exercises

Harms

Adverse effects related to either clonidine, lidocaine and/or NSAID. Includes hypotension, dysrhythmias.

Frequency/Dose/Duration

Three injections at weekly intervals. The single quality study used: 30µg clonidine plus 1mg/kg lidocaine plus 0.9% saline solution plus 5mg parecoxib (Frade et al., 2005). Because parecoxib is not available in the United States, other NSAIDs should be considered.

Indications for discontinuation

Adverse effects, reaching the end of the series of 3 injections.

Rationale

There is one moderate-quality trial suggesting that an intravenous (IV) COX-2 inhibitor (parecoxib) is superior to placebo as part of an intravenous regional blockade that includes clonidine and lidocaine (Frade et al., 2005). However, another moderate-quality pilot trial in 20 patients suggested IV parecoxib BID for 2 days was not superior to placebo (Breuer et al., 2014). Intravenous regional blockades are invasive, have adverse effects, are moderate to high cost, and have some evidence of efficacy when combined with clonidine. Therefore, they are selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Intravenous NSAIDs, IV NSAIDs; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 0 in CINAHL, 2 in Cochrane Library, 111 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PREOPERATIVE INTRAVENOUS REGIONAL ANESTHESIA WITH CLONIDINE FOR PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Intravenous regional anesthesia with clonidine is recommended for administration prior to surgery to prevent recurrence of complex regional pain syndrome (CRPS) in patients who have previously had CRPS. It may also be considered in patients undergoing surgery who are considered at increased risk for CRPS.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients undergoing surgery who have a prior history of CRPS. May be considered for those at high risk for CRPS.

Benefits

Potential prevention of CRPS

Harms

Hypotension, dysrhythmias.

Frequency/Dose/Duration

IV administration

Indications for discontinuation

Adverse effects, completion of a block.

Rationale

One moderate-quality study has suggested efficacy of intravenous clonidine for preventing CRPS recurrence in a perioperative timeframe (Reuben et al., 2004).

First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids, and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. Second line treatments are: mirror therapy, pain exposure therapy, VR, desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments. Third-line treatments are stellate ganglion blocks and bretylium blocks.

Epidural administration of clonidine is invasive, has adverse effects, and is moderate cost. However, it has demonstrable efficacy for prevention of recurrence of CRPS and is thus selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: clonidine; intravenous anesthesia; intravenous regional anesthesia; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 213 in Google Scholar,

and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 1 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SURGICAL CONSIDERATIONS

SPINAL CORD STIMULATORS FOR COMPLEX REGIONAL PAIN SYNDROME

Sometimes Recommended

Spinal cord stimulator (SCS) implantation is recommended as an option for highly select patients with complex regional pain syndrome (CRPS). Patients should understand that this intervention has no quality evidence indicating benefits greater than 3 years, during which time there is unequivocal patient commitment.

SCS is also a fourth-line treatment. First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror therapy and pain exposure therapy. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. Third-line treatments are stellate ganglion blocks and bretylium blocks. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments. At least two attempts at third-line treatments should have been trialed before consideration of SCS.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients should demonstrate the following:

1. Clear diagnosis of CRPS based on criteria that include objective measures, such as the Consensus Criteria.

2. Poor response to conservative treatment generally for at least 6 months,** including treatment in an experienced interdisciplinary clinic with proven good outcomes that included elements of a functional restorative program (i.e., at minimum including progressive strengthening, aerobic, image/mirror therapy exercises and CBT; also having trialed bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressant(s) and gabapentinoids) and for which the patient demonstrated good motivation.

3. Remedial surgery inadvisable or not feasible.

4. Major psychiatric disorders have been treated with expected responses. Somatic symptom disorder (formerly, somatization disorder) not amenable to treatment will disqualify the patient for use of invasive procedures, as the risk of the procedure is higher than the expected success rate. The candidate should have a successful independent, psychological evaluation and a structured interview performed by a psychologist specialized in chronic pain management including appropriate psychometric testing (see Appendix 1). (The psychological evaluation should be performed by a practitioner who is not employed by the requesting or treating physicians).***

5. Willingness to stop inappropriate drug use before implantation.

6. No indication that secondary gain is directly influencing pain or disability complaints.

7. Ability to give informed consent for the procedure.

8. Successful results of at least 50% pain reduction from a trial of a temporary external stimulator of approximately 2-3 days and reduction of use of opioid medication or other medication with significant adverse effects or functional improvement such as return to work that may be evaluated by an occupational or physical therapist prior to and before discontinuation of the trial.

Adapted from: (Kumar et al., 2006, Lee et al., 2006, Segal et al., 1998).

***Some authors advocate earlier intervention; however, quality evidence is lacking.*

****Presence of depression is common in patients with chronic pain, requires evaluation, and may require treatment. Depression that is particularly severe may require treatment prior to assessing appropriateness of SCS; however, the presence of depression does not preclude SCS.*

Benefits

Potential to engage and advance a progressive exercise program during the shorter term interval after implantation when there is some evidence of efficacy.

Harms

Medicalization, paralysis, fatality.

One-third of patients reportedly experienced adverse effects in one study (Turner et al., 2004). The complication rate was 34.6% of 234 consecutive patients at an academic center, with hardware complications causing 74.1%; both the revision and explantation rates were 23.9%, and 41.1% of explants were due to loss of efficacy (Hayek et al., 2015). Another consecutive case series reported that 30% of patients discontinued SCS use over a median follow-up period of 8 years (Hoikkanen et al., 2021). Patients with CRPS were reported to have less perioperative pain reduction, longer post-anesthesia unit stays, and higher hospital costs than do SCS patients with other underlying diagnoses (Martini et al., 2020). At another center, the explantation rate was 30% among 252 patients, with 26.6% having biological complications, 26.6% having paresthesia, 13.3% experiencing hardware complications, 28% reporting ineffective pain control, and 5.3% having no further need for stimulation therapy (Simopoulos et al., 2019).

Indications for discontinuation

Resolution of pain, complications necessitating discontinuation of therapy or device removal, or loss of therapeutic effect.

Rationale

Spinal cord stimulators have been used for treatment of complex regional pain syndrome (Duarte et al., 2020, Hoydonckx et al., 2019, Blackburn et al., 2021, Ho et al., 2022). There is evidence from one moderate-quality RCT that SCSs result in reduced pain for CRPS that is sustained over periods up to 3 years (Kemler et al., 2000, Kemler et al., 2004, Kemler et al., 2001). However, from years 3 to 5, there was no statistically significant benefit from SCS compared to physical therapy (Kemler et al., 2006). Another trial suggested modest benefits at up to 3 months compared with sham/placebo (Kriek et al., 2015), although a post-hoc analysis reported benefits for some but not all symptoms (Kriek et al., 2023). Sham-controlled trials have variously suggested no changes in sensory characteristics with SCS (Meier et al., 2015) and negative results (Sokal et al., 2020). A trial found modestly better results with low-frequency SCS (Canós-Verdecho et al., 2021). A crossover trial found that among patients trialed with both dorsal root ganglion stimulation and SCS, 10/12=83.3% preferred DRG stimulation, although the diagnosis of knee CRPS may limit the generalizability of the results (van Bussel et al., 2018), while another trial suggested somewhat more durable effects with DRG (Levy et al., 2020, Deer et al., 2019); low-quality data suggests there may be benefit from combined DRG-SCS treatment (Ghosh et al., 2021). Other case series report similar reductions in efficacy over time (Forouzanfar et al., 2004). Importantly, there is no quality study that appears to compare SCSs with a multidisciplinary treatment program that emphasizes functional restoration. Indications for SCSs for CRPS have been published (see Table 9). A case series suggests social and psychological factors should be considered (Segal et al., 1998). The literature also suggests that physical therapy exercises alone have benefits, and also are of benefit when combined with use of SCSs.

SCS is a fourth-line treatment. First-line treatments are education, strengthening exercises, aerobic exercise, fear avoidance belief/kinesiophobia training, NSAIDs, glucocorticosteroids and bisphosphonates (see Algorithm). There should be low threshold for early use of mirror

therapy and pain exposure therapy. Second-line treatments are: mirror therapy, pain exposure therapy, VR, Desensitization, antidepressants (TCA, SNRI), gabapentin, DMSO. Third-line treatments are stellate ganglion blocks and bretylium blocks. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments. At least two attempts at third-line treatments should have been trialed before consideration of SCS.

Spinal cord stimulators are invasive, have significant adverse effects, and are high cost. They are recommended for select patients (see Table 9).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: spinal cord stimulator, dorsal column stimulator, spinal cord stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 82 articles in PubMed, 12 in CINAHL, 14 in Cochrane Library, 4910 in Google Scholar, and 0 from other sources†. We considered for inclusion 21 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 0 from other sources. Of the 14 articles considered for inclusion, 10 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DORSAL ROOT GANGLION STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

No Recommendation

There is no recommendation for dorsal root ganglion (DRG) stimulation for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no sham-controlled trials of DRG stimulation and there also are no quality trials with a quality functional restoration program as the control group. One moderate-quality crossover trial compared DRG with spinal cord stimulation and reported that 10 of the 12

patients (83.3%) preferred DRG over spinal cord stimulation for CRPS of the knee (van Bussel et al., 2018). Small case series of DRG stimulation have reported some reductions in pain and opioids use (Graca et al., 2022, Van Buyten et al., 2015, Rosado Caracena et al., 2023). A cost-effectiveness analysis noted that the cost of DRG stimluation is higher than that of spinal cord stimulation; this difference was attributed to both higher efficacy and thus higher implantation rates, but also problems with battery life (Mekhail et al., 2021). DRG stimulation is invasive, has significant adverse effects, and is high cost. In the absence of quality evidence of efficacy and with one trial suggesting patient preference for SCS over DRG stimulation, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Dorsal root ganglion; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 35 articles in PubMed, 14 in CINAHL, 9 in Cochrane Library, 10,400 in Google Scholar, and 0 from other sources†. Of the 2 article considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PERIPHERAL NERVE STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Peripheral nerve stimulation (PNS) is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of peripheral nerve stimulation. PNS is invasive, associated with adverse effects, and high cost. In the absence of quality evidence of efficacy, PNS is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Peripheral Nerve Stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 39 articles in PubMed, 18 in CINAHL, 5 in Cochrane Library, 17,400 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MOTOR CORTEX STIMULATION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Motor cortex stimulation is not recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies assessing efficacy of motor cortex stimulation for treatment of CRPS. Motor cortex stimulation is highly invasive, has significant adverse effects, is high cost, has a lack of quality evidence of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Motor cortex stimulation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 3 in CINAHL, 14 in Cochrane Library, 16,600 in Google Scholar, and 0 from other sources†. Of the 2 articles considered for inclusion, 2 randomized trial and 0 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we

review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SYMPATHECTOMY FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Sympathectomy is not recommended for treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of either surgical or radiofrequency sympathectomy. These procedures are invasive, associated with adverse effects, and high cost. In the absence of quality evidence of efficacy, sympathectomy is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Sympathectomy; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 20 articles in PubMed, 9 in CINAHL, 3 in Cochrane Library, 2,710 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AMPUTATION FOR COMPLEX REGIONAL PAIN SYNDROME

Not Recommended

Amputation is not recommended for the treatment of complex regional pain syndrome (CRPS).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Amputation has been used for treatment of complex regional pain syndrome (Ayyaswamy B, 2019, Howard EL, 2023). There are no quality studies of amputation. A comparative case series reported modest differences in pain (median VAS 80 vs. 91) and greater differences in opioids (53% vs. 90%) between an amputated group and non-amputated group (Midbari et al., 2016). Another study reported worse pain in the past week of 8.7 decreasing to 5.2, while there were no differences in three quality-of-life measures (Schrier et al., 2019). Worse results after amputation were reported for patients with worse resilience, prior psychiatric disorder, current psychiatric disorder, and higher pain ratings. A psychiatric history and involvement in a lawsuit were both associated with CRPS recurrence in the surviving limb . A third case series reported 77% reported improved mobility, 73% reported an important reduction in pain, while 23-27% reported deteriorations in intimacy and self-confidence (Geertzen et al., 2020). Amputation has permanent adverse consequences, is high cost, does not have quality evidence of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Amputation; complex regional pain syndrome, CRPS; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 20 in CINAHL, 1 in Cochrane Library, 16,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trial and 2 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

COMPLICATIONS AND COMORBIDITIES

- Diabetes mellitus
- Alcohol
- Autoimmune disorders
- Nutritional deficiencies
- Herpes zoster/shingles
- Diabetic neuropathy
- Rheumatological disorders
- Stroke

- Multiple sclerosis
- Peripheral nerve injuries
- Radiculopathy
- Radiculitis
- Herpes zoster/Shingles
- HIV/AIDS
- Hypothyroidism
- Nutritional deficiencies
- Intracranial aneurysm
- Advocagenic influences
- Idiopathic

FOLLOW-UP CARE

It is recommended that patients with CRPS should have a follow-up visit every week by a clinician while still out of work and initiating treatments. Appointments throughout the treatment period should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaints and symptoms.

Initial visits should include initiating, and then subsequently an ongoing focus on function. These appointments should obtain more information from the patient, confirm that the history information is consistent, observe for injury/illness behaviors, confirm the diagnosis, and assess the need for psychological referral and evaluation. These initial appointments for CRPS should institute progressive strengthening and aerobic exercises, prioritize the selection of medications with demonstrated efficacy for CRPS treatment, include fear avoidance belief training, establish therapy care and pain psychological services if needed. Early referral for CBT is frequently of considerable benefit.

The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative, active exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. The clinician should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Those patients requiring treatments in pain programs require more frequent follow-ups. Subsequent follow-up is recommended to be less frequent and tailored to the patient's needs. In cases where the patient has returned to work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is recommended. However, in the active rehabilitation phase for patients with CRPS, follow-ups weekly for as much as 2 or 3 months is recommended to also be conducted if there is need for therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

JOB ANALYSIS

The primary purpose of job analyses for patients with CRPS is to identify job tasks that the worker may be able to perform. The job analysis may also be quite helpful in identifying progressively more demanding or graded job tasks that the patient could be transitioned into as key part of their functional restoration program.

FIBROMYALGIA

INTRODUCTION

Fibromyalgia is a chronic, anatomically widespread pain disorder of unknown etiology that is theorized to involve central sensitization [277-281]. The term *fibromyalgia* may inadvertently suggest a pathophysiological construct, and thus some researchers are eschewing its use. However, because the term remains in widespread use, this guideline is continuing to use "fibromyalgia" to describe this entity. It is characterized by diffuse muscle pain with pain sensitization that is typically accompanied by fatigue, sleep disturbance, waking unrefreshed, and cognitive symptoms [277-285]. It is thought to occur based primarily on abnormal central nervous system pain processing that mischaracterizes normal stimuli as unusually painful [52,286-308], although some involvement of peripheral pain mechanisms and peripheral sensitization has also been theorized [309,310].

Recently, fibromyalgia has been classified as a type of chronic primary pain [311-313]. The concept of chronic primary pain subsumes a number of chronic overlapping pain conditions [50,51]. It has been defined as “pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability (interference with activities of daily life and participation in social roles) and that cannot be better accounted for by another chronic pain condition” [314]. Primary pain is believed to be a “nociplastic” disease state, which involve structural and functional changes to the pain sensory system [311,314].

Physiologically, fibromyalgia has been associated with neuropathy in small peripheral nerve fibers associated with nociception [315-318]. In the CNS, fibromyalgia has been associated with both structural changes in the brain [223,319,320] and abnormal brain functioning [223-323].

Psychologically, fibromyalgia has been associated with anxiety or kinesiophobia [318,324-328], depression [318,324,327,328,329,330], prior psychological trauma [331,332], and catastrophizing cognitions [321,325,328], with reduced emotional expression [329,333].

Fibromyalgia is therefore a unique disorder that has important, major psychological components, especially depression and other problems typically affecting more than half of patients at some point [334-337]. While the strongest tendency is for depression, other risks include anxiety disorders, posttraumatic stress disorder (PTSD), physical abuse, sexual abuse, and childhood neglect (see below). Thus, evaluation(s) for depression and other conditions are usually required. There are also strong tendencies towards *prior* psychiatric disorders that predate the onset of symptoms [334].

Multiple other disorders may overlap with fibromyalgia, particularly other "functional disorders", such as irritable bowel syndrome [338-344], headaches and migraines [338,342,345,346], chronic fatigue syndrome [338,342,347,348,349], temporomandibular disorders and orofacial pain [350], and multiple chemical sensitivity [351].

Studies suggest fibromyalgia is not merely a pain disorder, as population-based studies reported the risk of coronary heart disease among those with fibromyalgia is more than doubled [352,353] and there is a 2.44-fold risk of motor vehicle crash [354]. Fibromyalgia is also associated with an increased risk of hospitalization, suicide, injuries, and lower quality of life [355].

As fibromyalgia is widely believed to primarily reside in the central nervous system, it is also widely considered non-occupational. While there is no quality evidence that fibromyalgia is work-related, this evidence-based guideline addresses the evaluation and treatment of patients with fibromyalgia because of the

- prevalence of the condition,
- lack of widespread knowledge regarding evidence-based treatment approaches to manage this disorder,
- significant evidence-based differences in clinical management,
- adverse impacts on the workforce, and
- the insights that may be gained by comparing and contrasting these patients with others with chronic pain.

Understanding the complex nature of fibromyalgia and other primary conditions may provide a conceptual framework for understanding the importance of a multidisciplinary approach to this condition.

Evidence-based treatment of patients with fibromyalgia consists primarily of progressive aerobic exercises, potentially combined with strengthening exercises and anti-depressant medication. There is evidence that patients with fibromyalgia respond to different therapies than do other patients with chronic pain. **Aerobic exercise is the most important exercise intervention and is typically introduced as a graded exercise intervention.** There is evidence that strengthening exercises are beneficial. Cognitive-behavioral psychotherapeutic interventions and physical and/or occupational therapy-based interventions to minimize the impact of fear avoidance beliefs ("kinesiophobia") are recommended. Fear avoidance belief training (FABT) appears required, as patients frequently believe that exercise is harmful [356]. FABT for fibromyalgia patients also potentially impacts on adherence to increasing occupational and non-occupational activities, as the main thrust of treatment is to maintain and increase activity, not decrease it through either self-limitations or prescribed restrictions.

Regardless of whether depression is present, antidepressants are the first-line pharmaceutical treatment for fibromyalgia. This is the only major pain disorder reviewed in the evidence-based ACOEM Clinical Practice Guidelines for which selective serotonin reuptake inhibitor (SSRI) antidepressants are effective, providing additional evidence that this is a unique disorder that is distinguished from other chronic pain conditions. Both tricyclic antidepressants and dual serotonin/norepinephrine reuptake inhibiting antidepressants are also effective. Increased efficacy has been documented in combining a low-dose tricyclic antidepressant with an SSRI. Treatment may also include NSAIDS. Studies also suggest modest benefits from gabapentin and pregabalin.

Addressing sleep disturbances is also an important consideration in the management of patients with fibromyalgia. This includes exercise prescriptions (which may help sleep hygiene), cognitive behavioral therapy, and consideration of type and timing of medication.

It is recommended that patients with fibromyalgia remain at full work duty to achieve optimum benefits and clinical outcomes [357,358]. Placing these patients on restricted or modified duty is believed to result in a substantially increased probability of the patient becoming partially or totally disabled. In situations where patients are placed on modified duty or self-reduce their activities, it is recommended that they gradually resume normal activities. When increasing their activity levels, frequent health care support and reinforcing to the patient that they are not injuring themselves is often required (see Fear Avoidance Belief Training).

INITIAL ASSESSMENT

HISTORY

Fibromyalgia involves long-standing, widespread pain that typically involves the entire body or multiple body regions [359,360]. It is generally thought the symptoms should be present for at least 3 months to diagnose it. Symptoms are always present, but may wax and wane with possible exacerbations due to perceived stresses. Patients with fibromyalgia are more sensitive to stimuli compared to patients without disease [289]. Poor sleep quality is a common symptom and may in part be etiologic. Muscle and joint stiffness is common. Paresthesia in the extremities may occur.

Mental health disorders are nearly universal and should be evaluated in all patients (see above). 'Cognitive problems are common and may include problems with concentration, thinking clearly, and memory. There may be increased sensitivity to light, noise, odors, and temperature.

Approximately one-third of patients with fibromyalgia also have migraines. Furthermore, the co-existence of fibromyalgia with irritable bowel syndrome is reported to be as high as 70% [361], suggesting significant psychosocial components. Other functional disorders are common and should be assessed (see above).

Somatic symptoms may include the following: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or memory problems, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

PHYSICAL EXAMINATION

The physical examination of patients with primary fibromyalgia is noteworthy for a lack of completely objective findings, as tenderness on examination requires subjective interpretation [362,363]. Although the diagnosis based on criteria may be made solely on subjective complaints, patients typically have tender points anywhere in the musculature or over bony structures. Those with secondary fibromyalgia may have prominent findings characteristic of a disorder (e.g., rheumatoid arthritis). An essential aspect of the physical

examination for fibromyalgia patients is the search for, and exclusion of, other disorders [294,364].

In the past, the physical examination focused on tender points at 18 sites defined by the 1990 American College of Rheumatology (ACR) criteria. Although they are currently not necessary for ascertaining the presence of fibromyalgia, examination of these and other sites remain helpful. However, evidence also suggests patients tend to have tenderness at "sham" tender points [365]. Palpation of structures beyond the original 18 standardized sites may help to determine the degree of tenderness and how widespread it is. Muscular sites are recommended. While palpating muscles, there should be inclusion of palpation of bony structures, such as the lateral epicondyle, scapular spine, C7 spinous process, and lumbar spinous process. Fibromyalgia may be associated with allodynia and hyperalgesia. There may be some limitation on range of motion. However, although active range of motion to an extreme may elicit or augment the patient's pain, the final extent of that range of motion is generally nearly or completely normal.

DIAGNOSTIC CRITERIA

The current diagnostic criteria, and thus the patient's history, should concentrate on establishing the presence of pain in at least four of five body regions:

- Left upper region, including the shoulder, arm, or jaw
- Right upper region, including the shoulder, arm, or jaw
- Left lower region, including hip, buttock, or lower extremity
- Right lower region, including hip, buttock, or lower extremity
- Axial region, including the neck, back, chest, or abdomen

The diagnosis of fibromyalgia is made solely based on the history and may be made without any objective findings and/or diagnostic tests. However, an examination is essential and some testing is often needed to rule out other diagnoses that may be causing or aggravating the symptoms.

Prior diagnostic research criteria required muscle tenderness (tender points[,366]. More recently, the criteria were changed as above to only require widespread pain due to reported: (1) lack of common performance of the tender points examination in clinical settings, and (2) improper performance of the tender points examination [282].

The diagnostic criteria are reported to have sensitivity of 86% and specificity of 90% [359]; however, particularly due to the subjectivity of the criteria, these estimates would not be applicable to compensation and litigation circumstances.

There are no quality studies to support the routine use of any diagnostic testing for the evaluation of patients with fibromyalgia. There are selective circumstances where certain tests may be helpful in identifying an underlying condition, such as a rheumatological disorder. Examples of common diagnostic tests for those other disorders include erythrocyte sedimentation rate, rheumatoid factor (and potentially other rheumatological studies such as ANA, cyclic citrullinated peptide), thyroid-stimulating hormone level, complete blood count, vitamin D, and celiac studies [367,368,369,370,371,372].

RISK AND CAUSATION

The prevalence of fibromyalgia has been estimated at 1-2%, or approximately 4-6 million US citizens [345,373,374]. A population-based study assessing both medical records and a survey of Olmsted County, MN estimated that 1.1% of the population had fibromyalgia by medical records, while 5.3% met criteria based solely on a mailed survey, resulting in an overall population-based prevalence estimate of 6.4% [375]. Another study that included assessing comparisons of three sets of criteria found the prevalence rates for the 1990, 2010, and revised 2010 American College of Rheumatology criteria were 1.7%, 1.2%, and 5.4%, with the 5.4% estimate resulting from only subjective criteria [374]. However, the use of surveys without examination methods may miss other confounding diagnoses, which may overestimate the true population-based prevalence rate.

Risk factors for fibromyalgia include the following: female sex, rheumatological disorders, anxiety, depression, bipolar disorder, PTSD, history of physical abuse, history of sexual abuse, childhood emotional abuse and neglect, stress, catastrophizing, panic disorder, psychological distress, phobias, social disadvantage, social support, cognitive difficulties, sleep disorders, obesity, family history, and genetic factors.

Numerous studies have reported increased risk among females [376,377,338,345,338], although large-scale studies show the risks among females are less pronounced when there are population-based survey methods used [374,375] compared with risks found based on clinical case series. Risk is higher among those who are obese [377,378,379,345]. A family history of fibromyalgia/widespread pain and genetics factors are also apparent risks [308,307,376,380-387].

Mental health disorders appear to be critically important risk factors [388]. Depression is the strongest and most widely reported risk and associated factor [338-340,373,377-379,390-405]. Other risks and associated factors include: anxiety [373,338,401,403,405-408], PTSD, history of physical/sexual/emotional abuse, stress [409], social disadvantage [345,373,390,410], social support [411], cognitive difficulties [390,405], psychological distress [347,390], phobias [398], catastrophizing [405,408,412,413], bipolar disorder [345,414], somatic symptom disorder (formerly somatoform pain disorder) [415], somatization [416,417], panic disorder [377,338], familial mood disorder [340], elevated somatic symptom scores [373,418-420], psychological distress [421], health anxiety [418] and even cosmetic use [422]. Personality factors have also been associated with higher Fibromyalgia Impact Questionnaire scores and symptom severity scores, including neuroticism, anxiety, depression, stress, lower self-efficacy, mindfulness, and social support [409]. Divorced or separated marital status is a reported risk, as is smoking [345]. Rates of depression have been described to be as high as 86% [395,397]. High rates of adverse life events and/or a family history of depression have also been reported [396,423,424].

A longitudinal consecutive case series reported 23% of patients with chronic disabling occupational musculoskeletal disorders in a chronic pain program also met criteria for fibromyalgia; those with fibromyalgia had higher MMPI disability profiles with much lower return to work status at one year [425]. However, the data were not adjusted for most of the common, major fibromyalgia risk factors. A second longitudinal consecutive case series from the same clinic found no associations with chronic widespread pain and reduced return to work status [426]. One study found widespread hyperalgesia to pressure and cold in knee osteoarthrosis patients, suggesting altered nociceptive system processing [427], thus suggesting a potential association with reduced exercise or activity.

Rheumatological disorders are well reported risks for fibromyalgia, including rheumatoid arthritis [338,345,360,390,428,429], osteoarthritis, Sjogren syndrome [430], systemic lupus erythematosus [338,391,431], and ankylosing spondylitis. Among rheumatological disorders, worsening disease is associated with greater risk of developing fibromyalgia [390]. There is some evidence fibromyalgia is associated with inflammatory markers (aka biomarkers) including IL-1RA, IL-6, and IL-8 [368,372,369,432,433,434], as well as immune system reactions [376,435-438].

Two large prospective studies found strong risks of widespread pain and fibromyalgia from nonrestorative sleep or sleep problems [439,440] and other studies have also suggested sleep disturbance is a significant associated factor [339,347,441,442]. Fatigue is frequently found [194,443-445] and altered hypothalamic-pituitary-adrenal axis function has been reported [446]. Adrenergic dysregulation is a reported risk [447].

There are many other reported risks including hemochromatosis [448], chronic hepatitis C infection [449,450,451,452], human T-cell lymphotropic virus type I infection [453], autoimmune thyroid disease [454], low vitamin D [378,455], low cortisol levels [456], and epilepsy [457]. One large study also reported increased risks with myocardial infarction, heart disease, stroke, liver disease, kidney disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, and stomach ulcer [345].

There are many commonalities reported between fibromyalgia and other somatic syndromes including: irritable bowel syndrome [338-344], headaches and migraines [338,342,345,346], chronic fatigue syndrome [338,342,347-349], temporomandibular disorders and orofacial pain [350], multiple chemical sensitivity [351], painful bladder syndrome and postural tachycardia syndrome. Risks as high as 20- to 30-fold have been reported with chronic fatigue syndrome. It also has been reported that patients with these somatic syndromes are *more* likely to be not working, suggesting a lack of improvement with work cessation [443].

There are no prospective cohort studies demonstrating occupational risk factors [458] and there is no quality epidemiological evidence that fibromyalgia (or *chronic widespread pain*) are occupational conditions [358,459]. There are no quality cohort or case-control studies. None of the few studies reported have adjusted for the major risk factors (see above). More disability has been reported in those with more physically demanding jobs [460] and one study reported more fibromyalgia among those with more demanding jobs [461]. An increased risk of widespread pain and "fibromyalgia-like syndromes" (at a prevalence rate of 4%) have been reported after motor vehicle collisions [462]. Quality epidemiological studies are necessary to demonstrate causal inferences.

PROGNOSIS

The prognosis for fibromyalgia is primarily (if not entirely) determined by compliance with progressive exercises, primarily aerobic and strengthening. Anti-depressants, cognitive behavioral therapy, fear avoidant belief training, and some other interventions may assist. Among those who are compliant with an evidence-based treatment program, especially the aerobic and strengthening exercises, the outcomes are very good with a high likelihood of recovery.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of fibromyalgia includes:

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatica
- Myositis
- Dermatomyositis
- Other inflammatory myopathies
- Ankylosing spondylitis
- Other spondyloarthropathies
- Myofascial pain syndrome
- Hypothyroidism
- Hyperparathyroidism
- Addison's disease
- Diabetes mellitus
- Anemia(s)
- Central neuropathies
- Systemic peripheral neuropathies
- Multiple sclerosis
- Chronic fatigue syndrome
- Lyme disease
- Chronic hepatitides, especially hepatitis C
- Somatization disorders
- Guillain-Barré syndrome
- Long COVID
- Personality disorders
- Pain disorder (formerly somatoform disorder; psychogenic pain disorder)
- Factitious disorder
- Malingering

One study reported that 34% of patients with fibromyalgia have some neuropathic pain [(463)]. When neuropathic pain is present, the probability of an alternate diagnosis rises and should be carefully evaluated. In the event the patient with confirmed fibromyalgia is found to also have neuropathic pain, the ACOEM Neuropathic Pain Guideline may be useful to supplement this Fibromyalgia Guideline.

There is potential overlap between fibromyalgia and myofascial pain. Fibromyalgia involves widespread pain, typically involving most body regions. Myofascial pain syndrome involves a limited area. A distinction of tender points (fibromyalgia) from trigger points (myofascial pain) has also been used to attempt to distinguish these disorders. “Tender points” is a term used to characterize unusually tender areas of muscle, tendon, or over boney prominences that reproduce the patient’s pain when palpated. Trigger points include those points with tenderness, “knots” of muscle or overlying connective tissue, reproduction of the patient’s pain when palpated, and elicitation of symptoms distally during palpation (see also Trigger Points and Myofascial Pain in the ACOEM Shoulder Disorders guideline).

DIAGNOSTIC RECOMMENDATIONS

ANTIBODY TESTING

ANTIBODY TESTING TO DIAGNOSE FIBROMYALGIA

Recommended

Antibody testing is strongly recommended as a selective screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) in patients with fibromyalgia.

Strength of evidence Strongly Recommended, Evidence (A)
Level of confidence High

Indications

Patients with fibromyalgia without prior diagnostic evaluations, or with incomplete evaluations who have symptoms suggestive of a systemic rheumatological disorder. Diagnostic testing should generally include an erythrocyte sedimentation rate. Other tests may include rheumatoid factor (Tan et al., 2016, Jalil et al., 2016, Silveira et al., 2007, Wolfe et al., 1991), antinuclear antibody level (Merrill et al., 2014), anti-citrullinated protein antibodies, and others (Metyas et al., 2016, Serdaroğlu et al., 2008). There should be a low threshold for thyroid stimulating hormone testing as autoimmune, anti-thyroid immunological problems have been reported in fibromyalgia patients (Bazzichi et al., 2007, Ahmad et al., 2015, Nishioka et al., 2017), and TSH is a normal test for evaluation of depressive disorders. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits

Diagnosing an unknown condition.

Harms

Negligible, other than may result in another medical evaluation for a false-positive test.

Frequency/Dose/Duration

One or two evaluations. IgM may require only one evaluation/test. A second evaluation may be indicated when either there is a significant change in symptoms. A second test approximately 4-6 weeks later is also needed where, e.g., the finding is IgG and there is a need to show at least 4-fold increased IgG to secure a diagnosis. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale

Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false

positives, especially if there is a low pre-test probability which may require additional evaluation(s). Measurement of antibody levels and TSH is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antibodies; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 26 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 26 articles, 2 in CINAHL, 3 in Cochrane Library, 14,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 6 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL MRI

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) FOR DIAGNOSING FIBROMYALGIA

Not Recommended

Functional magnetic resonance imaging (fMRI) is not recommended for diagnosing fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Many moderate-quality studies suggest that cortical changes identifiable on fMRI may differ between normal subjects and patients with fibromyalgia (Gracely et al., 2002, Lopez-Sola et al., 2014, Lopez-Sola et al., 2016, Aster et al., 2022, Martucci et al., 2019, Ichesco et al., 2016, Bosma et al., 2016, Truini et al., 2016, Staud, 2011, Jarrahi et al., 2017, Ioachim et al., 2023, Mosch et al., 2023). Although there are research studies with suggested changes, there are no quality studies indicating that the findings on fMRIs are of use to alter the

clinical course. There also are a lack of sufficiently sized studies to indicate that fMRI has adequate sensitivity and specificity to permit identification of the presence or absence of fibromyalgia. The clinical applications of fMRI have thus not been defined. Functional MRI is minimally invasive, has low adverse effects, is high cost, has some evidence of showing differences in patients with fibromyalgia, but has no quality evidence suggesting that it affects the clinical course. Therefore, the use of fMRI is not recommended for the diagnosis of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Functional magnetic resonance imaging, fMRI; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 115 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 115 articles, 3 in CINAHL, 11 in Cochrane Library, 9440 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 7 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) OR POSITRON EMISSION TOMOGRAPHY (PET) FOR DIAGNOSING FIBROMYALGIA

Not Recommended

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are not recommended for the evaluation of patients with fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Two moderate-quality studies suggest abnormal findings are present among patients with fibromyalgia compared with controls (Seo et al., 2021, Albrecht et al., 2019). One moderate-quality study suggested that SPECT was helpful in predicting ketamine response in

hyperalgesic patients with fibromyalgia (Guedj E, 2007). SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions. However, aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with fibromyalgia. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. SPECT and PET scanning are minimally invasive, have negligible adverse effects, are high cost, and have no quality evidence on their ability to affect the management of fibromyalgia. Therefore, SPECT or PET are not recommended for the evaluation of patients with fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Single-photon emission computed tomography, SPECT, Positron emission tomography, PET; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 21 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 21 articles, 5 in CINAHL, 5 in Cochrane Library, 812 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NONSPECIFIC INFLAMMATORY MARKERS

NONSPECIFIC INFLAMMATORY MARKERS TO SCREEN FOR INFLAMMATORY DISORDERS

Sometimes Recommended

Erythrocyte sedimentation rate, C-reactive protein (CRP), and other inflammatory markers are selectively recommended to screen for signs of systemic inflammation in patients with fibromyalgia.

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Patients with fibromyalgia without prior diagnostic evaluations, or with incomplete evaluations who have symptoms suggestive of a systemic rheumatological disorder. These tests particularly include erythrocyte sedimentation rate (Sanada et al., 2015) and C-reactive protein.

Benefits

Diagnosing an unknown condition.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale

Erythrocyte sedimentation rate is the most commonly used systemic marker for nonspecific, systemic inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein has been linked with an increased risk of coronary artery disease. However, it is also a nonspecific marker for other inflammation. Other nonspecific markers of inflammation include ferritin and an elevated protein-albumin gap; however, those two markers appear to have no known clinical roles. Cytokines are also being evaluated among fibromyalgia patients (Wallace et al., 2015). CRP and ESR measurements are minimally invasive, have low risk of adverse effects, and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with fibromyalgia without clear definition of a diagnosis and/or with incomplete explanation of rheumatological symptoms. However, test results should be interpreted cautiously as the specificity is not high. The ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended, as the utility of such wide batteries of tests is unclear.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Non-specific inflammatory markers; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 0 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 0 articles, 11 in CINAHL, 0 in Cochrane Library, 5,670 in Google Scholar, and 0 from other sources†. Of the 4 articles considered for inclusion, 4 randomized trial and 0 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANSAR TESTING

ANSAR TESTING FOR DIAGNOSING FIBROMYALGIA

Not Recommended

ANSAR testing is not recommended to assist in diagnosing fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

ANSAR has not been shown to alter the clinical management of patients with fibromyalgia. The value of identifying abnormalities in autonomic tone, if they exist, has not been demonstrated. The value of pharmacologically treating such abnormalities if they are clinically silent and manifested by positive test results has also not been identified. ANSAR is noninvasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with fibromyalgia. There may be a very limited indication for those with autonomic neuropathy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ANSAR, autonomic nervous system; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 53 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 53 articles, 8 in CINAHL, 18 in Cochrane Library, 13,600 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NEEDLE EMG AND NERVE CONDUCTION STUDIES

NEEDLE ELECTROMYOGRAPHY (EMG) AND NERVE CONDUCTION STUDIES TO DIAGNOSE FIBROMYALGIA

Not Recommended

Needle electromyography (EMG) and nerve conduction studies are not recommended for evaluation of patients with fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Needle EMG and nerve conduction studies are often helpful to define the location and extent of neurological impairments (e.g., see the ACOEM Low Back Disorders, Cervical and Thoracic Spine Disorders, and Hand, Wrist and Forearm Disorders Guidelines). Needle EMG and nerve conduction studies are minimally invasive, have minimal adverse effects, are moderately costly, and have not been found to be diagnostically helpful outside of the evaluation of symptoms consistent with neurological impingement. Therefore, they are not recommended for routine diagnosis in patients with fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: nerve conduction study, needle EMG; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 0 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 0 articles, 2 in CINAHL, 1 in Cochrane Library, 1,740 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SURFACE EMG

SURFACE ELECTROMYOGRAPHY (EMG) FOR DIAGNOSING FIBROMYALGIA

Not Recommended

Surface electromyography (EMG) is not recommended for the evaluation of fibromyalgia. There are selective indications for use with biofeedback.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

Surface EMG has no demonstrated value in the diagnosis or treatment of fibromyalgia by way of altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training and gait analysis for musculoskeletal and/or neurologic disorders. However, it has no established use in the management of fibromyalgia and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: surface EMG, surface electromyography; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 6 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 6 articles, 0 in CINAHL, 3 in Cochrane Library, 1160 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOCAL ANESTHETIC INJECTIONS

LOCAL ANESTHETIC INJECTIONS FOR DIAGNOSING FIBROMYALGIA

Not Recommended

Local anesthetic injections are not recommended for diagnosing fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

There are no quality studies demonstrating the clinical utility of injections for the diagnosis and evaluation of fibromyalgia. These injections are invasive, have adverse effects, are moderate to high cost, and have no evidence of efficacy. Therefore, they are not recommended for the diagnosis of fibromyalgia. However, there are other indications for the use of local anesthetic injections.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: local anesthetic injections, anesthetics, local; fibromyalgia, CRPS; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 9 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 9 articles, 1 in CINAHL, 2 in Cochrane Library, 7750 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL CAPACITY EVALUATIONS

FUNCTIONAL CAPACITY EVALUATIONS (FCES) FOR FIBROMYALGIA

Not Recommended

Functional capacity evaluations (FCEs) are not recommended for evaluating patients with fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

FCEs are one of the few means to attempt to objectify limitations and are frequently used in the workers' compensation system. However, there are no quality studies of FCEs for evaluation of patients with fibromyalgia.

Additionally, patients with fibromyalgia are believed to be particularly prone toward self-limitations making these evaluations less reliable and particularly challenging in patients

with fibromyalgia. FCEs have no quality evidence for evaluation of fibromyalgia, are prone towards significant patients supplying poor effort in these evaluations, are high cost and thus, are not recommended for evaluation of patients with fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Functional capacity evaluations, FCE; fibromyalgia; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 34 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 34 articles, 0 in CINAHL, 4 in Cochrane Library, 16,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TREATMENT RECOMMENDATIONS

The primary purpose of treatment recommendations for fibromyalgia is to replace maladaptive coping with more adaptive coping skills, reduce inactivity or bed rest and improving functional daily activities and quality of life. Therapies should assist physical functioning but also improve level of confidence. Shared decision-making may be a useful strategy, although education about the primacy of progressive aerobic exercise often needs to be emphasized. Ultimate benefits include improving pain, increasing function, physical capacity and endurance.

ACTIVITY MODIFICATION AND EXERCISE

REDUCED ACTIVITY OR BED REST FOR FIBROMYALGIA

Not Recommended

Reduced activity and/or bed rest is not recommended for fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

There is no evidence that reduced activity and/or bed rest is helpful for fibromyalgia; it has been found to be unhelpful for low back pain and other conditions. Although reduced activity and bed rest have been used to treat patients with fibromyalgia, they are believed to be strongly contraindicated based on promoting debility and reduced functional capacity. While noninvasive, reduced activity and/or bed rest are costly (due to lost time) and have documented adverse effects beyond those associated with deconditioning (e.g., worse 6-minute walk, muscle weakness, torque generation, sit-stand), such as pulmonary emboli (Koop et al., 2015). Reduced activity and bed rest are also thought to be strongly contraindicated because patients with fibromyalgia are known to benefit from exercise rather than sedentary activities or bed rest. Therefore, reduced activity and/or bed rest are not recommended for fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: bedrest, bed rest; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 1320 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FEAR AVOIDANCE BELIEF TRAINING FOR FIBROMYALGIA

Recommended

Inclusion of fear avoidance belief training during the course of treatment is recommended as first line treatment for the treatment of fibromyalgia. Other first line treatments are aerobic exercise, education, and, if medication is indicated, anti-depressant medications (SSRIs, Norepinephrine reuptake inhibitors are first line).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

All patients with fibromyalgia, especially with vocalized fear avoidance beliefs.

Benefits

Faster return to normal activities

Harms

Negligible

Frequency/Dose/Duration

Variable as needed

Rationale

There are no quality trials of fear avoidance belief training. One post hoc analysis of a moderate quality trial found better results among those with reduced fear avoidance beliefs ("kinesiophobia"). One study documented that patients expected stress management to be efficacious (82%), while 50% felt aerobic exercise would be beneficial, and 30% felt aerobic exercise would worsen symptoms (Wigers et al., 1996). The patients mostly desired usual care and felt it would be beneficial (70%). Yet, the aerobic exercise group experienced the greatest benefits compared to the other treatments. As the evidence supporting exercise for fibromyalgia is strong, this suggests that fear avoidance beliefs ("kinesiophobia") are prevalent in these patients. These beliefs may also require additional supervised appointments to encourage and demonstrate the efficacy of exercise prior to transitioning to a home-based program. Fear avoidance belief training is not invasive, has negligible adverse effects, is low cost, is believed to be important in managing these patients and inclusion of these principles in the course of exercise training or supervision is thus recommended as first line treatment for the treatment of fibromyalgia. Other first line treatments are aerobic exercise, fear avoidance belief training and antidepressants (SSRIs, Norepinephrine reuptake inhibitors are first line).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Fear of avoidance belief training, fear, avoid, avoidability, avoidance, avoidances, avoidant, beliefs, culture, education, training, train, trained, trainings, trains; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 4 in CINAHL, 4 in Cochrane Library, 12,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AEROBIC EXERCISE FOR FIBROMYALGIA

Recommended

Aerobic exercise is moderately recommended as first-line treatment for the treatment of fibromyalgia. Other first-line treatments are education, fear avoidance belief training, and, if indicated, antidepressant medications (SSRIs and norepinephrine reuptake inhibitors are first-line treatments).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence High

Indications

All patients with fibromyalgia are thought to benefit from aerobic exercise. Motivation is an important factor. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (Liguori G, 2020) with regard to health screening and risk stratification. There is quality evidence of an additive benefit with cognitive behavioral therapy (CBT,van Koulil et al., 2011, van Koulil et al., 2010, Serrat et al., 2022).

Benefits

Improved pain, function, physical capacity, and endurance. Improved sleep.

Harms

Negligible. Vocalized pain worsening when beginning aerobic exercise is common in fibromyalgia patients, but is mandatory to work through to experience meaningful functional gains. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Intolerance of weight bearing in severe lower extremity osteoarthrosis, resulting in the need to potentially switch to aquatic or other reduced weight-bearing aerobic exercise. Other musculoskeletal disorders are possible (e.g., plantar heel pain).

Frequency/Dose/Duration

A structured, progressive walking program at least 60-120 minutes per week, targeting at least 60-85% of predicted maximum heart rate (Da Costa D, 2005). One study used two 50-minute sessions per week for 20 weeks (Acosta-Gallego et al., 2018). One study suggested better results with greater numbers of steps taken per day (Kaleth AS, 2014). Stationary exercise cycles and bicycling are generally not thought to be as helpful due to static use of the torso, although are superior to inactivity and may be reasonable options for select motivated patients. The activity that the patient will adhere to is believed to be the one most likely to be effective, given that compliance is a recognized problem. Patients should be encouraged to maintain aerobic exercises on a long-term basis for preventive health consideration. Typically initiated with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional supervised visits. Additional supervised appointments may be selectively needed, but should demonstrate ongoing, incremental functional gains. Transition to home exercise program.

Indications for discontinuation

Aerobic exercise should not be abandoned in these patients, excepting short term for significant disease, myocardial infarction, etc. Discontinuation of supervised exercise may be considered based on non-compliance, failure to progress, development of another disorder, or reaching a 4- to 6-week timeframe.

Rationale

Aerobic exercise has been used for treatment of fibromyalgia (Sosa-Reina et al., 2017, Bidonde J, 2017, Andrade et al., 2019, Chen et al., 2022, Zhang et al., 2022, Albuquerque et al., 2022, Couto et al., 2022, Correyero-León et al., 2023). Aerobic exercise has been consistently shown to be beneficial for treating patients with fibromyalgia (see evidence table). Motivation is also an important factor. A few trials have compared aerobic with strengthening exercises, mostly finding comparable efficacy (Hooten et al., 2012, Kayo et al., 2012), and superior to flexibility/stretching exercises (McCain et al., 1988, Valim et al., 2003, McCain, 1986).

Although few studies have directly assessed low vs. moderate vs. high-intensity of aerobic exercise, the available studies generally suggest better results with more intense aerobic exercise programs than low intense programs (e.g., self-paced walking). One trial of moderate- (45 min at 65-70% HR max.) compared with high-intensity interval cycle ergometer training (4 cycles of 4min at 80-95% HR max with 3min recovery intervals at 70% HR max.) for 35 min sessions for 5 weekly sessions for 6 weeks in addition to strengthening and stretching and found no significant differences other than superiority to a usual care group (Atan et al., 2020).

Combinations of exercises have been found superior to individual types of exercise (Rooks et al., 2007), and addition of stretching was found helpful in one study (Gómez-Hernández et al., 2020). One study found superiority of aerobic exercise to Qigong (Stephens S, 2008). One study reported equivalence with tai chi, however had selection biases for subject

inclusion and lack of progressive aerobic exercise which was "walking" for 30 min without pace specifications (Wang et al., 2018). These findings indicate the primacy of aerobic exercises for treatment of fibromyalgia, likely supplemented by strengthening exercises.

Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong benefits, and thus is highly recommended. Patients need to be eventually transitioned to a sustainable, home-based program after showing independence. Aerobic exercise is recommended as first line treatment for the treatment of fibromyalgia. Other first-line treatments are aerobic exercise, fear avoidance belief training and, if indicated, anti-depressant medications (SSRIs and norepinephrine reuptake inhibitors).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Aerobic exercise, cardiovascular exercise; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 52 articles in PubMed, 23 in CINAHL, 60 in Cochrane Library, 11,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 14 from PubMed, 9 from CINAHL, 0 from Cochrane Library, 13 from Google Scholar, and 0 from other sources. Of the 75 articles considered for inclusion, 63 randomized trials and 12 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STRENGTHENING, STABILIZATION, AND RESISTANCE EXERCISE FOR FIBROMYALGIA

Recommended

Strengthening, stabilization, and resistance exercise is moderately recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs and norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as strengthening exercises.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

All fibromyalgia patients, generally added either after or with initiation of an aerobic exercise program. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (Liguori G, 2020) with regard to health screening and risk stratification. There is quality evidence of an additive benefit of cognitive behavioral therapy (CBT) to aerobic exercise, which may apply to strengthening exercise prescriptions (van Koulil et al., 2011, van Koulil et al., 2010, Serrat et al., 2022, Jay et al., 2015).

Benefits

Improved function, strength, and endurance. Improved ability to perform strength-demanding job tasks

Harms

Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Other musculoskeletal disorders possible (e.g., strain).

Frequency/Dose/Duration

Typically start with 2-3 visits a week; demonstrate evidence of functional improvement within first 2-3 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises.

Indications for discontinuation

Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4- to 6-week timeframe.

Rationale

Strengthening, stabilization, and/or resistance exercise have been used for treatment of fibromyalgia (Jones, 2015, Nelson, 2015, Sosa-Reina et al., 2017, Andrade et al., 2019, Bidonde J, 2017, Kim et al., 2019, Vilarino et al., 2021, da Silva et al., 2022, Bastos et al., 2023, Rodríguez-Domínguez et al., 2023).

There is quality evidence that strengthening exercise is helpful for treatment of fibromyalgia (see evidence table). Studies have suggested benefits associated with strengthening exercises as compared to either flexibility/stretching exercises (Jones et al., 2002, Park et al., 2021, McCain et al., 1988, Valim et al., 2003, McCain, 1986), no exercise (Hakkinen et al., 2001), or sophrology (Silva et al., 2019). Strengthening exercises have also been found to be comparable to aerobic exercises in a few studies (Hooten MW, 2012, Kayo AH, 2012),

although the evidence base is significantly stronger and more sizable for aerobic exercise; as well, one of those studies advanced the strengthening exercises at twice the pace of advancing the aerobic exercises. Measures of strength and function improved in one trial (Kingsley JD, 2005). Resistance exercise has been found superior to relaxation (Larsson et al., 2015). Balance training has also been shown to have benefits compared with flexibility (Kibar et al., 2015). Combinations of exercises has been found superior to individual types of exercise (Rooks et al., 2007, Castel et al., 2013, Sanudo et al., 2011), and addition of stretching was found helpful in one study (Gómez-Hernández et al., 2020).

Strengthening, stabilization, and resistance exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for indications, and thus are recommended. As a considerably larger evidence base suggests at least equivalence if not superiority of aerobic exercise, strengthening exercises should generally be adjunctive to aerobic exercise. Patients need to be eventually transitioned to a sustainable, home-based program after showing independence. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as strengthening exercises.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Strengthening exercise, stabilization, resistance training; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 59 articles in PubMed, 23 in CINAHL, 7 in Cochrane Library, 16,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 20 from PubMed, 2 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 58 articles considered for inclusion, 49 randomized trials and 9 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STRETCHING EXERCISES FOR FIBROMYALGIA (NON-YOGA)

Not Recommended

Stretching and flexibility exercise is not recommended for treatment of fibromyalgia, other than for use by patients with significant functional deficits.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Stretching exercise has been used for treatment of fibromyalgia (de Lorena et al., 2022, Kim et al., 2019). There is no quality evidence that proves that stretching exercises are solely helpful for treatment of fibromyalgia despite widespread use. Stretching and flexibility exercises have been found to be inferior to aerobic exercise in multiple trials (Valim et al., 2013, Bricout et al., 2015, Reid et al., 2014, Pica et al., 2014) and other trials have reported stretching exercises were inferior to strengthening exercises (Jones et al., 2002)(Park et al., 2021)(McCain et al., 1988, Valim et al., 2003, McCain, 1986), Tai Chi (Wang C, 2010), and balance training (Kibar S, 2015). One trial suggested superiority of stretching to treatment as usual (de Lorena et al., 2022); however that study design is susceptible to attention/treatment-as-usual bias. One trial suggested equivalency with CBT (Matsutani et al., 2023). A Cochrane review also found somewhat similar results of low-to-no efficacy (Kim et al., 2019). Combinations of different types of exercise have evidence of efficacy (Castel et al., 2013, Sanudo et al., 2010, Hammond et al., 2006).

Stretching exercises are often used in combination with aerobic and strengthening exercises, from which a patient commonly then selects only stretching as a surrogate for exercise compliance; in the case of fibromyalgia, data suggest that that substitution would result in lack of, or minimal progress. Stretching exercises are not invasive, have no adverse effects other than potentially delaying improvement when used preferentially over more effective exercises, are moderate cost in aggregate, have evidence of minimal to no efficacy and thus are generally not recommended. Stretching/flexibility exercises may be selectively indicated when a patient has treatable, functionally significant reductions in range of motion.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Stretching exercises, Muscle stretching exercises; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 17 articles in PubMed, 8 in CINAHL, 42 in Cochrane Library, 1930 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 39 articles considered for inclusion, 37 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

YOGA FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of yoga to treat patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are two moderate-quality trials by the same research group that have been suggested as showing potential efficacy; however, both trials are comparisons with wait-listed controls and thus are significantly biased in favor of the intervention (Carson JW, 2010, Carson JW, 2012). Yoga is not invasive, has negligible adverse effects, and is low to moderate cost in aggregate. However, the literature base is slim and susceptible to large biases. Therefore, there is no recommendation on the use of yoga to treat fibromyalgia. There are other exercises with proven efficacy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Yoga; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 2 in CINAHL, 1 in Cochrane Library, 10,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 2 randomized trial and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PILATES FOR FIBROMYALGIA

Sometimes Recommended

Pilates is selectively recommended to treat patients with fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as pilates.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Because the quality evidence is markedly more robust for and the development of improved functional capacity is more likely with either progressive land-based aerobic and/or aquatic exercise, pilates is selectively recommended for patients who strongly prefer pilates. Pilates may be an option for severely affected patients as a step towards progressive aerobic and/or aquatic exercises.

Benefits

Reduced fibromyalgia symptoms. Evidence of improved objective measures and functional capacity is present for aerobic exercises and somewhat for aquatic exercise, but is not yet shown for pilates.

Harms

Negligible. May be associated with delayed recovery in comparison with either progressive land-based aerobic and/or aquatic exercise.

Frequency/Dose/Duration

The highest-quality trial used 50 minutes twice per week for 12 weeks (Medeiros et al., 2020).

Indications for discontinuation

Independence in performing exercises, advancement to other progressive exercises, non-compliance.

Rationale

Pilates has been used for the treatment of fibromyalgia (Jesus et al., 2022). One trial suggested comparable efficacy between mat pilates and aquatic therapy (Medeiros et al., 2020). Another moderate-quality comparative trial showed comparable efficacy with ill-defined, non-benchmarked aerobic exercise doses (Franco et al., 2023). Another moderate-quality trial found pilates to be effective compared with usual care (Komatsu et al., 2016). There is one low-quality study suggesting potential efficacy (Altan et al., 2009).

Pilates is not invasive, has negligible adverse effects, is low to moderate cost in aggregate depending on the degree of supervision, and has some quality evidence of efficacy. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as pilates.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: pilates; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 11 articles in PubMed, 6 in CINAHL, 27 in Cochrane Library, 1600 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AQUATIC THERAPY FOR FIBROMYALGIA

Sometimes Recommended

Aquatic therapy, including deep water running, is moderately recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as aquatic therapy.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Moderate to severe fibromyalgia, non-weight bearing status or partial weight-bearing (e.g., extreme obesity, significant hip/knee joint disease). Motivation is an important factor. May also be preferential, and therefore aquatic therapy is selectively recommended for patients who prefer swimming over walking. Must be highly motivated, especially to maintain exercises after cessation of formal therapy (Andrade et al., 2019).

Benefits

Improved pain, function, fatigue, depression, improved endurance, increased ventilatory anaerobic threshold, reduced fibromyalgia symptoms (Andrade et al., 2017, Acosta-Gallego et al., 2018). Improved sleep.

Harms

Negligible

Frequency/Dose/Duration

One trial of deep water running (60-minute sessions, 3 times per week) targeted the anaerobic threshold for 40 min of the session for 15 weeks (Assis et al., 2006). Another study was of aquatic therapy 3 times/week at 50-80% of predicted heart rate maximum for up to 16 weeks (Munguia-Izquierdo et al., 2008). Another study used 50 min/day, 3 days a week for 6 weeks. In infrequent cases, may need up to 12 weeks to become independent . Another study used two 50-minute sessions per week for 20 weeks (Acosta-Gallego et al., 2018).

Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2-3 weeks to justify additional supervised visits. Program should include up to 4 weeks of swimming or aquatic therapy with a significant aerobic component. Subsequent progression to a land-based, self-directed physical activity or self-directed aquatic therapy program by 6-8 weeks. For a minority of patients with fibromyalgia, aquatic exercise may be the preferred method. In these few cases, the program should become self-managed and if any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program that is primarily aerobically-based.

One trial that followed patients after cessation of therapy documented reduction in gains, which indicates the importance of ongoing exercise (Andrade et al., 2019).

Indications for discontinuation

Failure to attend, non-tolerance, failure to progress, or reaching a 4- to 6-week timeframe.

Rationale

Aquatic therapy has been used for the treatment of fibromyalgia (Galvão-Moreira et al., 2021, Plata et al., 2022). Motivation is an important factor.

There are multiple trials suggesting efficacy of aquatic therapy (Mannerkorpi et al., 2009, Munguia-Izquierdo et al., 2008, Gusi N, 2006, Tomas-Carus P, 2008, Tomas-Carus P, 2009, Andrade et al., 2017, Andrade et al., 2019, Cedraschi C, 2004, Vitorino DF, 2006, Assis MR,), including deep water running (Assis et al., 2006). The components and structures of the programs differed among the heterogeneous trials, making direct comparisons difficult. Three trials suggested comparable efficacy to a land-based walking program that targeted same heart rates and time commitments (Acosta-Gallego et al., 2018, Jentoft et al., 2001, Fernandes G, 2016). One trial of only one session per week with only 30 minutes of unspecified "active exercises" suggested lack of efficacy, as it had comparable efficacy with health education, yet the lack of structuring and potential lack of progressive exercises limits the conclusions to draw from this study (Fonseca et al., 2021). A low-quality quasi-experimental trial suggested efficacy of an aquatic program in male patients (Sajedi Sabegh et al., 2021).

First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as aquatic therapy. There are circumstances where aquatic exercise may be particularly indicated for treatment of patients with fibromyalgia. These include patients who are either non-weight-bearing, limited weight-bearing, or highly motivated patients who prefer water-based exercises. Aquatic therapy and swimming is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, and has fairly consistent evidence of efficacy. Therefore, aquatic therapy is recommended for those who would comply with aquatic therapy/swimming.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: non-swimming aquatic therapy, aquatic therapy, hydrotherapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 10 articles in PubMed, 6 in CINAHL, 6 in Cochrane Library, 2520 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 4 from

Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 16 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TAI CHI FOR FIBROMYALGIA

Sometimes Recommended

Tai chi is selectively recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as Tai Chi.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Because evidence for aerobic exercise is considerably stronger, tai chi is generally warranted for selective use among patients who either refuse to perform aerobic exercises, have a strong predilection towards tai chi, and/or have severe debility with a need to begin performing other exercises prior to transitioning to an exercise program that is centered on progressive aerobic exercise. The highest quality study for fibromyalgia excluded patients with thyroid disease or inflammatory arthropathies.

Benefits

Improved FIQ scores, global assessment scores, 6-minute walk test results, and depression symptoms.

Harms

Negligible

Frequency/Dose/Duration

The highest-quality study used twice-weekly sessions lasting 60 minutes for 12 weeks (Wang C, 2010) using 10 forms from the classic yang style of tai chi. The sessions included warm-up,

self-massage, breathing techniques, and relaxation. Home-based tai chi was prescribed for at least 20 min/day.

Indications for discontinuation

Failure to attend, non-tolerance, failure to progress, or reaching a 4- to 6-week timeframe.

Rationale

Tai chi has been used for the treatment of fibromyalgia (Cheng et al., 2019). There are several moderate-quality trials of tai chi for fibromyalgia. The highest-quality trial compared tai chi of different appointment frequencies/durations with aerobic exercise, suggesting trends towards greater results from tai chi of longer duration or higher frequency. However, the trial excluded those who had prior experience with tai chi, while neither excluding nor measuring prior aerobic exercise, providing potential for a significant treatment-as-usual bias; furthermore, the home-based components differed materially (Wang et al., 2018). Another trial by the same research group suggested that tai chi is superior to an education and stretching control group; this trial found evidence of efficacy, although the exercise durations differed significantly between the two groups (60 min vs. 20 min,Wang C, 2010). Another trial suggested efficacy of tai chi compared with an educational control (Jones et al., 2012). One trial of pool-based tai chi reported comparability to a stretching program (Calandre et al., 2009), which is at least somewhat concerning because stretching was found both in this guideline and in a Cochrane review to have no to limited impact on fibromyalgia (Kim et al., 2019). One trial showed improvements compared with a non-treatment control (Wong et al., 2018).

Tai chi is not invasive, has negligible adverse effects, is moderate cost in aggregate when supervised, has some evidence suggesting efficacy, and thus is selectively recommended. Because evidence for aerobic exercise is considerably stronger, tai chi is generally warranted for selective use among patients who either have refused to perform aerobic exercises, have a strong predilection towards tai chi, have severe debility with a need to begin performing other exercises prior to transitioning to an exercise program that is centered on progressive aerobic exercise, and/or have a desire to do both tai chi and aerobic exercise. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as Tai Chi.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: tai chi; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 15 articles in PubMed, 8 in CINAHL, 7 in Cochrane Library, 4,240 in Google Scholar,

and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 6 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SPA THERAPY AND BALNEOTHERAPY FOR FIBROMYALGIA

Not Recommended

Spa therapy and balneotherapy are not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Spa and balneotherapy have been used for the treatment of fibromyalgia (Cao et al., 2021). Spa therapy and balneotherapy are European-based treatments that may be quite heterogenous in content, variously consisting of thalassotherapy, hot baths, exercise, education, mud baths, etc. Many available trials have likely wait-list/delayed treatment/usual care biases (Maindet et al., 2021, Pérez-Fernández et al., 2019, Bağdatlı et al., 2015)(Maindet et al., 2021), while others have differences in dose/attention (Kurt et al., 2016). One trial flew patients from the Netherlands to Tunisia for seaside spa treatments and claimed efficacy versus usual care (Zijlstra et al., 2005). One trial claimed blinding and measured patient blinding success, but it did not report those data; furthermore, patients were administered either a "strongly acidic..sulfate water" or tap water (Fioravanti et al., 2018), thus causing a strong susceptibility to at least partial unblinding. One trial of balneotherapy used an in-pool exercise group, but it did not target exercise, heart rate, or anaerobic goals (Altan et al., 2004). One trial found comparable results with consecutive vs. intermittent treatments, thus showing comparable (in)efficacy (Eröksüz et al., 2020).

Spa therapy and balneotherapy are not invasive, have negligible adverse effects, are high cost, typically consist of quite heterogenous treatments, have no quality evidence of proven efficacy, and thus are not recommended. They are also largely unavailable in the United States.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Spa, balneology, balneotherapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 19 articles in PubMed, 11 in CINAHL, 4 in Cochrane Library, 4070 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 9 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

WHOLE BODY VIBRATION FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against whole body vibration to treat fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Whole body vibration has been used for the treatment of fibromyalgia (Collado-Mateo et al., 2015, Moretti et al., 2018, Bidonde et al., 2017, Dong et al., 2019).

Multiple trials have suggested modest effects or minimal differences (Olivares PR, 2011) and/or reported and emphasized outcomes of unclear importance such as static balance (Adsuar JC, 2012) or dynamic balance (Gusi N, 2010). One trial suggested additive benefits of whole body vibration plus exercise (Alentorn-Geli et al., 2008), although another similar trial emphasized stretching plus strengthening exercises without any apparent aerobic exercise component (Alev et al., 2017). Most of the remaining literature has minimal differences, is susceptible to usual care and contact time biases, and thus efficacy is unclear (Alentorn-Geli et al., 2008, Olivares et al., 2011, Gusi et al., 2010)(Mingorance et al., 2021, Alentorn-Geli E, 2009, Adsuar et al., 2012, Alev et al., 2017, Sanudo et al., 2013, Olivares PR, 2011). Availability and use in the United States is limited. A Cochrane review concluded there was very low quality evidence, high risk of biases, lack of measurement of meaningful outcomes and uncertainty regarding whether it was effective (Bidonde et al., 2017). Whole body vibration device is not invasive, has minimal adverse effects, is moderate cost in aggregate,

has limited evidence of efficacy that needs replication with important outcomes measures, reduced biases and comparisons with known effective therapies, and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: whole body vibrations; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 12 articles in PubMed, 9 in CINAHL, 1 in Cochrane Library, 2,980 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 8 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

WEIGHT REDUCTION FOR FIBROMYALGIA

Recommended

Weight reduction is recommended for treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which weight loss is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Obese patients with fibromyalgia

Benefits

Improved FIQ score, depression, sleep quality and tender point count (Senna et al., 2012).

Harms

Negligible

Frequency/Dose/Duration

1200 kcal/day dietary instruction, with 12-20% protein, 50-55% carbohydrate, 30% fat calories in the quality study (Senna et al., 2012).

Rationale

Weight reduction/weight management has been used for the treatment of fibromyalgia (D'Onghia et al., 2021). There is one moderate-quality trial suggesting some efficacy for weight reduction (Senna et al., 2012). Weight reduction instruction is not invasive, has negligible adverse effects, is low cost, has evidence of efficacy and thus is recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which weight loss is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Weight loss, weight reduction, weight management; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 31 articles in PubMed, 9 in CINAHL, 2 in Cochrane Library, 18,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DIETARY INTERVENTIONS FOR FIBROMYALGIA

Not Recommended

Dietary management, such as a gluten-free diet, is not recommended for treatment of fibromyalgia. There are other indications for dietary management, especially weight loss.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Dietary interventions have been used for the treatment of fibromyalgia (Sanada et al., 2015, Silva et al., 2019, Silva et al., 2021, Lowry et al., 2020, Kadayifci et al., 2022, Almutairi et al., 2022, Cuevas-Cervera et al., 2022)(Maddox et al., 2023). There is one moderate-quality trial suggesting comparable (in)efficacy between a gluten-free diet and a hypocaloric diet (Slim et al., 2015). However, both groups experienced comparable weight reduction and evidence suggests weight reduction is effective (Senna et al., 2012), thus these study results are likely confounded. Dietary changes such as gluten-free diet instruction is not invasive, has negligible adverse effects, is low initial, but may be high cumulative cost, has no quality evidence of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: dietary interventions, diet therapy, dietary therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 27 articles in PubMed. We retrieved 4079 in CINAHL, 18 in Cochrane, 996 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 13 from PubMed, 2 from Cochrane, 3 from CINAHL, 2 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 3 randomized trials and 7 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MEDICATIONS

ORAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) FOR FIBROMYALGIA

Sometimes Recommended

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are selectively recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as NSAIDs.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Fibromyalgia sufficiently severe to require medication. Generally should have been initially treated with aerobic exercises and antidepressants. Although NSAIDs may provide some synergistic effects with tricyclic antidepressants (Abrams P., 2003), NSAIDs also may be less effective with SSRIs than other antidepressants.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best pain medications, especially for workers in safety-sensitive jobs.

Harms

Gastrointestinal (GI) adverse effects are especially prominent in those with past history of gastrointestinal bleeding, the elderly, and those with other diseases, such as diabetes mellitus and rheumatoid arthritis. For those, either cytoprotection or Cox-2 agents are advisable. There is some evidence for increased cardiovascular risks, especially with more selective NSAID agents. There is no clear evidence of cardiovascular harm from the nonselective NSAIDs ibuprofen and naproxen (see further discussion in Low Back Disorders Guideline). Despite widespread use, diclofenac has not demonstrated clear superiority (at least for low back pain, where it has been trialed), yet it may have increased risks for adverse cardiovascular events (McGettigan et al., 2006). Therefore, it is neither recommended nor not recommended for use either alone or in combination with misoprostol.

Frequency/Dose/Duration

Generally, generic ibuprofen, naproxen, or other older-generation NSAIDs are recommended as second-line medications. Acetaminophen is a reasonable alternative, or it can be used as an adjunct, although evidence suggests it is modestly less efficacious for typical musculoskeletal disorders (see Low Back Disorders and Hip and Groin Disorders Guidelines). Over-the-counter (OTC) agents may suffice and may be tried first. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however,

concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastroprotection. For most patients, scheduled dosage may be preferable to as-needed; however prescribing NSAIDs as-needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities generally require more frequent monitoring.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

Oral NSAIDs have been used for treatment of fibromyalgia (Derry et al., 2017). One trial suggested amitriptyline is superior to naproxen, but a combination of those medications trended towards being best (Goldenberg DL, 1986). Thus, there is no unequivocal evidence of NSAID efficacy for the treatment of fibromyalgia. NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for multiple musculoskeletal disorders, and thus are inferred to be mildly effective for fibromyalgia. Therefore, NSAIDs are selectively recommended for patients with fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as NSAIDs. However, diclofenac is not recommended due to apparent increased adverse cardiovascular events (, thus other NSAIDs are recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Oral NSAID, non-steroidal anti-inflammatory drugs; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 10 articles in PubMed, 4 in CINAHL, 18 in Cochrane Library, 14,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACETAMINOPHEN FOR TREATMENT OF FIBROMYALGIA

Sometimes Recommended

Acetaminophen is selectively recommended for select patients with fibromyalgia, particularly those with contraindications for NSAIDs. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as acetaminophen.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Fibromyalgia sufficiently severe to require medication. Generally should have been initially treated with aerobic exercises and antidepressants. Generally, generic ibuprofen, naproxen, or other older-generation NSAIDs are recommended for use unless the patient has a contraindication to NSAIDs. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious for typical musculoskeletal disorders and may be similarly less efficacious for fibromyalgia.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.

Harms

Negligible if used as prescribed in working age populations. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.

Frequency/Dose/Duration

Maximum daily dosage recommendations in healthy adults range from 3g-4g/day. Generally prescribed up to 3.5g/day in divided doses, usually QID dosing. Adults with lower body weight (<150#) and/or significant alcohol use and/or hepatic impairment should generally not exceed 3g/day. Those with major hepatic impairments are often recommended to not consume acetaminophen.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There is one moderate-quality trial suggesting modest efficacy for central pain syndromes, including FM (Meeus M, 2013). There are no sizable quality trials of acetaminophen against placebo for treatment of fibromyalgia. Paracetamol, a close analog, has also not been studied for fibromyalgia, but does have evidence of efficacy for treatment of LBP, although not as successful as diflunisal (Hickey, 1982), mefenamic acid (Evans et al., 1980), indomethacin (Evans et al., 1980), or aspirin (Evans et al., 1980). Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of LBP and is thought to have modest efficacy and thus is recommended for some patients with fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as acetaminophen.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Acetaminophen; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 4 in CINAHL, 1 in Cochrane Library, 5,680 in Google Scholar, and 0 from other sources†. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NOREPINEPHRINE REUPTAKE INHIBITORS (NRIS) FOR FIBROMYALGIA

Recommended

Norepinephrine reuptake inhibitors (NRIs; especially tricyclic antidepressants) are recommended as a first-line treatment for fibromyalgia when medication is needed. Other first-line treatments are aerobic exercise, fear avoidance belief training, and education.

Strength of evidence Recommended, Evidence (C)
Level of confidence High

Indications

Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, antidepressants are trialed before NSAIDs. Some anti-depressants, e.g., some tricyclic and SNRIs may be used for their sedating properties for nocturnal sleep disturbance due the fibromyalgia.

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

TCAs (including amoxapine, amineptine, amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, maprotiline, mianserin, nortriptyline, protriptyline, etc.): Tricyclic antidepressants most commonly cause anticholinergic effects, orthostatic hypotension, weight gain, sedation, and sexual dysfunction. Less common adverse effects include problems with cardiac conduction (Medical Letter, 2023, Medical Letter, 2018). Tricyclic antidepressants during pregnancy have reported jitteriness and convulsions in newborns (Medical Letter, 2023). Some TCAs have been associated with somnolence (Medical Letter, 2018). Amitriptyline: sedation, dry mouth, and weight gain (Medical Letter, 2017, Medical Letter, 2018). In addition, it can cause orthostatic hypotension, sexual dysfunction, and anticholinergic effects such as urinary retention, constipation, blurred vision, and confusion (Medical Letter, 2018).

Frequency/Dose/Duration

Amitriptyline at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until sufficient effects are achieved, a sub-maximal or maximal dose is reached, or adverse effects occur. Trials have also been successful that did not escalate dose beyond starting dose of 25mg/day (Carette et al., 1995). Esreboxetine 2mg/day, increase to 4mg/day at 2 weeks (Arnold et al., 2010, Arnold et al., 2012). Duration of use for pain associated with fibromyalgia patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercise.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

Most trials (Caruso et al., 1987, Goldenberg et al., 1996, Ware MA, 2010, Heymann RE, 2001, Carette S, 1995, Scudds RA, 1989) but not all trials (Carette et al., 1986, Fors et al., 2002) suggest efficacy of norepinephrine reuptake inhibitor anti-depressants for treatment of fibromyalgia pain. Most of the efficacy data are for amitriptyline (Scudds et al., 1989, Heymann RE, 2001, Carette et al., 1995). Data on long-term efficacy are lacking.

Norepinephrine reuptake inhibiting anti-depressants (especially tricyclic antidepressants) are not invasive, have adverse effects that range from modest to intolerable, are low cost, have evidence of some efficacy for treatment of fibromyalgia, and thus are recommended as first-line treatment for the treatment of fibromyalgia when medication is needed. Other first-line treatments are aerobic exercise, fear avoidance belief training, and education.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Norepinephrine reuptake inhibitor, TCAs; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 23 articles in PubMed, 8 in CINAHL, 10 in Cochrane Library, 6,050 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 15 articles considered for inclusion, 15 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) FOR FIBROMYALGIA

Recommended

Selective serotonin reuptake inhibitors (SSRIs) are moderately recommended for patients with fibromyalgia as first-line treatment for the treatment of fibromyalgia when medication is needed. Other first-line treatments are aerobic exercise, fear avoidance belief training, and education.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence High

Indications

Fibromyalgia sufficiently severe to require medication, especially with depression. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on severity of symptoms. Generally, antidepressants are trialed before NSAIDs. If there is significant sleep disturbance, tricyclic antidepressants may be preferable.

Benefits

Improved pain control, improved depression symptoms.

Harms

Common adverse effects observed for the use of selective serotonin reuptake inhibitors can include sleep disturbances, nausea, diarrhea, headache, dizziness, fatigue, sexual dysfunction. Some patients experience weight gain, increased risk of non-vertebral fractures or bleeding. Abrupt discontinuation of SSRIs can cause anxiety, mood destabilization, insomnia, dizziness, nausea, vomiting, or even electric-shock sensations (Medical Letter, 2023).

Frequency/Dose/Duration

Fluoxetine 60mg QD-BID, although there appears to be either a minimal or no advantage of the BID dosing over the 60mg QD dosing. Other SSRI antidepressants include citalopram, escitalopram, fluvoxamine, paroxetine and sertraline (Wolfe et al., 1994, Goldenberg et al., 1996, Anderberg et al., 2000, Norregaard et al., 1995, Arnold et al., 2002, Patkar et al., 2007). Citalopram doses 20-40mg/day. Duration for patients with fibromyalgia may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercise.

Indications for discontinuation

Resolution, development of adverse effects, failure to adhere to a restoration program.

Rationale

Selective serotonin reuptake inhibitors (SSRIs) have been used for treatment of fibromyalgia (Koechlin et al., 2021, Albunayyan, 2022). Multiple moderate-quality trials suggest SSRI antidepressants are effective for treatment of fibromyalgia (Arnold et al., 2002, Goldenberg et al., 1996, Patkar AA, 2007, Anderberg UM, 2000, Pae et al., 2009) in contrast with other pain disorders, with only one negative trial (Norregaard et al., 1995). Studies suggest reduction in symptoms of depression as well as modest reductions in pain. Data for

citalopram conflict regarding efficacy (Anderberg et al., 2000, Norregaard et al., 1995). Data for paroxetine somewhat conflict regarding efficacy (Patkar et al., 2007, Pae et al., 2009).

SSRI antidepressants are not invasive, have low to moderate adverse effects, are moderate cost, have evidence of efficacy for fibromyalgia, and thus are recommended as first-line treatment for the treatment of fibromyalgia when medication is needed. Other first-line treatments are aerobic exercise, fear avoidance belief training, and education.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: selective serotonin reuptake inhibitors, SSRI, citalopram, escitalopram, fluoxetine; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 27 articles in PubMed, 6 in CINAHL, 1 in Cochrane Library, 9070 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 10 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS) FOR FIBROMYALGIA

Recommended

Serotonin norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and milnacipran, are moderately recommended for limited use as second-line treatment of patients with fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as SNRIs.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, antidepressants are trialed before NSAIDs, gabapentin or pregabalin. If there is significant sleep disturbance, SNRI or tricyclic antidepressants may be preferable. Adjunctive cognitive behavioral therapy is an option to provide adjunctive benefit (Ang et al., 2013).

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

Sedating properties may be intolerable and contributing to high dropout rates in the trials. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also have adverse effects including nausea, constipation, diarrhea, dizziness, fatigue, elevated heart rate, elevated blood pressure (Trugman et al., 2014).

Frequency/Dose/Duration

Duloxetine 60mg QD (Murakami M, 2015, Russell et al., 2008) and 120mg PO QD (Arnold et al., 2010, Russell et al., 2008). Milnacipran 50mg BID to 100mg BID (100, 150, 200 mg/day,Matthey et al., 2013, Branco et al., 2011). Duration for patients with fibromyalgia may be as long as indefinitely (Clauw et al., 2013), although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercises.

Indications for discontinuation

Resolution, adverse effects, improvement sufficient to not require medication.

Rationale

Many, but not all quality trials indicate that SNRI antidepressants, including duloxetine and milnacipran, are modestly effective for treatment of fibromyalgia (see evidence table).

SNRI antidepressants are not invasive, have moderate adverse effects, are moderate cost, have extensive evidence of modest efficacy for fibromyalgia and thus are recommended after institution of first-line treatments, especially progressive aerobic exercises. When medications are needed, SSRIs and norepinephrine reuptake inhibitors are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as SNRIs.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Serotonin Norepinephrine Reuptake Inhibitors, SNRI SNRIs; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 57 articles in PubMed, 6 in CINAHL, 10 in Cochrane Library, 2,330 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 26 articles considered for inclusion, 26 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANTS FOR FIBROMYALGIA

Recommended

Noradrenergic and specific serotonergic antidepressants (mirtazapine) are recommended for second-line treatment for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, SSRIs and norepinephrine reuptake inhibitors are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as noradrenergic and specific serotonergic antidepressants.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Low

Indications

Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, more traditional antidepressants are trialed before mirtazapine, NSAIDs, gabapentin or pregabalin. If there is significant sleep disturbance, SNRIs or tricyclic antidepressants may be preferable.

Benefits

Improved pain control, may include reduced sleep disturbance. May reduce symptoms of depression.

Harms

More severe adverse effects include: risky behavior, suicidal ideation, increased depression, rash, blisters, racing or uneven heartbeat, hyponatremia, sudden rigidity, high fever, hallucinations, tremors, profuse sweating and confusion. More common adverse effects include; drowsiness, dizziness, vision changes, (including blurred vision), constipation, weight gain, and dry mouth

Frequency/Dose/Duration

Mirtazapine 15mg QHS for one week, then 30mg QHS. Duration for patients with fibromyalgia may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercises.

Indications for discontinuation

Resolution, adverse effects, improvement sufficient to not require medication.

Rationale

Noradrenergic and specific serotonergic antidepressants have been used for treatment of fibromyalgia (Welsch et al., 2018). There are two moderate-quality trials suggesting substantial efficacy compared with placebo, one of which is large (Miki K, 2016). Another smaller trial also suggested efficacy (Yeephu et al., 2013).

Mirtazapine is not invasive, has moderate adverse effects, is moderate cost, has evidence of efficacy, and thus is selectively recommended as second-line treatment for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, SSRIs and norepinephrine reuptake inhibitors are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, such as noradrenergic and specific serotonergic antidepressants.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Noradrenergic, specific serotonergic antidepressants; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 3 in CINAHL, 3 in Cochrane Library, 9,470 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SEROTONIN RECEPTOR ANTAGONISTS FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of serotonin reuptake antagonists for the treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Studies substantially conflict. One short-term trial of 5 days used IV administrations and suggested short-term but no long-term efficacy (Spath et al., 2004); a second trial of 5 days suggested 2 weeks of benefits (Stratz et al., 2001). Another trial suggested benefits of oral treatment for 10 days (Farber et al., 2001), but another trial suggested non-dose response relationships with response at 5mg but not at 10mg or 15mg (Farber et al., 2000). Serotonin receptor antagonists are either oral or IV, have low to moderate adverse effects, are moderate to high cost in aggregate, and have conflicting evidence of efficacy for fibromyalgia. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TREATMENT TERMS; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 5 in CINAHL, 0 in Cochrane Library, 7,040 in Google Scholar, and 0 from other sources†. Of the 4 articles considered for inclusion, 4 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BUPROPION, TRAZODONE, OR PRAMIPEXOLE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of bupropion, trazadone, and pramipexole for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of bupropion or trazodone for fibromyalgia. There is one trial of pramipexole suggesting efficacy, but no replication after over 10 years (Holman et al., 2005). Bupropion and trazodone are not invasive, have low to moderate adverse effects, and are low to moderate cost. However, in the absence of efficacy, there is no recommendation for the treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bupropion, Trazodone, Pramipexole; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 6 in CINAHL, 3 in Cochrane Library, 2,740 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ATYPICAL ANTIPSYCHOTICS FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of atypical antipsychotics for the treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Data are sparse and conflict regarding efficacy of atypical antipsychotics for treatment of fibromyalgia (Walitt et al., 2016, McIntyre et al., 2014, Calandre et al., 2014)(Potvin et al.,

2012). One trial suggests reduction in depression and pain (McIntyre et al., 2014). One trial of adjunctive use suggested no reduction in pain but improved sleep and mood (Potvin et al., 2012). One comparative trial suggests inferiority to amitriptyline (Calandre et al., 2014). Atypical antipsychotics are not invasive, have moderate adverse effects, are low to moderate cost, but in the absence of efficacy, there is no recommendation for treatment of fibromyalgia. There may be limited indications involving failure of other medications such as progressive exercise, amitriptyline, SNRI antidepressants, and gabapentin.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Atypical Antipsychotics; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 1,800 in Google Scholar, and 0 from other sources†. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NMDA RECEPTOR ANTAGONISTS FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of NMDA receptor antagonists (memantine) for the treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

NMDA receptor antagonists have been used for treatment of fibromyalgia (Kurian et al., 2019). Data are sparse, with only two trials from one research group of memantine. One trial suggested modest reductions in pain (Olivan-Blazquez et al., 2014) and a second study with small sample size suggested changes on MR spectroscopy (Fayed et al., 2014). Memantine is not invasive, has low adverse effects, and is moderate cost. However, with results from only one research group, a second trial from another group is needed before developing guidance on this topic, especially when there is evidence of efficacy for many other treatments.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: NMDA receptor antagonists, Receptors, N-Methyl-D-Aspartate; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 1 in CINAHL, 3 in Cochrane Library, 4,430 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTICONVULSANTS FOR FIBROMYALGIA

Sometimes Recommended

Anticonvulsant medications (gabapentin and pregabalin) are selectively recommended for the treatment of severe fibromyalgia. There is evidence for adjunctive use with antidepressant medications. First-line treatments are aerobic exercise, fear avoidance belief training, and education.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Fibromyalgia sufficiently severe to require medication, often also having sleep disturbance. Aerobic exercises are initially indicated, and/or followed by antidepressants. Generally, antidepressants are trialed before NSAIDs. If there is significant sleep disturbance, SNRI or tricyclic antidepressants may be preferable. Having sufficient pain and other treatments have failed or results have been suboptimal so that generally considered a potential adjunct as a fourth- or fifth-line treatment, after attempting other treatments (aerobic exercise plus, e.g., antidepressant(s), NSAIDs, strengthening exercise, other exercise).

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness, nystagmus, ataxia.

Frequency/Dose/Duration

Frequency and dosing are based on the medication prescribed. Gabapentin dosing in the highest quality study required titration at 300mg a day for 1 week at bedtime, then 300mg BID for 1 week, then 1,200mg/day for 2 weeks, then 600mg TID for 2 weeks, then 600mg BID, and 1,200mg QHS. If not tolerated, 2,400mg/day, dose reduced and mean dose 1,800mg/day (Arnold, 2007). Pregabalin dosing in the higher quality studies is 300-450 mg PO QD (Ohta et al., 2012, Roth et al., 2012), with an initial dose prescribed of 150mg PO QD. Duration of use for fibromyalgia patients may be indefinite, although many of these patients do not require indefinite treatment as the condition usually often resolves or improves.

Indications for discontinuation

Resolution of pain, lack of efficacy, or development of adverse effects. Monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.

Rationale

Placebo-controlled trials have investigated the use of anticonvulsants, particularly pregabalin, for treatment of fibromyalgia (Roth T, 2012, Roth T, 2016, Mease et al., 2008, Pauer L, 2011, Ohta H, 2012, Arnold et al., 2007, Crofford LJ, 2005). Multiple trials have also suggested efficacy of combining pregabalin with antidepressant treatment, including paroxetine treatment, which was also superior to combinations with either amitriptyline or venlafaxine. Another trial suggested that the combination of pregabalin with duloxetine was superior to monotherapy (Pauer et al., 2011). Pregabalin combined with duloxetine was proven effective (Gilron I, 2016). Pregabalin added to treatment with various antidepressants (Arnold et al., 2015), as was milnacipran (Mease PJ, 2013).

Gabapentin and pregabalin are not invasive, have significant adverse effects, are moderate cost, and have evidence of modest efficacy. Therefore, they are selectively recommended for patients with fibromyalgia after treatment with aerobic exercise and antidepressants proves insufficient. There is also consistent evidence for an additive benefit of pregabalin during treatment with various antidepressants. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments, of which anti-convulsants are one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Anticonvulsants, Lacosamide; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 16 in CINAHL, 13 in Cochrane Library, 6,960 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 17 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GLUCOCORTICOSTEROIDS FOR FIBROMYALGIA

Not Recommended

Glucocorticoids are not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one low-quality trial, which suggests a lack of efficacy for prednisone (Clark et al., 1985). Glucocorticoids are not invasive in oral forms, have high adverse effects, and are low cost. However, in the absence of evidence of efficacy, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Glucocorticoids, glucocorticosteroids; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 4,870 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DEHYDROEPIANDROSTERONE (DHEA) FOR FIBROMYALGIA

Not Recommended

Dehydroepiandrosterone (DHEA) is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial suggesting a lack of efficacy for DHEA (Finckh et al., 2005). Although DHEA is not invasive in oral forms, it has adverse effects, is low to moderate cost, and has evidence of inefficacy. Therefore, DHEA is not recommended for fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Dehydroepianrosterone, DHEA; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 2 in CINAHL, 2 in Cochrane Library, 1,230 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CALCITONIN FOR FIBROMYALGIA

Not Recommended

Calcitonin is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial suggesting a lack of efficacy for calcitonin (Bessette et al., 1998). Calcitonin is minimally invasive, but it has some adverse effects, is moderate cost, and has evidence of inefficacy. Therefore, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Calcitonin; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 4 in Cochrane Library, 3,350 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VITAMIN D FOR FIBROMYALGIA

Not Recommended

Vitamin D is not recommended for the treatment of fibromyalgia. However, many patients with fibromyalgia may have other indications for treatment with vitamin D.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Vitamin D has been used for treatment of fibromyalgia (Makrani et al., 2017, Ellis et al., 2018, Erkilic et al., 2023, Ali, 2022, Lombardo et al., 2022, Qu et al., 2022, Yang et al., 2023). Many studies have documented low vitamin D levels among many patients with fibromyalgia (Ellis et al., 2018, Elaziz Labeeb et al., 2015, Makrani et al., 2017, Dogru et al., 2017, Ali, 2022), which is not surprising considering the combination of older average age and typically reduced levels of activity in these patients. Quality placebo-controlled trials assessing impacts of vitamin D supplementation on fibromyalgia symptoms somewhat

conflict. Although some trials suggest efficacy (Wepner et al., 2014, Mirzaei et al., 2018)(Wepner et al., 2014), most studies suggest either inconsistent results (Arvold et al., 2009) or lack of efficacy (Knutsen et al., 2014, Lozano-Plata et al., 2021, Warner et al., 2008). The largest study (n=251) which included two different doses of supplementation in addition to placebo was negative both for effects and dose-response relationship (Knutsen et al., 2014). Vitamin D is not invasive, has low adverse effects, and is low cost. However, because most evidence is negative, it is not recommended for the treatment of fibromyalgia. There are many other indications for treatment with vitamin D that are common in this population.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Vitamin D, cholecalciferol; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9 articles in PubMed, 7 in CINAHL, 4 in Cochrane Library, 13,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 6 randomized trials and 6 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MELATONIN FOR FIBROMYALGIA

Recommended

Melatonin is recommended for the treatment of fibromyalgia with sleep disturbance.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Moderate to severe fibromyalgia with sleep disturbance. The sole quality trial required a Visual Analog Scale (VAS) score of at least 50 mm.

Benefits

Improved pain symptoms, improved sleep.

Harms

Negligible

Frequency/Dose/Duration

Melatonin 10mg QHS. May be combined with amitriptyline 25mg QHS (de Zanette et al., 2014) or fluoxetine 20mg QD (Hussain et al., 2011) because both demonstrated some evidence of synergistic effects.

Indications for discontinuation

Sufficient improvement, completion of a course, adverse effects.

Rationale

There is one moderate-quality trial suggesting both efficacy for treatment of fibromyalgia and evidence of synergy with amitriptyline (de Zanette et al., 2014). Another trial suggested efficacy of adjunctive use with fluoxetine, although effects of fluoxetine alone were greater than those of melatonin (Hussain et al., 2011). Melatonin is not invasive, has low adverse effects, is low cost, and has evidence of efficacy. Therefore, it is recommended for selective use in the treatment of fibromyalgia among those with sleep disturbance.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Melatonin; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 7 articles in PubMed, 5 in CINAHL, 6 in Cochrane Library, 3,940 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HORMONE REPLACEMENT THERAPY FOR FIBROMYALGIA

Not Recommended

Hormone replacement therapy is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial suggesting lack of efficacy for treatment of fibromyalgia (Stening et al., 2011). Hormone replacement therapy is not invasive, has low adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended. There are other indications for this treatment.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Hormone replacement therapy, HRT; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 3 in CINAHL, 2 in Cochrane Library, 7,480 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

RALOXIFENE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against raloxifene for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence. Raloxifene is not invasive, has adverse effects, is low to moderate cost, and has no quality evidence; thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Raloxifene; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 231 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OXYTOCIN FOR FIBROMYALGIA

Not Recommended

Oxytocin is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial suggesting lack of efficacy for treatment of fibromyalgia (Mameli et al., 2014). Oxytocin is not invasive by nasal spray, has low adverse effects, is moderate cost, and has evidence of inefficacy; thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Oxytocin; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 3 in Cochrane Library, 2,120 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GROWTH HORMONE FOR FIBROMYALGIA

Sometimes Recommended

Growth hormone is selectively recommended for treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which growth hormone is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe fibromyalgia, at least 5 years duration, with documented low insulin-like growth factor levels <160ng/mL. Negative evaluation for other pituitary diseases, including hormone evaluation and MRI. The highest quality trial also excluded major depression and diabetes mellitus (Bennett et al., 1998).

Benefits

Improved fibromyalgia symptoms, reduced numbers of tender points.

Harms

Edema, arthralgia, muscle pain, diabetes, gynecomastia, carpal tunnel syndrome.

Frequency/Dose/Duration

Growth hormone 0.0125 mg/kg QD for one month. Dose adjusted monthly to maintain IGF-1 level of ~250ng/mL. One study was 9 months and another 12 months duration.

Indications for discontinuation

Sufficient improvement, adverse effects

Rationale

Two moderate-quality trials suggest efficacy in this select fibromyalgia patient population with low IGF-1 levels (Cuatrecasas et al., 2007, Cuatrecasas et al., 2012, Bennett et al., 1998). Growth hormone is minimally invasive, has significant adverse effects, is high cost, has evidence of efficacy in patients with low IGF-1 levels, and thus is highly selectively recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which growth hormone is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Growth Hormone, GH; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 11 in CINAHL, 7 in Cochrane Library, 12,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PYRIDOSTIGMINE FOR FIBROMYALGIA

Not Recommended

Pyridostigmine is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial with two reports suggests lack of efficacy of pyridostigmine (Jones et al., 2007, Jones et al., 2008). Pyridostigmine is not invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Pyridostigmine, Mestinon, Pyridostigmine Bromide; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 3 in CINAHL, 4 in Cochrane Library, 400 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

RITANSERIN FOR FIBROMYALGIA

Not Recommended

Ritanserin is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial suggests lack of efficacy of ritanserin (Olin et al., 1998). Ritanserin is invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ritanserin; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 43 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

S-ADENOSYLMETHIONINE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against S-adenosylmethionine for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

RCT results conflict. Two moderate-quality trials suggest lack of efficacy (Jacobsen S, 1991, Tavoni A, 1987), while one trial suggests some modest efficacy (Volkmann et al., 1997). S-methionine is not invasive, has some adverse effects, and is low cost, but has conflicting evidence of efficacy. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: S-Adenosylmethionine, SAMe, AdoMet; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 70 articles in PubMed, 37 in CINAHL, 3 in Cochrane Library, 317 in Google Scholar, and 0 from other sources†. Of the 4 articles considered for inclusion, 4 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CREATINE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against creatine for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one moderate-quality trial that suggested no differences in fibromyalgia pain and symptoms, although it was associated with improved muscle strength (Alves et al., 2013). Creatine is not invasive, has low adverse effects, and is low cost. One trial suggested no improvement in fibromyalgia scores, although it reported improved strength. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Creatine; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 5 in CINAHL, 3 in Cochrane Library, 5,830 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TERGURIDE FOR FIBROMYALGIA

Not Recommended

Terguride is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial suggests lack of efficacy of terguride (Distler et al., 2010). Terguride is not invasive, has some adverse effects, is low cost, and has evidence of inefficacy. Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Terguride, Teluron; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 1 in CINAHL, 1 in Cochrane Library, 19 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VALACYCLOVIR FOR FIBROMYALGIA

Not Recommended

Valacyclovir is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial suggests lack of efficacy of valacyclovir (Kendall et al., 2004). Valacyclovir is not invasive, has some adverse effects, is low cost, and has evidence of inefficacy. Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Valacyclovir; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 431 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SODIUM OXYBATE FOR FIBROMYALGIA

Recommended

Sodium oxybate is moderately recommended for selective treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which sodium oxybate is one.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Severe fibromyalgia with sleep disturbance.

Benefits

Reduced pain, reduced fatigue, improved sleep

Harms

Nausea, extremity pain, dizziness, headaches, paresthesia, somnolence, renal and urinary disorders.

Frequency/Dose/Duration

Sodium oxybate 4.5-6g QHS (Russell et al., 2009). There was very little advantage of 6g compared with 4.5 g (Russell et al., 2011), but adverse effects were considerably higher.

Indications for discontinuation

Sufficient improvement, adverse effects, intolerance.

Rationale

Several moderate-quality trials suggest that treatment of fibromyalgia with sodium oxybate improved pain, fatigue, and sleep disturbance (Scharf et al., 2003, Russell et al., 2009, Russell et al., 2011, Spaeth et al., 2012, Moldofsky et al., 2010). Sodium oxybate is not invasive, has significant adverse effects, is moderate cost, and has evidence of efficacy for treatment of fibromyalgia. Thus, it is selectively recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which sodium oxybate is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Sodium Oxybate, Xyrem, Alcove; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 9 in CINAHL, 14 in Cochrane Library, 327 in Google Scholar, and 0 from other sources†. Of the 5 articles considered for inclusion, 5 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ZOLPIDEM FOR FIBROMYALGIA

Not Recommended

Zolpidem is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality trial suggests short-term treatment of fibromyalgia with zolpidem improved sleep, but had no effect on fibromyalgia symptoms (Moldofsky et al., 1996). Zolpidem is not invasive, has adverse effects, is low cost, has no evidence of inefficacy for

treatment of fibromyalgia, and thus is not recommended. There are other indications for this medication.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Zolpidem; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 1,110 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

COENZYME Q FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of coenzyme Q for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one small crossover trial suggesting potential efficacy (Sawaddiruk et al., 2019). Another comparative trial comparing acupuncture and coenzyme Q may have a randomization failure in addition to other weaknesses (Vittorio et al., 2020). Two low-quality trials suggest some possible efficacy for coenzyme Q (Wepner et al., 2014, Di Pierro et al., 2017). Coenzyme Q is not invasive, has low adverse effects, and is low cost. However, the available evidence has significant methodological weaknesses. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Coenzyme Q, Ubiquinone; fibromyalgia; controlled clinical trial, controlled trials,

randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 5 in CINAHL, 6 in Cochrane Library, 1,550 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACETYL-1-CARNITINE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against acetyl 1-carnitine for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality trial suggested differences after the midpoint of the trial that favored acetyl 1-carnitine (Rossini et al., 2007). However, at that same point, the dropout rates rose. The results have not been duplicated. Another open-label trial found both groups improved, yet there was no clear explanation for a late difference and possible but erratic effects (Salaffi et al., 2023). Acetyl 1-carnitine is not invasive, has low adverse effects, is low cost, and has two trials suggesting some potential promise. However, both trials have study flaws and somewhat unusual findings, which raises concern on whether there are meaningful results that preclude an evidence-based conclusion. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Acetyl-1-carnitine; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 2 in CINAHL, 2 in Cochrane Library, 368 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTIDIENCEPHALON FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against antidiencephalon to treat patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence for antidiencephalon for treatment of fibromyalgia. Antidiencephalon is not invasive, has adverse effects, is low cost, and has no quality evidence of efficacy to treat fibromyalgia. Thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Anridiencephalon; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 374 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DOLASETRON FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against dolasetron to treat patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Indications

Moderate or severe fibromyalgia.

Benefits

Improvement in pain.

Harms

Constipation. Other reported adverse effects included dizziness, nausea, fatigue, headache.

Frequency/Dose/Duration

12.5mg IV, once a month for 4 months.

Indications for discontinuation

Sufficient improvement, completion of a course, intolerance, adverse effects

Rationale

One trial of dolasetron suggested evidence of efficacy (Vergne-Salle et al., 2011). Dolasetron is invasive, has adverse effects, is moderate to high cost, and has only one trial suggesting efficacy. With intravenous administration required and a lack of replication of the results from the single published trial, another trial of efficacy is needed to make a recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Dolasetron, Anzemet; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 2 in CINAHL, 2 in Cochrane Library, 83 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ZOPICLONE FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against zopiclone to treat patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are two quality studies of zopiclone for treatment of fibromyalgia. The higher quality study suggested no improvement in fibromyalgia, although there was improvement in sleep (Drewes et al., 1991). The second study suggested some improvements in fibromyalgia (Gronblad et al., 1993). All sleep medications may produce habituation, although zopiclone does not produce physical dependency. Zopiclone is not invasive, has adverse effects, and is low cost, but it has conflicting data regarding its utility to treat fibromyalgia. Thus, there is no recommendation. There may be indications regarding sleep, but there are less habituating options for that indication.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Zopiclone, eszopiclone; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 0 in CINAHL, 2 in Cochrane Library, 434 in Google Scholar, and 0 from other sources†. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ONDANSETRON FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against ondansetron to treat patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Rationale

One small trial of ondansetron from 1996 has not been replicated (Hrycaj et al., 1996). Ondansetron is not invasive, has adverse effects, is low to moderate cost, and has some preliminary evidence of efficacy. However, a larger RCT is needed to confirm efficacy before a recommendation can be formulated.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ondansetron, zofran; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 1 in CINAHL, 2 in Cochrane Library, 1,140 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SKELETAL MUSCLE RELAXANTS FOR FIBROMYALGIA

Not Recommended

Skeletal muscle relaxants are not recommended for patients with fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of skeletal muscle relaxants for treatment of fibromyalgia. There is one moderate-quality trial suggesting potential for improved sleep with cyclobenzaprine 1-4mg QHS (Moldofsky et al., 2011), although cyclobenzaprine is unique among skeletal muscle relaxants and is thought to have some antidepressant action. These agents may be counterproductive in patients with depression or dysthymia. One low-quality trial reported a 50% dropout rate (Bennett et al., 1988). Skeletal muscle relaxants are not invasive, have adverse effects, are low cost, have no quality studies showing efficacy and so are not recommended for treatment of fibromyalgia. There are other indications for the use of these agents.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Neuromuscular Agents, Skeletal muscle relaxants, Baclofen, Carisoprodol; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 8 articles in PubMed, 3 in CINAHL, 8 in Cochrane Library, 1.020 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ALPHA1-ANTITRYPSIN FOR FIBROMYALGIA

Not Recommended

Alpha1-antitrypsin is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

One moderate-quality trial found alpha1-antytripsin ineffective for treatment of fibromyalgia (Alegre et al., 2012). Alpha1-antitrypsin is not invasive, has some adverse effects, is moderately costly, has evidence of lacking efficacy, and thus is not recommended for treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Alpha 1 - Antitrypsin; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 4 in CINAHL, 1 in Cochrane Library, 203 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ALPHA-LIPOIC ACID FOR FIBROMYALGIA

Not Recommended

Alpha-lipoic acid is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Two moderate-quality RCTs failed to show clear evidence of efficacy for alpha-lipoic acid in the treatment of fibromyalgia (Gilron et al., 2023, Gilron et al., 2021). Therefore, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Alpha-lipoic acid; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 3 in CINAHL, 2 in Cochrane Library, 893 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SUVOREXANT FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of suvorexant for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Because the sole trial had many methodological issues (Roehrs et al., 2020), there is no quality evidence for use of suvorexant for treatment of fibromyalgia. Therefore, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Suvorexant; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 2 in Cochrane Library, 192 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NALTREXONE FOR FIBROMYALGIA

Not Recommended

Naltrexone is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Naltrexone has been used for the treatment of fibromyalgia (Yang et al., 2023, Partridge et al., 2023, Aitcheson et al., 2023). One high-quality blinded crossover trial found lack of efficacy (Bested et al., 2023), while another similar trial found evidence of modest efficacy

attributable to low-dose naltrexone (Younger et al., 2013). One high-quality, four-arm trial suggested that low-dose naltrexone plus direct transcranial stimulation was not superior to sham/placebo (de Paula et al., 2023). A moderate-quality blinded dose-ranging trial using eight doses (0.75-6.0 mg/day) reported a nonlinear dose-response curve of low magnitude (Bruun-Plesner et al., 2020). Naltrexone is not invasive, has low adverse effects, and is low to moderate cost depending on duration of treatment. However, clear evidence of efficacy is lacking in the highest quality trials. Therefore, it is not recommended. There are other interventions with much stronger evidence of efficacy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Naltrexone, Naloxone, Vivitrol; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 18 articles in PubMed, 3 in CINAHL, 14 in Cochrane Library, 2,050 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 6 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TOPICAL MEDICATIONS AND LIDOCAINE PATCHES FOR FIBROMYALGIA

Not Recommended

Topical medications, such as capsaicin, lidocaine patches, and sports creams, are not recommended to treat patients with fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Capsaicin, lidocaine patches, and sports creams do not have quality evidence of efficacy. They also act peripherally. These agents are not invasive, have low adverse effects, and are low cost (although cumulatively, can be high cost). In the absence of efficacy, they are not recommended for fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: topical treatment, creams, ointments, lidocaine patches; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 8 articles in PubMed, 1 in CINAHL, 6 in Cochrane Library, 2,340 in Google Scholar, and 0 from other sources†. Zero articles met inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OPIOIDS FOR FIBROMYALGIA

Not Recommended

There is consensus that opioids are inappropriate medications for management of fibromyalgia and guidelines advise against use of opioids for these patients (Ngian et al., 2011, Halpern et al., 2015, Carville et al., 2008, Fitzcharles et al., 2011, Fitzcharles et al., 2013, Hauser et al., 2011)(Cunningham et al., 2016, Bruce et al., 2021, da Rocha et al., 2020, Goldenberg et al., 2016, Hermans et al., 2018, Peng et al., 2015, Sarmento et al., 2019). One consecutive case series of fibromyalgia patients at Mayo Clinic found improved pain-related measures after opioids tapering after completion of a rehabilitation program (Cunningham et al., 2016).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Opioids have been used for the treatment of fibromyalgia (Goldenberg et al., 2016, da Rocha et al., 2020).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: opioids, opiates; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies.

We found and reviewed 33 articles in PubMed, 26 in CINAHL, 16 in Cochrane Library, 16,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HYPERBARIC OXYGEN FOR FIBROMYALGIA

Not Recommended

Hyperbaric oxygen is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Hyperbaric oxygen (HBO) has been used for the treatment of fibromyalgia (Cao et al., 2023). There are no sham-controlled trials of HBO. There is one moderate-quality trial suggesting some efficacy for HBO, but it had no sham HBO arm and differences in treatment time were 40 sessions of 90 minutes (3,600 minutes) vs. zero minutes (Efrati et al., 2015).

Another study trialed medication against 60 HBO sessions of 90 minutes (5,400 minutes) vs. undefined minutes of contact time for the medication group (Ablin et al., 2023). Another trial compared HBO, "low-intensity physical exercise," and control (Izquierdo-Alventosa et al., 2020). One low-quality study had low sample sizes and wait-control biases (Curtis et al., 2021). Thus, the available studies are all susceptible to considerable attention/treatment-time biases producing a potentially heavily biased set of studies. HBO is not invasive, other than rare accidents has mostly low adverse effects, is quite high cost, and thus in the absence of clear evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Hyperbaric oxygen therapy, HBOT, Hyberbaric oxygen; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review,

retrospective, prospective studies. We found and reviewed 8 articles in PubMed, 2 in CINAHL, 4 in Cochrane Library, 747 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HOT AND COLD THERAPIES

HOT AND COLD THERAPIES FOR FIBROMYALGIA

No Recommendation

There is no recommendation for the use of hot and cold therapies to treat fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

There is no quality evidence evaluating heat and cryotherapies as stand-alone treatments for fibromyalgia. There is one moderate quality trial of halogen lamp heating unit in addition to multimodal treatment was superior to the treatment alone, but there was no sham or similar control treatment (Brockow et al., 2007). Several studies use cold and/or heat as part of a group of interventions, precluding assessment of an independent effect. Non-proprietary, self-applications are not invasive, have low adverse effects provided excessive cold or heat are not used, and may have no associated costs. However, there are other treatment strategies with demonstrated efficacy in the treatment of fibromyalgia and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Hot therapy, Cold therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 12 articles in PubMed, 4 in CINAHL, 44 in Cochrane Library, 9,840 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of

the 5 articles considered for inclusion, 5 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ALLIED HEALTH INTERVENTIONS

KINESIOTAPING OR TAPING FOR FIBROMYALGIA

Not Recommended

Kinesiotaping is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Moderate

Rationale

One moderate-quality three-arm trial reported no significant benefits from kinesiotaping compared with sham laser or active laser (Hauser et al., 2011). Because laser therapy does not have quality evidence of efficacy, this also suggests that kinesiotaping is ineffective. One trial reported dry needling was superior to cross-tape therapy (Castro-Sánchez et al., 2017). One trial suggested additive benefit of extensive kinesiotaping to spinal stabilization exercises, but appears to have not reported between group differences and had baseline differences (Celenay et al., 2020). Taping is not invasive, has low adverse effects, and is high cost, with most evidence suggesting a lack of efficacy. Therefore, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: athletic tape, kinesiotaping, kinesio tape, taping; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 4 in CINAHL, 2 in Cochrane Library, 1,160 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term

algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MAGNETS OR MAGNETIC STIMULATION FOR FIBROMYALGIA

Not Recommended

Magnets and magnetic stimulation are not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Moderate

Rationale

Magnets and magnetic stimulation have been used for the treatment of fibromyalgia. A sham-controlled trial reported mostly negative results at 6 months (Alfano et al., 2001). Magnets and magnetic stimulation are not invasive, have low adverse effects, are moderately costly, and have no evidence of efficacy. Therefore, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Magnetic Field Therapy, Magnets, Magnetic stimulation; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 57 articles in PubMed, 28 in CINAHL, 29 in Cochrane Library, 12,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 19 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 2 randomized trials and 10 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MUSIC THERAPY FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of music therapy for patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Music therapy has been used for the treatment of fibromyalgia (Vicznesky, 2019). One trial suggested music added to aerobic exercise provided additive benefit; however, it was subject to attention biases (Espí-López GV, 2016). A trial compared to usual care suggested efficacy; however, it was subject to usual care and attention biases (Torres et al., 2018). There are two low-quality studies of music therapy for treatment of fibromyalgia, both suggesting some potential efficacy (Onieva-Zafra et al., 2013), but another suggesting no differences between music and sounds of nature (Lepping et al., 2022). Music therapy may be self-administered, has no adverse effects, may be low cost when self-administered, has no quality evidence of efficacy, and thus there is no recommendation. However, the threshold for attempting this form of treatment when self-administered in conjunction with aerobic and strengthening exercise is low.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: music therapy, music intervention, musical therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 7 articles in PubMed, 7 in CINAHL, 6 in Cochrane Library, 7,050 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HOMEOPATHIC AND HERBAL TREATMENTS FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against the use of herbal or other preparations in patients with fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Herbal, alternative, complementary, or other preparations have been used for the treatment of fibromyalgia (Perry et al., 2017, Vasileios et al., 2022). There is no consistent evidence of efficacy for any herbal or other preparations for treatment of patients with fibromyalgia. One trial compared one combination (ginger, acerola, vitamin C, medowsweet, royal jelly, passiflora, camomile, quackgrass and L-tyrosine) with another combination (magnesium, valerian, escholtzia, white ginseng roots, willow, acerola, sage and L-triptophan) and found no significant differences in the FIQ score, but some secondary measures favored the intervention (Barmaki et al., 2019). There is no recommendation for or against the use of harpagoside, willow bark (Salix), Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica Montana, Curcuma longa, Tanacetum parthenium, or Zingiber officinale for treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: herbal medicine, alternative treatment, complementary treatment, ginseng, plants medicinal, herbs; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 178 articles in PubMed, 28 in CINAHL, 192 in Cochrane Library, 17,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REIKI FOR FIBROMYALGIA

Not Recommended

Reiki is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Rationale

Reiki is energy medicine that involves light touch and positive healing intention. It has been used for fibromyalgia (Assefi et al., 2008). There is one moderate quality sham-controlled trial of Reiki suggesting no adjunctive benefit for treatment of fibromyalgia (Assefi et al., 2008). A second, smaller study suggested some improvements at some timeframes and not others (Gökdere Çinar et al., 2023). Reiki is not invasive, has low adverse effects, is moderate cost in aggregate, has evidence of a lack of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: reiki, reiki energy, reiki therapy, energy healing, reiki energy healing, therapeutic touch; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 3 in CINAHL, 4 in Cochrane Library, 11,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

QIGONG FOR FIBROMYALGIA

Not Recommended

Qigong is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Qigong has been used for the treatment of fibromyalgia (Sawynok et al., 2017). Qigong-based exercises have been shown to be inferior to aerobic-based exercise treatment in one

moderate-quality study (Stephens S, 2008), while also being shown to be inferior to an active exercise intervention in another trial (Rodríguez-Mansilla et al., 2021). Qigong is not invasive, has low adverse effects, and is moderate cost in aggregate when supervised; however, there is evidence of its inferiority to more aerobically-based exercise treatments in two trials. Therefore, qigong is not recommended for most patients with fibromyalgia. Because there is some evidence of superiority to a sham treatment (Sarmento et al., 2020), it may have limited use in the treatment of severely debilitated patients who both refuse to comply with an aerobic exercise treatment and are drawn to traditional Chinese treatment methods as a means to initiate exercise before transitioning to an aerobic-based exercise treatment.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Qigong; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 5 in CINAHL, 2 in Cochrane Library, 2580 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic review met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACUPUNCTURE FOR FIBROMYALGIA

Sometimes Recommended

Acupuncture is selectively recommended for use in patients with chronic moderate to severe fibromyalgia, but only as an adjunct to more efficacious treatments that particularly include aerobic exercise, strengthening exercises, and antidepressants. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which acupuncture is one.

Strength of evidence Recommended, Evidence (C)

Level of confidence Low

Indications

Acupuncture is selectively recommended for use in patients with chronic moderate to severe fibromyalgia as an adjunct to more efficacious treatments. Although not fully tested in a trial, one RCT's post-hoc analyses suggest beneficial effects are among those with lower pain thresholds. Patients should already have had a progressive aerobic exercise program instituted, been compliant with it, and should remain compliant with progressive aerobic exercises while undergoing acupuncture (Targino et al., 2008). Also should have had prior anti-depressant medication(s) prescribed (Targino et al., 2008). May have had other exercises and medication treatment(s).

Benefits

Improved pain control with improved tolerance of exercises and resumption of normal daily activities.

Harms

Negligible in experienced hands. However, pneumothorces and other severe complications have been reported from excessively deep penetrations.

Frequency/Dose/Duration

An initial trial of 5-6 appointments in combination with a conditioning program of aerobic and possibly including strengthening exercises with measurement of objective outcomes. Data do not support traditional acupuncture over non-traditional acupuncture or simulated needle insertion (Harris et al., 2009, Harris et al., 2005, Yuan et al., 2016, Yang et al., 2014, Assefi et al., 2005, Deluze et al., 1992) raising questions about overall efficacy and suggesting different methods may be used. Further treatment should be based on ongoing objective improvement that is continuing throughout the treatment period. Additional treatments beyond the maximum should only occur based on progressively greater, incremental objective gains.

Indications for discontinuation

Resolution of symptoms, completion of a course of treatment, intolerance, non-compliance, including non-compliance with aerobic and strengthening exercises.

Rationale

Acupuncture and dry needling have been used for the treatment of fibromyalgia (Beckmon-Forrester, 2019, Zhang et al., 2019, Almutairi et al., 2022, Valera-Calero et al., 2022).

Two meta-analyses reported no differences between real acupuncture and sham (Yuan et

al., 2016, Yang et al., 2014), which is supported by the original studies (Harris et al., 2005, Assefi et al., 2005, Deluze et al., 1992, Harris et al., 2009). Some more recent studies have suggested superiority of acupuncture to sham, although they were also subjected to some methodological problems, often having baseline differences in outcomes measures. All trials failed to report on the success of blinding (Vas et al., 2016, Baelz et al., 2023, Karatay et al., 2018). Some other reviews have suggested efficacy (Almutairi et al., 2022, Berger et al., 2021, Valera-Calero et al., 2022, Zhang et al., 2019, Pereira et al., 2021).

There is evidence suggesting simulated needle insertion is equally efficacious (Assefi et al., 2005), raising further questions about overall efficacy of acupuncture for fibromyalgia. Electroacupuncture has been reportedly effective (Deluze et al., 1992) and superior to mock laser (Mawla et al., 2021). One study found acupuncture of additive benefit over traditional treatment with exercise and TCA, although it had considerable differences in contact time (Targino et al., 2008). Dry needling is reportedly superior to myofascial release (Castro Sánchez et al., 2019) and cross taping (Castro-Sánchez et al., 2017) and superior to education in one trial (Mist et al., 2018) but not another (Moreira et al., 2023). A trial found mostly no differences between acupuncture and core stabilization exercises (Garrido-Ardila et al., 2020). Another trial found acupuncture equivalent to treatment with hot pack, TENS, and ultrasound (Ozen et al., 2019). One trial suggested acupuncture superior to fluoxetine at 4 weeks but not 1 year, although the inclusion criteria did not preclude prior SSRI treatment; thus, the study was potentially biased against fluoxetine (Hadianfard MJ, 2012).

Acupuncture is minimally invasive, has low adverse effects, and has some evidence suggesting efficacy. However, there is no clear superiority of traditional acupuncture or simulated insertion, raising concerns about the overall efficacy of acupuncture for fibromyalgia. Thus, acupuncture is selectively recommended but only as an adjunct to more efficacious treatments that include progressive aerobic exercise, strengthening exercises, and anti-depressant(s). First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which acupuncture is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: acupuncture, dry needling, acupuncture treatment, acupuncture therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 49 articles in PubMed, 35 in CINAHL, 129 in Cochrane Library, 4,580 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 3 from CINAHL, 0 from Cochrane

Library, 8 from Google Scholar, and 0 from other sources. Of the 23 articles considered for inclusion, 19 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MANIPULATION AND MOBILIZATION FOR FIBROMYALGIA

Not Recommended

Manipulation and mobilization are not recommended to treat fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Manipulation and mobilization has been used for the treatment of fibromyalgia (Schulze et al., 2020). One moderate-quality trial found no differences after treatment of additive benefit of cervical manipulation to education, cognitive behavioral therapy, and exercise (Moustafa et al., 2015), although after the trial, there were further improvements in the group that received manipulation that are not explained. An attempted sham-controlled trial found no benefit one week after a 3-week series of manipulation treatments (Ince et al., 2023), while another had usual care and attention/time biases (Castro-Sanchez et al., 2014). Another trial with multiple co-interventions found the two arms were (in)effective (Ozen et al., 2019). There are no sizable quality studies indicating manipulation or mobilization are efficacious for treating patients with fibromyalgia. A systematic review found there overall quality of studies for manual therapy were of low quality, inconclusive and insufficient to support use in patients with fibromyalgia (Schulze et al., 2020). Manipulation and mobilization are not invasive, have generally low adverse effects, are moderately costly in aggregate, have no quality evidence of efficacy, and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Manipulation, mobilization; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 11 articles in PubMed, 9 in CINAHL, 44 in Cochrane Library, 13,900 in Google Scholar, and __ from other sources†. We considered for

inclusion 1 from PubMed, from 0 CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MASSAGE FOR FIBROMYALGIA

Sometimes Recommended

Massage is recommended for use in select patients with moderate to severe fibromyalgia, but only as third line treatments and as an adjunct to more efficacious treatments. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which massage is one.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Massage is recommended for use in select patients with moderate to severe fibromyalgia as an adjunct to more efficacious treatments. Patients should already have had a progressive aerobic exercise program instituted, been compliant with it, and should remain compliant with progressive aerobic exercises while undergoing massage. Also should have had prior anti-depressant medication(s) prescribed. May have had other exercises and medication treatment(s).

Benefits

Improved pain control with improved tolerance of exercises and resumption of normal daily activities.

Harms

Negligible.

Frequency/Dose/Duration

An initial trial of 5-6 appointments in combination with a conditioning program of aerobic and possibly including strengthening exercises with measurement of objective outcomes. Further treatment should be based on ongoing objective improvement that is continuing throughout the treatment period. Additional treatments beyond the maximum should only occur based on progressively greater, incremental objective gains.

Indications for discontinuation

Resolution of symptoms, completion of a course of treatment, intolerance, non-compliance, including non-compliance with aerobic and strengthening exercises.

Rationale

Massage has been used for the treatment of fibromyalgia (Yuan et al., 2015). There are no quality trials with sham massage or placebo treatment. There are a few moderate quality trials suggesting additive benefit of massage to an aerobic (target 65-70 to 75-80% of max. heart rate) and strengthening exercise program (Toprak Celenay et al., 2017), as well as superiority of massage to some comparative treatments such as amitriptyline. One randomized clinical trial showed Pilates was superior to massage (Ekici et al., 2016). Massage is not invasive, has low risk of adverse effects aside from short-term pain (Cherkin et al., 2001), is moderately costly, and has some evidence of efficacy although inferiority to exercise. Thus, massage is recommended for select treatment of fibromyalgia only as third line treatments and as an adjunct to an aerobic exercise program (target 65-70 to 75-80% of max. heart rate) plus strengthening exercises (Toprak Celenay et al., 2017) and potentially including antidepressant medication (i.e., SSRI, Norepinephrine reuptake inhibitors). First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which massage is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Massage therapy, Massage; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 18 articles in PubMed, 11 in CINAHL, 45 in Cochrane Library, 9,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MYOFASCIAL RELEASE FOR FIBROMYALGIA

Not Recommended

Myofascial release is not recommended for fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Moderate

Rationale

Myofascial release has been used for the treatment of fibromyalgia (Ughreja et al., 2021). There are no sham-controlled trials. The highest quality trial suggested significant superiority of dry needling to myofascial release (Castro Sánchez et al., 2019). There is one moderate quality study suggesting reductions in tender points, FIQ scores and pain (Castro-Sanchez et al., 2011). A wait-list control study suggested modest benefits of myofascial release (Ceca et al., 2017). Myofascial release is not invasive, has low adverse effects, is moderate to high cost in aggregate, has high-quality evidence of inferiority to dry needling in fibromyalgia patients and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Myofascial release therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 8 articles in PubMed, 11 in CINAHL, 36 in Cochrane Library, 5,320 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REFLEXOLOGY FOR FIBROMYALGIA

Not Recommended

Reflexology is not recommended for fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

There is no quality evidence showing reflexology is efficacious in the treatment of fibromyalgia. Reflexology is not invasive, has negligible adverse effects, is moderately costly, but in the absence of evidence of efficacy is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Reflexology, musculoskeletal manipulations; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 23 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 809 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OZONE FOR FIBROMYALGIA

Not Recommended

Ozone is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Ozone has been used for the treatment of fibromyalgia. There are no sham- or placebo-controlled trials of ozone (Sucuoğlu et al., 2023, Shen et al., 2022). This treatment requires either treatment of the patient's blood (autohemotherapy) or rectal insufflation. Ozone treatments are high cost, have significant potential adverse effects, lack quality evidence of efficacy, and thus are not recommended for treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ozone, ozone therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 5 in CINAHL, 2 in Cochrane Library, 1,010 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 1 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ELECTRICAL THERAPIES

INTERFERENTIAL AND ULTRASOUND THERAPIES FOR FIBROMYALGIA

Not Recommended

Interferential and ultrasound therapies are not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Interferential or ultrasound has been used for the treatment of fibromyalgia (Silva et al., 2017). There are no quality sham-controlled trials. There is one moderate quality trial of once-weekly vs. twice-weekly combined treatments of ultrasound and interferential with no differences between the groups, raising questions of (in)efficacy. These therapies are not invasive, have low adverse effects, are moderate to high cost depending on numbers of treatments, have no quality evidence of efficacy and thus are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Interferential, ultrasound; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 38 articles in PubMed, 7 in CINAHL, 28 in Cochrane Library, 12,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PULSED ELECTROMAGNETIC THERAPY FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against pulsed electromagnetic therapy for fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Pulsed electromagnetic therapy has been used for the treatment of fibromyalgia (Honda et al., 2018, Paolucci et al., 2020). One moderate-quality trial suggested lack of efficacy (Multanen et al., 2018). Another trial suggested short-term benefits and then the sham group became superior in the later timeframes (Paolucci, 2016). Two small moderate-quality studies suggest potential short-term efficacy (Sutbeyaz et al., 2009, Giovale et al., 2022); however, both have considerable methodological weaknesses. There also do not appear to be intermediate to long-term benefits. Pulsed electromagnetic therapy is not invasive, has low adverse effects, and is moderate to high cost in aggregate. Because the data materially conflict, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Pulsed Eletromagnetic Therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies.

We found and reviewed 6 articles in PubMed, 1 in CINAHL, 2 in Cochrane Library, 1,500 in Google Scholar, and 1 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 1 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MICROCURRENT CRANIAL ELECTRICAL STIMULATION FOR FIBROMYALGIA

Not Recommended

Microcurrent cranial electrical stimulation is not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one moderate quality trial with sparse results reported consisting of 3 graphs possibly suggesting efficacy, but no table of results presented (Taylor et al., 2013). Cranial electrical stimulation is not invasive, has low adverse effects, is moderate to high cost in aggregate and there are no reports with data provided, thus it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Microcurrent cranial electrical stimulation; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 2 in CINAHL, 3 in Cochrane Library, 93 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we

review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CORTICAL ELECTROSTIMULATION FOR FIBROMYALGIA

Not Recommended

Cortical electrostimulation is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is one low quality trial with 2 reports (Hargrove et al., 2012, Hargrove et al., 2012) that appears to have a randomization failure. Cortical electrostimulation is not invasive, has low adverse effects, is moderate to high cost in aggregate and in the absence of quality data, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Cortical electrostimulation; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 2 in CINAHL, 6 in Cochrane Library, 374 in Google Scholar, and __ from other sources†. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR FIBROMYALGIA

Sometimes Recommended

Transcranial direct current (TDC) stimulation is selectively recommended for treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and

compliance assured prior to utilizing second-line treatments. Multiple second-line treatments should also have been trialed with documented compliance and outcomes prior to trials of third-line treatments, of which TDC stimulation is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Fibromyalgia with insufficient and unsatisfactory treatment results with progressive aerobic exercise, strengthening exercises and anti-depressants. Patients should also have 19+ score on Hamilton scale for anxiety (HAM-A) and 8+ score on Hamilton scale for Depression (HAM-D,Loreti et al., 2023).

Benefits

Reduced pain and Fibromyalgia Impact Questionnaire score (Loreti et al., 2023).

Harms

Pruritis, headache, burning sensation, discomfort.

Frequency/Dose/Duration

10 daily sessions. Electrodes applied with anode over C3 and cathode over the right supraorbital region, with 2mA stimulated for 13 min, 20min pause, then 13 mins of additional stimulation (Fregni et al., 2006, Loreti et al., 2023).

Indications for discontinuation

Completion of a treatment course, sufficient improvement, non-compliance.

Rationale

Transcranial direct current (TDC) has been used for the treatment of fibromyalgia (Zhu et al., 2017, Chaturvedi et al., 2018)(Lloyd et al., 2020, Teixeira et al., 2022). There are many short-duration RCTs for transcranial direct current stimulation, and sham-controlled trials also suggest strong placebo effects. However, one small sham-controlled trial of 10 days of treatment with 90 days of followup suggested significant and durable improvements in pain and FIQ scores (Loreti et al., 2023). Other small studies suggested beneficial effects of tDCS (Valle et al., 2009, Jales J, 2015, Riberto, 2011, Brietzke et al., 2020, Khedr et al., 2017, Khedr et al., 2017, Caumo et al., 2022), including improvements at 30 days (Brietzke et al., 2020, Khedr et al., 2017, Caumo et al., 2022) and at 30 and 60 days after the last treatment session compared with sham (Valle et al., 2009). Some small trials found no benefits of active treatment compared with sham (Arroyo-Fernández et al., 2022, Samartin-Veiga et al., 2022, Samartin-Veiga et al., 2022, Ramasawmy et al., 2022). Many of the other moderate-

quality trials were 5 days or less and thus essentially hypothesis generating (Mendonca et al., 2011, Villamar et al., 2013, Fagerlund et al., 2015, Fregni et al., 2006).

One moderate-quality trial suggested short term benefit of combined stimulation with aerobic exercise, but aerobic exercise alone tended to be superior at 1 month. A 2018 Cochrane review found the evidence to be of "very low-quality" that single doses of transcranial direct current stimulation "may have short-term effects on chronic pain and quality of life but multiple sources of bias exist that may have influenced the observed effects". Another systematic review concluded there was "tentative evidence of pain reduction" compared with sham, but data were heterogeneous and there was high risk of bias (Lloyd et al., 2020). A third systematic review and meta-analysis found evidence supporting analgesic effects but "[d]efinite conclusions are inadequate given the large heterogeneity and limited quality of evidence (Teixeira et al., 2022). Transcranial direct stimulation is not invasive, has low adverse effects, is moderate cost in aggregate and most of the sham-controlled trial suggesting significant effects at up to 90 days and thus is selectively recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which TDC is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Transcranial direct current stimulation, tDCS; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 36 articles in PubMed, 7 in CINAHL, 26 in Cochrane Library, 4,540 in Google Scholar, and 0 from other sources†. We considered for inclusion 14 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 0 from other sources. Of the 30 articles considered for inclusion, 26 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCRANIAL MAGNETIC STIMULATION FOR FIBROMYALGIA

Not Recommended

Transcranial magnetic stimulation is not recommended for fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Transcranial magnetic stimulation (TMS) has been used for the treatment of fibromyalgia (Pacheco-Barrios et al., 2022, Toh et al., 2022). The highest quality trial suggests a lack of efficacy (Baudic et al., 2013). Many but not all other moderate quality studies suggest lack of efficacy to reduce pain (Boyer et al., 2014, Mhalla et al., 2011, Short et al., 2011, Carretero et al., 2009, Lee et al., 2012). Transcranial magnetic stimulation is not invasive, has low adverse effects, is moderate to high cost in aggregate and most trials suggest lack of efficacy including the highest quality trial, thus transcranial magnetic stimulation is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Transcranial magnetic stimulation, TMS; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 33 articles in PubMed, 23 in CINAHL, 25 in Cochrane Library, 4,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 9 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOW-LEVEL LASER THERAPY FOR FIBROMYALGIA

Not Recommended

Low-level laser therapy is not recommended for fibromyalgia.

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Moderate

Rationale

Low-level laser therapy has been used for the treatment of fibromyalgia (Yeh et al., 2019). Two moderate-quality trials suggest a lack of benefit compared with sham (Vayvay ES, 2016, Panton et al., 2013), with one of them also finding comparable results with kinesiotaping (Vayvay ES, 2016). One moderate quality trial suggested no additive benefit of laser over stretching exercises alone (Matsutani et al., 2007) and another found no additive benefits to functional exercises (Germano Maciel et al., 2018). One trial appears to have suffered a randomization failure (Ruaro et al., 2014), and one small study suggested modest benefits (Armagan et al., 2006) Low-level laser therapy is not invasive, has negligible adverse effects, is high cost cumulatively, has moderate quality evidence mostly suggesting a lack of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Low Level Laser Therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 11 articles in PubMed, 8 in CINAHL, 5 in Cochrane Library, 7,510 in Google Scholar, and 4 from other sources†. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 4 from other sources. Of the 11 articles considered for inclusion, 10 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) FOR FIBROMYALGIA

Not Recommended

Transcutaneous electrical nerve stimulation (TENS) is not recommended to treat fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Transcranial electrical nerve stimulation (TENS) has been used for the treatment of fibromyalgia (Johnson et al., 2017, Arienti, 2019, Amer-Cuenca et al., 2023)(Batista de Aguiar et al., 2022). The two highest quality sham-controlled trials somewhat conflict. One compared maximal-frequency active stimulation with minimal-frequency sham stimulation and found a lack of efficacy over 3 months (Jamison et al., 2022). The other compared active TENS with sham and a third arm of usual care/no TENS and suggested efficacy, but included no intermediate or long-term follow-up (Dailey et al., 2020).

There are three moderate-quality trials, only one of which is sham-controlled. That sham-controlled trial is hypothesis generating as it consisted of only one treatment; even though aspects of it suggested potential efficacy, it is thus not usable for guidelines development (Dailey et al., 2013). Another trial suggested TENS was of no additive benefit to supervised exercise (Mutlu et al., 2013), while a second, smaller trial with more methodological weaknesses suggested it was of additive benefit (Carbonario et al., 2013). One moderate-quality trial with sparse methods suggested pain reductions over one week, and no longer follow-up (Lauretti et al., 2013). The other trial had no sham arm and found comparable efficacy with superficial warmth (Lofgren et al., 2009), raising questions about lack of efficacy. A Cochrane review found "a small number of inadequately powered studies" and concluded the overall evidence was very low quality and that there was "little confidence in the effect estimates where available" (Johnson et al., 2017).

TENS is not invasive, has low adverse effects, and is moderate cost. Therefore, with most quality data suggesting lack of efficacy, TENS is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Transcutaneous electrical nerve stimulation, TENS; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 31 articles in PubMed, 126 in CINAHL, 38 in Cochrane Library, 6,530 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 3 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 16 articles considered for inclusion, 12 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OTHER ELECTRICAL THERAPIES FOR FIBROMYALGIA

Not Recommended

Other forms of electrical therapies are not recommended for fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Other electrical therapies have been used for the treatment of fibromyalgia (de Silva Salazar et al., 2017). There are no quality studies evaluating the use of electrical therapy to treat fibromyalgia. These therapies are not invasive, have low adverse effects, are moderate to high cost, have no quality evidence of efficacy, do not address the central mechanism of pain, and are not recommended for treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Electrical therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 76 articles in PubMed, 4 in CINAHL, 51 in Cochrane Library, 15,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

IONTOPHORESIS FOR FIBROMYALGIA

Not Recommended

Iontophoresis is not recommended for fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

There are no quality studies evaluating the use of iontophoresis to treat fibromyalgia. Iontophoresis is not invasive, has low adverse effects, is moderately costly, has no quality evidence of efficacy, does not address the central mechanism of pain, and is not recommended for treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: iontophoresis, electrophoresis; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 640 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INJECTION THERAPIES

GANGLION BLOCKS FOR FIBROMYALGIA

Not Recommended

Ganglion blocks are moderately not recommended for fibromyalgia.

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Moderate

Rationale

There are two quality studies suggesting lack of efficacy of spheno-palatine ganglion blocks (Janzen et al., 1997). Ganglion blocks are invasive, have adverse effects, are moderate to high cost depending on number of injections administered, have evidence of inefficacy, and thus are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ganglion blocks; fibromyalgia; controlled clinical trial, controlled trials, randomized

controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2 articles in PubMed, 3 in CINAHL, 3 in Cochrane Library, 5,460 in Google Scholar, and 0 from other sources†. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

KETAMINE INFUSIONS FOR FIBROMYALGIA

Not Recommended

Ketamine infusions are not recommended for treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There is one moderate-quality trial comparing ketamine with midazolam and finding some differences over a few hours, but no significant differences from 2-8 weeks (Noppers et al., 2011). Ketamine infusions are invasive, have adverse effects, are moderate to high cost depending on number of infusions, have evidence of inefficacy, and thus are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ketamine infusion; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4 articles in PubMed, 5 in CINAHL, 4 in Cochrane Library, 1,930 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LIDOCAINE INFUSIONS FOR FIBROMYALGIA

Not Recommended

Lidocaine infusions are not recommended for the treatment of fibromyalgia.

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Moderate

Rationale

Lidocaine has been used for the treatment of fibromyalgia (de Carvalho et al., 2022). Two quality trials have reported that lidocaine infusions are ineffective for treatment of fibromyalgia (Albertoni Giraldes AL, 2016, Vlainich et al., 2011). These infusions are invasive, have adverse effects, are moderate to high cost depending on number of injections administered, have evidence of inefficacy, and thus are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Lidocaine, lidocaine infusions; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 14 in CINAHL, 4 in Cochrane Library, 1,640 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

C2 NERVE STIMULATION FOR FIBROMYALGIA

Not Recommended

C2 nerve stimulation is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Rationale

The highest quality study suggests a lack of efficacy (Paccione et al., 2022). One 2-week crossover trial of an implantable stimulator device with sparsely reported results and methods suggested very high adverse effects (Plazier et al., 2015). The implantable stimulator device is invasive, 50% reportedly had adverse effect(s), is high cost, has evidence suggesting lack of efficacy, and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: C2 Nerve Stimulation; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 23 in CINAHL, 7 in Cochrane Library, 1,460 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PROLOTHERAPY INJECTIONS FOR FIBROMYALGIA

Not Recommended

Prolotherapy injections are not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

There are no quality studies documenting benefits of prolotherapy for treatment of fibromyalgia. These injections are invasive, have some adverse effects, are moderate to high cost depending on number of injections administered, have no quality evidence of efficacy, do not treat the theoretical central mechanism of pain, and thus are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Prolotherapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 0 in CINAHL, 4 in Cochrane Library, 366 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BEHAVIORAL AND PSYCHOLOGICAL INTERVENTIONS

See also the sections on Rehabilitation and Behavioral Interventions for additional Chronic Pain recommendations, including Psychological Evaluation, Cognitive Behavioral Therapy, Work Conditioning/Work Hardening, Early Intervention, Interdisciplinary Pain Rehabilitation, and Biofeedback.

EDUCATION FOR FIBROMYALGIA

Recommended

Education is recommended as first-line treatment for the treatment of fibromyalgia. Other first-line treatments are aerobic exercise, fear avoidance belief training, and, if indicated, antidepressants (SSRIs and norepinephrine reuptake inhibitors).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Education is recommended for adjunctive treatment of fibromyalgia. Education may include general education, as well as specific educational interventions (e.g., fear avoidant belief training, impacts of catastrophization).

Benefits

Improved understanding and theoretically improved compliance.

Harms

Negligible

Frequency/Dose/Duration

Generally once at diagnosis and periodically during treatment to provide appropriate content- and stage-specific training.

Indications for discontinuation

N/A

Rationale

Education strategies have been used for the treatment of fibromyalgia (Saracoglu et al., 2022, Suso-Martí et al., 2022). Two trials reported efficacy (Van Oosterwijck et al., 2013, Luciano et al., 2011). One trial suggested education was of no additive benefit to exercise (Ceballos-Laita, 2020). Three RCTs suggest education was superior to usual care (Barrenengoa-Cuadra et al., 2021, Saracoglu et al., 2021, Musekamp et al., 2019), although all are subject to usual care and contact time biases. One trial found education to be inferior to exercise (King et al., 2002). Another trial found equivalency between motivational interviewing and education (Ang DC, 2013). Education has been used in multiple other trials as part of a battery of treatments, which preclude assessments of independent effects.

Education has low adverse effects, is low cost, and is believed to be important to help improve compliance, especially with exercise and other at-home treatments. Thus, it is recommended as a first-line treatment for the treatment of fibromyalgia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Education strategies, education; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 48 articles in PubMed, 52 in CINAHL, 75 in Cochrane Library, 17,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 20 articles considered for inclusion, 17 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ATTENTION MODIFICATION FOR FIBROMYALGIA

Not Recommended

Attention modification is not recommended for the treatment of fibromyalgia.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

There are two moderate-quality trials, with the large trial from the same author's group suggesting a lack of efficacy of attention modification (Carleton et al., 2011, Carleton et al., 2020). Attention modification is not invasive, has negligible adverse effects, has evidence of a lack of efficacy, and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Attention modification; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 1 articles in PubMed, 1 in CINAHL, 8 in Cochrane Library, 17,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

GUIDED IMAGERY FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against guided imagery for the treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Rationale

Guided imagery has been used for the treatment of fibromyalgia (Zech et al., 2017, Gomez-de-Regil et al., 2020). There are a few RCTs but they have considerable weaknesses, such as contact time/attention biases and combinations of interventions that preclude assessment of efficacy. Some trials suggest efficacy (Onieva-Zafra et al., 2019, Molinari et al., 2018, Torres et al., 2018), but other trials suggest lack of efficacy (Verkaik R, 2014, D''Amico, 2020), and another has multiple interventions (Montero-Marín et al., 2018).

Guided imagery is not invasive, has negligible adverse effects, but has conflicting evidence among trials, with many weaknesses that preclude assessment of efficacy. Therefore, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: guided imagery, imagery psychotherapy, guided relaxation, visualization techniques; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 16 articles in PubMed, 10 in CINAHL, 17 in Cochrane Library, 16,600 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 10 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACCEPTANCE AND COMMITMENT TRAINING FOR FIBROMYALGIA

Recommended

Acceptance and commitment training is recommended for fibromyalgia, especially moderate or severe. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, of which acceptance and commitment training is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Fibromyalgia, especially moderate or severe.

Benefits

Reduced fibromyalgia symptoms, depressive symptoms, anxiety symptoms, pain, pain catastrophizing, kinesiophobia and increased physical function (Varallo et al., 2023, Simister et al., 2018).

Harms

Negligible

Frequency/Dose/Duration

One study used 12 weekly group sessions.

Indications for discontinuation

Completion of a training course, sufficient improvement, non-compliance

Rationale

Acceptance and commitment therapy have been used for the treatment of fibromyalgia (Haugmark et al., 2019). There are a few trials suggesting efficacy (Wetherell, 2011, Varallo et al., 2023, Simister et al., 2018, Wicksell et al., 2013), although with likely exercise and activity cointerventions (Wetherell, 2011). One trial found comparable effects with cognitive behavioral therapy (Wetherell, 2011). Acceptance and commitment training is not invasive, has negligible adverse effect(s), is moderate cost in aggregate, has some quality data suggesting efficacy, and thus is recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, of which acceptance and commitment training is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Acceptance and commitment therapy, acceptance, commitment, act; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic,

systematic review, retrospective, prospective studies. We found and reviewed 76 articles in PubMed, 19 in CINAHL, 8 in Cochrane Library, 17,600 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 6 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PSYCHOEDUCATIONAL TREATMENT FOR FIBROMYALGIA

Recommended

Psychoeducational treatment programs are recommended for fibromyalgia, especially moderate or severe. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs and norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, of which psychoeducational treatment is one.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Fibromyalgia, especially moderate or severe.

Benefits

Improved physical function, mental health; reduced symptoms, depressive symptoms, stress, treatment costs, and disability pensions

Harms

Negligible

Frequency/Dose/Duration

One trial consisted of 2 one-on-one sessions (Van Oosterwijck et al., 2013). Trials have used computer-based methods (Davis et al., 2013), as well as sessions. Sessions have included 2.5-hour weekly sessions for 8 weeks (Sephton et al., 2007).

Indications for discontinuation

Completion of a training course, sufficient improvement, non-compliance

Rationale

Psychoeducation treatment has been used for the treatment of fibromyalgia (Galvez-Sánchez et al., 2023). Trials suggest that psychoeducational and pain educational programs for fibromyalgia are associated with improved global functional status and lower costs (Luciano et al., 2011, Luciano et al., 2013, Van Oosterwijck et al., 2013). Components of the programs differ. Psychoeducational programs are not invasive, have negligible adverse effect(s), are moderate cost in aggregate, have some quality data of efficacy, and thus are recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs and norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments, of which psychoeducation treatment is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Psychoeducational treatment; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 3 in CINAHL, 7 in Cochrane Library, 4,360 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 5 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MINDFULNESS INTERVENTION FOR FIBROMYALGIA

Recommended

Mindfulness intervention is recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are

first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments of which mindfulness is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Fibromyalgia, especially moderate or severe.

Benefits

Reduced symptoms, depressive symptoms, stress, treatment costs, and disability pensions

Harms

Negligible

Frequency/Dose/Duration

Trials have used computer-based methods (Davis et al., 2013), as well as sessions. Sessions have included 2.5-hour weekly sessions for 8 weeks (Sephton et al., 2007).

Indications for discontinuation

Completion of a training course, sufficient improvement, non-compliance

Rationale

Some moderate-quality trials suggest evidence of efficacy (Van Gordon et al., 2017, Sanabria-Mazo et al., 2020). Trials suggested mindfulness was effective, but involved multiple interventions (Serrat et al., 2021, Schmidt et al., 2011). A trial with multiple interventions also suggested mindfulness was associated with improvements in fear avoidant beliefs (Jay, 2016) One trial was negative (Grossman et al., 2017). There are multiple low quality trials involving mindfulness therapy, with this preliminary evidence suggesting reductions in fibromyalgia symptoms (Cash et al., 2015), depressive symptoms (Sephton et al., 2007), stress (Cash et al., 2015) and reduced disability pensions. Mindfulness therapy is not invasive, has negligible adverse effect(s), is low to moderate cost in aggregate and depending on numbers of appointments, has no quality data of efficacy, has low quality evidence suggesting considerable benefits, and thus is recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments of which mindfulness is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Mindfulness intervention, mindfulness treatment, mindfulness therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 37 articles in PubMed, 16 in CINAHL, 17 in Cochrane Library, 12,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 7 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 21 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SHARED DECISION-MAKING FOR FIBROMYALGIA

Recommended

Shared decision-making is recommended for the treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments of which shared decision making is one.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

All fibromyalgia patients

Benefits

Improved engagement, coping and satisfaction.

Harms

Negligible

Frequency/Dose/Duration

Inclusion in all clinical visits

Indications for discontinuation

Patients who prefer to not be involved in shared decision-making.

Rationale

One moderate-quality trial suggests improved coping, although health outcomes were comparable regardless of shared decision-making (Bieber et al., 2006). Shared decision-making is not invasive, has negligible adverse effect(s), is low cost, has some quality data suggesting potential efficacy, and thus is recommended. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments of which shared decision making is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Shared decision making; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 3 in CINAHL, 0 in Cochrane Library, 17,600 in Google Scholar, and 0 from other sources†. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VIRTUAL REALITY FOR FIBROMYALGIA

Sometimes Recommended

Virtual reality (VR) training is selectively recommended for treatment of fibromyalgia. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which VR is one.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Virtual Reality is recommended for those with interest in exercise using VR and/or those with inadequate results from progressive aerobic exercise, strengthening exercise, CBT and anti-depressants.

Benefits

Improved strength, aerobic measures, pain tolerance, reduced pain, reduced FIQ scores. However, one trial suggested comparable results for aerobic exercise compared with VR (Polat 2021).

Harms

Negligible.

Frequency/Dose/Duration

One trial used a VR device for two 60-minute sessions/week for 6 months (Martín-Martínez et al.,(Villafaina et al., 2020).

Indications for discontinuation

Sufficient recovery, noncompliance.

Rationale

Virtual reality has been used for the treatment of fibromyalgia. There are several RCTs, with multiple trials suggests improvements in strengthening and aerobic measures (Martín-Martínez et al., 2019, Villafaina et al., 2020)., reduced pain tolerance (Christensen et al., 2023), reduced pain and FIQ scores (Collado-Mateo et al., 2017). One trial found comparable results from either an aerobic exercise group or VR (Polat et al., 2021) Another trial found superior results from Pilates and VR compared with pilates (Gulsen et al., 2022). VR has some evidence of efficacy, although without clear superiority to exercise without VR, thus VR is selectively recommended for those with either interest in exercising using VR or for those with inadequate results from progressive aerobic exercise, strengthening exercise, CBT and anti-depressants. First-line treatments are aerobic exercise, fear avoidance belief training, and education. When medications are needed, antidepressants (SSRIs, Norepinephrine reuptake inhibitors) are first line. First-line treatments should generally have all been trialed first and compliance assured prior to utilizing second-line treatments. Multiple second line treatments should also have been trialed with documented compliance and outcomes prior to trials of third line treatments of which VR is one.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Virtual reality, VR, virtual reality therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 4 in CINAHL, 3 in Cochrane Library, 5,150 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 8 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

EXPOSURE THERAPY FOR FIBROMYALGIA

No Recommendation

There is no recommendation for or against exposure therapy for treatment of fibromyalgia.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is only one trial which is subject to waitlist control bias and, while it suggests some efficacy, the weaknesses preclude formulation of a recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Exposure therapy, Implosive therapy; fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 19 articles in PubMed, 7 in CINAHL, 6 in Cochrane Library, 18,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

COMPLICATIONS AND COMORBIDITIES

Complications and comorbidities of fibromyalgia, which are also common for many other chronic pain disorders, include the following:

- Depression
- Anxiety
- Panic disorder
- Bipolar
- Adverse childhood experiences
  - Physical abuse
  - Emotional abuse
  - Sexual abuse
  - Neglect
- Physical abuse in adulthood
- Sexual abuse in adulthood
- Stress
- Psychological distress
- Familial mood disorder
- Catastrophization
- Advocagenesis
- Pain disorder (formerly somatoform disorder; psychogenic pain disorder)
- Low vitamin D levels
- Chronic Hepatitis C infection
- Human T-cell lymphotropic virus type I infection
- HIV
- Autoimmune thyroid disease
- Epilepsy
- Hemochromatosis
- Fatigue
- Sleep disturbances
- Cognitive difficulties
- Alcohol
- Autoimmune disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatic
- Myositis

- Dermatomyositis
- Ankylosing Spondylitis
- Hypothyroidism
- Neuropathies
- Chronic fatigue syndrome
- Lyme Disease
- Somatization disorders
- Guillain-Barre
- Hypothyroidism
- Irritable bowel syndrome
- Chronic headaches
- Temporomandibular joint disorders
- Orofacial pain
- Multiple chemical sensitivity

FOLLOW-UP CARE

It is recommended that patients with fibromyalgia should have a follow-up visit every 1 to 2 weeks initially by a new clinician or while still out of work and initiating effective, evidence-based treatments. Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. The initial appointments should focus on identifying prior treatment(s) instituted, degree of compliance with treatments known to be effective, identifying contributory behavioral factors, instituting effective treatments and addressing behavioral and/or psychological factors.

Initial visits should include an ongoing focus on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be the cornerstone of the medical management plan for the patient's pain. The threshold for institution of anti-depressant medication should be low, as evidence of efficacy is high. Secondary pharmaceutical means of managing pain should be considered if, after the initial treatments have been instituted and complied with, the results are considered inadequate. Initial visits for fibromyalgia should also include information to avoid bed rest, reductions in activity levels, excessive rest or appliances. The clinician should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is recommended to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance exercises and medication(s), follow-up every 6 to 12 months is recommended. However, in the active rehabilitation phase for patients with fibromyalgia, follow-ups weekly for as much as 2 or 3 months is recommended to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

Psychological and behavioral factors are key components of fibromyalgia are of critical importance and are addressed in the Behavioral Interventions section of the Chronic Pain guideline.

NEUROPATHIC PAIN

INTRODUCTION

OVERVIEW

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. It can be broadly classified as central or peripheral.[312] The most common causes of central and peripheral pain are spinal cord injury, brain injury, stroke, and multiple sclerosis.

While radicular pain and chronic CRPS are also typically classified as forms of neuropathic pain, they are usually discussed as separate entities, as are acute forms of neuropathic pain that can be addressed by specific interventions. It is important to note that many times, neuropathic pain is not able to be objectively demonstrated, although objective findings are sometimes present.

Chronic neuropathic pain has an estimated prevalence of approximately 8-10% of adults [464-466]. A pooled study of 50,112 patients reported that 30.0% of patients with diabetes mellitus have peripheral neuropathy, with 31.5% of individuals with type 2 diabetes and 17.5% of those with individuals with type 1 diabetes having peripheral diabetic neuropathy [467], likely largely reflecting the effects of disease duration. Post-stroke pain has been estimated to affect 11% of stroke patients, while affecting up to 50% of those with medullary or thalamic strokes [468,469]. The prevalence of neuropathic pain in females with multiple sclerosis is 2.6-fold greater (74.2%) compared with males (28.9%),[470]. Other disorders considered to be neuropathic include: channelopathies (e.g., familial episodic pain syndrome, inherited erythromelalgia), intracranial tumor, peripheral nerve entrapment, trigeminal neuralgia, polyneuropathy (e.g., post-chemotherapy, alcoholic, HIV disease), postherpetic neuralgia, radiculopathy, some spinal cord injuries, syringomyelia, syrinx of the central canal in the brainstem or spinal cord, traumatic nerve injury (identifiable separate from the pain complaint, e.g. amputation).

Systematic reviews have shown that the quality of literature is relatively weak for treatment of neuropathic pain [471] and post-herpetic neuralgia [472].

This neuropathic pain guideline is intended to be used for the treatment of work-related peripheral neuropathies (e.g., toxic manifestations of chemicals) and central pain mechanisms that are potentially work-related but not elsewhere addressed in an ACOEM Guideline. Literature that was not relevant (e.g., multiple sclerosis, rheumatoid arthritis, HIV) was excluded. Where a more specific diagnosis is able to be made (e.g., radiculopathy, entrapment mononeuropathies such as carpal tunnel syndrome) and for which another ACOEM Guideline has been developed for that diagnosis (e.g., respectively, Low Back Disorders; Hand, Wrist and Forearm Disorders), that guidance supersedes this Neuropathic Pain guidance, as more specific treatments tailored to a discrete diagnosis are far more likely to result in superior clinical outcomes.

RISK AND CAUSATION

A method for determining work-relatedness is discussed in detail in the Work-Relatedness Guideline. A discussion of work-relatedness of radicular pain is discussed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Complex regional pain syndrome is addressed elsewhere in this guideline. Peripheral entrapment neuropathies are discussed in respective guidelines (e.g., Hand, Wrist and Forearm Disorders; Elbow Disorders; Ankle and Foot Disorders).

The work-relatedness of toxic neuropathies can be determined using the process outlined in the ACOEM Work-Relatedness Guideline:

1. *Evidence of Disease*. What is the history of specific chemical exposure(s), including frequency, intensity and duration(s) of exposure(s)? What is the specific neuropathy? Is the neuropathy peripheral or central? What certainty is there that the diagnosis is correct? What evidence supports or fails to support that diagnosis? Is the diagnosis supported using a generally accepted case criteria definition?

2. *Epidemiology*. What is the epidemiological evidence for the specific neuropathy? Is there support for a relationship with specific chemical(s)? At what dose(s), frequency(ies), and duration(s) of exposure(s)?

3. *Evidence of Individual Exposure*. What evidence of exposure to that specific chemical(s) is available (e.g., Safety Data Sheet(s); workplace industrial hygiene survey data, and whether by individual vs. area sampling strategy)? What objective evidence is there that the level of the patient's exposure(s) is of the frequency, intensity, duration, and temporal pattern of exposure associated with work-relatedness of the specific neuropathic pain disorder?

4. *Consideration of Other Relevant Factors*. What other potentially causal factors are present? For example, does the worker with systemic polyneuropathy also have diabetes mellitus? Other systemic diseases (e.g., inflammatory rheumatic disease, thyroid disorder, multiple sclerosis)?

5. *Validity of Testimony*. Are the opinions and sources reliable and credible? If an expert opinion has been rendered, is the person professionally qualified to render that opinion? Is there verification for the basis of the testimony, that is, the importance attributed to various areas of the information reviewed, and the conclusions that were drawn? Is there information that suggests that the information above is inaccurate, for example, from a collateral source (e.g., exposure data)?

6. *Conclusions*. This step is a synthesis of the above five steps.

CENTRAL NEUROPATHIC PAIN

The most common causes of central neuropathic pain include: transient ischemic attacks (TIAs), cerebrovascular accidents/infarcts [468,473-485], brain cancers and metastases, especially to the brain [464,479,486-488], spinal cord injury [489-492], multiple sclerosis [473,493-503], and spinal cord injuries [473,489-491,504-506]. Post-stroke pain has been estimated to affect 30% of patients [507]. As most of these are considered non-occupational conditions, most are not

reviewed further. Causation of spinal cord injuries is based on the mechanism of the accident/injury and thus is not usually considered controversial.

Some lung cancers are considered occupational due to significant occupational exposures. A determination of work-relatedness of a cancer metastatic to the brain is generally complex, and importantly includes elements of frequency, intensity, and duration of the exposure. Measurements or at least estimates of occupational exposure (dose) are generally required, with industrial hygiene data being particularly important when available. For many, there are confounding exposures that may overwhelm an occupational exposure (e.g., smoking); yet for some such as significant asbestos exposure, epidemiological evidence provides assurance that a high occupational exposure likely contributed to the cancer [346,416,508-518].

PERIPHERAL NEUROPATHIC PAIN

There are many causes of painful peripheral neuropathies [519,520]. Risk factors for peripheral neuropathic pain include increasing age, genetics/inherited neuropathies [417,521-526], diabetes mellitus [527-533], alcohol use disorder [527,534-536], rheumatological disorders [537], other autoimmune disorders [538,539], prior varicella zoster infection [540-545], HIV/AIDS [546,547], leprosy [548,549], and chemotherapeutics [550,551,552]. Diabetes mellitus is thought to be the most common population-based cause [464,553,554]. Idiopathic cases are also common, estimated at 20-30% [555].

Occupational causes of peripheral neuropathies include exposures to n-hexane [556-563], acrylamide [564-566], arsenic [567-576], carbon disulfide [577-587], lead [588-594], and mercury [595,596,597]. A determination of work-relatedness of a peripheral neuropathy is generally complex, and importantly includes elements of frequency, intensity, and duration of the exposure. Measurements or at least estimates of occupational exposure (dose) are generally required, with industrial hygiene data being particularly important when available.

Infrequently, trauma to a peripheral nerve may also cause peripheral neuropathic pain. Peripheral entrapment neuropathies may be occupational depending on the job's physical factors (see Hand, Wrist, and Forearm Disorders). Postsurgical trauma is a reported cause [486,598,599,600], and the work-relatedness of the postsurgical neuropathy would depend on the cause of the underlying condition requiring surgery. Paramalignant peripheral neuropathies also occasionally occur.

SIGNS AND SYMPTOMS

Signs and symptoms include the following:

- Burning, lancinating, shooting, stabbing pain
- Pain distribution typically has a neurological distribution, which can range from one nerve to many nerves and from to one nerve root to homuncular (i.e., that distribution included in a segment of affected brain tissue).
- Pain largely independent of activity. Often more noticeable at night, perhaps due to less distraction by other issues.

- May have allodynia (pain from something normally not painful), hyperalgesia (extreme pain from something normally somewhat painful), dysesthesia (unusual pain sensations), hyperesthesia (extreme sensitivity to touch; see also the CRPS guideline)
- Hypoalgesia (i.e., something normally painful is not that painful)
- Tingling, numbness
- Weakness. May be either neurological distribution similar to the pain distribution above (e.g., distribution of that nerve; myotomal; or in the distribution of the brain-spinal cord tissue's innervated muscles). May also be more generalized to secondary deconditioning, or avoidance of pain
- May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch reflex abnormalities

INITIAL ASSESSMENT

The initial assessment is focused on determining the type of neuropathic pain, which is most commonly categorized into two categories for which different treatment options are typically provided: central neuropathic pain and peripheral neuropathic pain (including painful radiculopathies). The next step is to define the exact mechanism and diagnosis for the cause of the pain.

Neuropathic pain is generally classified into two categories, central and peripheral. Due to the prevalence and incidence in working populations, radicular pain is also included in the three categories below:

- ***Central neuropathic pain*** is pain that develops due to central nervous system dysfunction (e.g., infarcts and brain tumors may cause pain; multiple sclerosis; spinal cord injuries). Such disorders are generally nonoccupational and therefore are not discussed in this guideline, unless, for example, the tumor is of occupational origin or there is a penetrating occupational traumatic brain or spinal cord injury (see ACOEM Traumatic Brain Injury guideline).
- ***Radicular neuropathic pain*** is pain in the extremities (arms, hands, legs, and/or feet) that is caused by an associated nerve being compromised ("pinched") in or adjacent to the spine. See Cervical and Thoracic Spine Disorders and Low Back Disorders Guidelines for management of those conditions.
- ***Peripheral neuropathic pain*** may be due to entrapment neuropathies such as carpal tunnel syndrome, ulnar neuropathy at the elbow and tarsal tunnel syndrome; these are addressed with evidence-based guidance in the ACOEM Hand, Wrist and Forearm Disorders; Elbow Disorders; and Ankle and Foot Disorders Guidelines. Peripheral neuropathic pain may also be caused by occupational exposures to toxins, and this guideline applies to their evaluation and treatment. Other peripheral neuropathies are most often due to nonoccupational causes such as diabetes mellitus, alcohol, vitamin deficiencies, infections, inherited traits, or as consequences of autoimmune disorders. While the principles of managing pain apply, medical management of those other peripheral neuropathic disorders are outside the scope of this guideline.

Complex regional pain syndrome is considered neuropathic pain. (Please see the section on Complex Regional Pain Syndrome to manage this condition.) Traumatic nerve injuries may occasionally cause peripheral neuropathic pain. Management of these traumatic nerve

injuries is discussed in the appropriate ACOEM Guidelines. Where they are not addressed, this guideline is designed to help guide their evaluation and treatment.

Toxic occupational peripheral neuropathies are relatively uncommon and there are no quality studies of treatments. Interventions are primarily inferred based primarily on treatment of two common, non-occupational peripheral neuropathies, diabetic neuropathy and post-herpetic neuralgia together which constitute the majority of the relevant quality studies. The pain from those occupational neuropathies that has persisted despite efforts to directly treat the underlying conditions should be managed in accordance with the principles of neuropathic pain treatment that are outlined in this Chronic Pain Guideline.

HISTORY

The history of neuropathic pain varies depending on the type of neuropathic pain. Regardless, the initial queries follow standard lines of questioning for patients with pain (e.g., vocational and avocational function, onset, trauma history, location of pain, presence of tingling/numbness, aggravating factors, relieving factors). Initial queries should be sufficient to identify and categorize the neuropathic pain into one of the categories (central, radicular, peripheral). After preliminary categorization, additional questions should especially be asked to identify causal and/or contributing factors of each, remembering that more than one disorder may be present (e.g., toxic neuropathy in someone with alcohol use disorder). Still, asking all questions across these categories is generally needed for the initial evaluation to assure proper categorization as well as identification of causal, aggravating, and contributing factors. Use of questionnaires such as Douleur Neuropathique en 4 Questions (DN4), I-DN4 (self-administered DN4), and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) may help.

Care should be taken to identify potential causal factors and address both occupational and non-occupational components to optimize the clinical outcome. A detailed occupational history to identify potentially causative factors is highly recommended. Some exposures may have industrial hygiene data available, or data obtainable on request to help verify and quantify exposures.

There are many causes of central neuropathic pain, thus a general approach is provided. The more common questions to particularly include regarding central neuropathic pain include any history of any type central nervous system dysfunction (e.g., transient ischemic attacks (TIAs), infarcts, lifetime history of cancer, brain tumors, traumatic brain injury, spinal cord injury [489-491], multiple sclerosis [468]. Infectious causes should be queried, including hepatitis C, HIV, syphilis, and herpes viruses. Autoimmune disease should be sought. Thoughtful queries to ascertain disorders not previously diagnosed are required (e.g., prior symptoms of transient ischemic attacks (TIAs) that were ignored). Tumors most likely to metastasize to the brain include breast, lung, melanoma, colorectal and renal. While some cancers are considered occupational, lung cancers are particularly prominent among the cancers considered to be work-related due to significant occupational exposures (e.g., arsenic, asbestos, beryllium, cadmium, chromium (IV) compounds, coal-tar pitch, diesel exhaust, nickel, radon, silica, sulfur mustard, bis(chloromethyl)ether, chloromethyl methyl ether, smoke; see Work-Relatedness).

Questions about radicular neuropathic pain should address radiating pain in the extremities (arms, hands, legs, and/or feet). A history of spinal disorders is often present. See Cervical and Thoracic Spine Disorders and Low Back Disorders Guidelines for evaluation and management of radicular neuropathic pain.

There are many causes of painful peripheral neuropathies [519,520,601-603]. This results in a highly heterogeneous clinical presentation that includes sensory, motor, and mixed sensory-motor neuropathies. A few examples of toxic neuropathies prominently include acrylamide, arsenic, carbon disulfide, mercury, and n-hexane. The general approach is to particularly query and evaluate for peripheral neuropathic pain including nerve trauma, post-surgical nerve injuries [486,598,599], entrapment neuropathies, diabetes mellitus, alcohol use disorder, vitamin deficiencies (e.g., B6, B12), infections (zoster, herpes simplex, HIV, leprosy, syphilis[548,549], family history of neuropathy, rheumatoid arthritis, lupus, and other autoimmune disorders. For those with history(ies) of these systemic disorders, questions addressing duration and adequacy of control is important (e.g., history of lifetime maximum, typical and recent hemoglobin A1c measures; complications of rheumatoid arthritis).

Complex regional pain syndrome is considered neuropathic pain. Please see the CRPS guidance to manage this condition. For radicular pain, please see either the Low Back Disorders and/or Cervical and Thoracic Spine Disorders guideline.

PHYSICAL EXAMINATION

Physical examination maneuvers should include a comprehensive neuromusculoskeletal examination to identify all positive and negative aspects in an attempt to secure a correct diagnosis. These maneuvers include observation, inspection, palpation, cranial nerve examination, range of motion, strength, stretch reflexes, coordination, balance, and sensory exam.

Signs of central neuropathic pain presentations are highly variable and depend on the diagnosis and precise neurological lesion(s). CVAs, MS, and tumors all may present with heterogenous abnormal neurological symptoms and signs.

Signs of peripheral neuropathy differ based on the cause and distributions of lesions. Most are symmetrical and some are asymmetrical. The most common are due to diabetes mellitus and alcohol; thus, most have symmetrical presentations (e.g., reduced monofilament sensation in both feet). Sensory neuropathies usually start with distal abnormalities in the lower extremities, typically including reduced sensation of fine touch that moves proximally as it becomes more severe. Later involvement of the fingers and hands is typical. Motor neuropathies more typically affect distal extremities prior to clinically affecting the proximal extremities. Peripheral neuropathies due to trauma involve that distribution alone and are nearly always mixed sensory-motor, as most nerves have combined functions.

For radicular pain, please see either the Low Back Disorders and/or Cervical and Thoracic Spine Disorders guideline. For complex regional pain syndrome, please see the CRPS guidance.

DIAGNOSTIC CRITERIA

Diagnostic criteria for neuropathic pain categories are as follows:

Probable Diagnosis of Neuropathic Pain	Symptoms, History	Signs	Tests
Central Neuropathic Pain	Burning, lancinating, independent of activity; weakness. History of, or symptoms of, transient ischemic attack, cerebrovascular accident, multiple sclerosis, cancer (especially lung, breast, colorectal, melanoma, renal), traumatic brain injury (especially penetrating), spinal cord injury	May have normal examination or may have abnormalities that include muscle weakness, atrophy, sensibility decrements, stretch reflex abnormalities, gait disturbance. May have signs consistent with underlying diseases (see box to left for examples)	Magnetic resonance Imaging of brain Lumbar puncture Fundoscopic (eye) exam Tests for underlying diseases (e.g., chest x-ray, mammography, urinalysis, skin examination, colonoscopy)
Radicular Neuropathic Pain (see the Low Back Disorders and Cervical and Thoracic Disorders Guidelines)	Burning, radiating pain typically in only one nerve root. Sensory symptoms in the same dermatomal distribution(s) Myotomal symptoms in the same nerve root distribution as above sensory symptoms.	May have normal examination or may have abnormalities in usually only one myotomal/dermatomal distribution(s), including muscle weakness, atrophy, sensibility decrements, stretch reflex abnormalities.	Magnetic resonance imaging EMG/NCS
Peripheral Neuropathic Pain	Burning, lancinating, independent of activity; weakness May have symptoms of a systemic disease (e.g., diabetes mellitus, alcoholism, rheumatoid arthritis, lupus, other	May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch reflex abnormalities, neurotrophic skin changes Signs of zoster, herpes simplex	EMG/NCS Glucose tolerance testing, fasting glucose and/or hemoglobin A1c if risks for diabetes mellitus Possible testing for alcohol (e.g., MCV,

	inflammatory rheumatic disease, myopathies, HIV/AIDS)		GGTP, hepatic enzymes) Rheumatological panels, ESR if concerns about those disorders

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of neuropathic pain is extensive. Below are the more common causes, rather than a complete list.

- Diabetic neuropathy
- Alcoholic neuropathy
- Autoimmune neuropathies
- Stroke pain
- Multiple sclerosis pain
- Amputation
- Peripheral nerve injury
- Radiculopathy
- Radiculitis
- Herpes zoster/Shingles
- HIV/AIDS
- Hypothyroidism
- Nutritional deficiencies
- Pernicious anemia
- Guillain-Barre syndrome
- Intracranial aneurysm
- Bell's palsy
- CNS tumor
- Idiopathic

PROGNOSIS

The prognosis for neuropathic pain is largely determined by the cause and the ability to treat or remove the underlying cause, or causes if multiple. For occupational toxicological causes, the prognosis is generally for slow recovery if exposure ceases. This means that permanent workplace restrictions are usually employed. Similarly, for diabetic neuropathy, intensive management of glucose control generally stops progression and may improve neuropathic symptoms for some. For alcoholic neuropathy, abstinence often slowly reverses the disease. For autoimmune processes, progressive disease usually results, as these are typically untreatable unless related to a treatable rheumatological disorder.

For radicular spine conditions, see the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines.

DIAGNOSTIC RECOMMENDATIONS

LABORATORY TESTS

LABORATORY TESTS FOR PERIPHERAL NEUROPATHIC PAIN

Recommended

Laboratory tests are recommended as a screen to evaluate specific disorders (e.g., diabetes mellitus, alcohol) that may cause or contribute to peripheral neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Patients with peripheral neuropathies of unknown or unclear etiology and without prior diagnostic evaluations. Diagnostic testing should generally include fasting glucose, hemoglobin A1c, a complete blood cell count with differential, thyroid stimulating hormone, creatinine, and hepatic enzymes/functions (AST, ALT, GGTP, albumin), vitamin-B12, and immunofixation. Testing for both diabetes mellitus and signs of alcohol should be routinely performed (i.e., CBC with Mean Cell Volume, GGTP, AST and ALT), as this testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another treatable and common contributing factor. Heavy metals and other occupational tests are usually ordered based on workplace exposure(s, Horlings CGC, 2020, Koszewicz M, 2021).Genetic tests may be appropriate for select patients.

Benefits

Diagnosing a latent condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when either there is a significant change in exposure (e.g., substantial weight gain) or symptoms change.

Rationale

Laboratory tests have been used for the treatment of neuropathic pain. The identification of diabetes mellitus (glucose intolerance) or alcohol use disorder is important to prevent peripheral neuropathy and progression (Hanewinckel et al., 2016, Callaghan et al., 2015, Kazamel et al., 2015, Ziegler et al., 2014, Lazo Mde et al., 2014, Boulton, 2014, Russell et al., 2014, Sadosky et al., 2008, Ziegler, 2011, Ziegler, 2006, Ferrari et al., 2010, Lehmann et al.,

2020,Horlings CGC, 2020, Koszewicz M, 2021). Serological tests are minimally invasive, are unlikely to have substantial adverse effects, are low to moderately costly depending on the specific test ordered, have evidence of diagnostic efficacy, and are thus recommended for focused testing of a few diagnostic considerations.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Laboratory testing, clinical laboratory techniques, laboratory diagnostic, clinical laboratory; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 944 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 944 articles, 20 in CINAHL, 145 in Cochrane Library, 16.700 in Google Scholar, and 0 from other sources.†

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

OCCUPATIONAL NEUROTOXIN EXPOSURE MEASUREMENTS

OCCUPATIONAL NEUROTOXIN EXPOSURE MEASUREMENT FOR DIAGNOSIS OF NEUROPATHIC PAIN

Recommended

Measurement of occupational neurotoxins is recommended to evaluate peripheral neuropathic pain. Examples include n-hexane, acrylamide, arsenic, carbon disulfide, lead (including zinc protoporphyrin), and mercury.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Most workers with neuropathic pain who are exposed to n-hexane, acrylamide, arsenic, carbon disulfide, lead and/or mercury. There are other less common neurotoxins that may also require measurement, particularly based on the occupational and non-occupational histories and exposure(s). Rationale to not obtain measurements may include that the exposures were too long ago to be elevated from that exposure given that compounds half-life; still, measuring them may be relevant for non-occupational exposures and verifying the tests are negative. For lead, zinc protoporphyrin typically remains elevated for two to three

months. Previously obtained temporal measurements may potentially obviate the need to re-measure.

Benefits

Assessing the probability of a work-related cause or material contribution. May provide evidence to reduce or eliminate exposure(s) and improve the prognosis.

Harms

Negligible, however it is possible for both false positive and false negative testing results.

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when there is a significant change in exposure (e.g., work processes change).

Rationale

Examples include n-hexane (Neghab et al., 2012, Kutlu et al., 2009, Sendur et al., 2009, Huang, 2008, Misirli et al., 2008, Puri et al., 2007, Paulson et al., 1976, Centers for Disease Control and Prevention, 2008), acrylamide (Yu et al., 2015, Calleman et al., 1994, Bachmann et al., 1992), arsenic (Sinczuk-Walczak et al., 2014, Sinczuk-Walczak et al., 2010, Barton et al., 2013, Singh et al., 2007, Tseng et al., 2006, Fujino et al., 2006, Baker et al., 2005, Gerr et al., 2000, Gerr et al., 2000, Lagerkvist et al., 1994), carbon disulfide (Rao et al., 2014, Gelbke et al., 2009, Godderis et al., 2006, Huang et al., 2002, Reinhardt et al., 1997, Reinhardt et al., 1997, Chu et al., 1996, Hirata et al., 1996, Ruijten et al., 1993, Aaserud et al., 1990, Grasso, 1988), lead (including zinc protoporphyrin, Gilron et al., 2015, Baker et al., 1984, Bordo et al., 1982, Melgaard et al., 1976, Seppalainen et al., 1972, Seppalainen, 1982, Catton et al., 1970), and mercury (Franzblau et al., 2012, Kazantzis, 2002).

Occupational exposure measurements are not invasive, have no adverse effects, are moderate cost or high cost depending on the number of specific tests ordered, have evidence of accuracy when assayed in reputable laboratories, and are thus recommended for focused environmental testing to assist in the evaluation of patients with peripheral neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: occupational neurotoxin exposure; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match

tab to find and review 3 articles, 0 in CINAHL, 1 in Cochrane Library, 2,890 in Google Scholar, and 0 from other sources†.
Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTIBODY TESTING

ANTIBODIES TO CONFIRM SPECIFIC DISORDERS

Recommended

Antibodies are recommended as a screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) when assessing patients with chronic peripheral neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Patients with peripheral neuropathies without prior diagnostic evaluations, or with incomplete evaluations. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits

Diagnosing an unknown condition. Because there is evidence that multiple disorders interact to raise the risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two because initial testing is known to occasionally become positive with the passage of time.

Rationale

Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases (Lang et al., 2016, Abdulkhaliq A, 2021, Cheng CF, 2021, Foddai SG, 2023, Motta F, 2023). However, routine use of these tests may result in inaccurate diagnoses due to false-positive results, especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. These tests are recommended for focused evaluation of a few diagnostic considerations. However, ordering a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antibody testing, antibodies; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 414 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 414 articles, 1 in CINAHL, 142 in Cochrane Library, 17,500 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANSAR TESTING

ANSAR TESTING FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Not Recommended

Autonomic nervous system (ANSAR) testing is not recommended to assist in diagnosing chronic neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

ANSAR testing has not been shown to alter the clinical management of patients with chronic neuropathic pain. The value of identifying abnormalities in autonomic tone, if they exist, has

not been demonstrated. The value of pharmacologically treating such abnormalities if they are clinically silent and manifested by positive test results has also not been identified. ANSAR is noninvasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with chronic neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Autonomic nervous system, ANSAR testing, ans testing; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 579 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 579 articles, 16 in CINAHL, 2 in Cochrane Library, 200 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NONSPECIFIC INFLAMMATORY MARKERS

NON-SPECIFIC INFLAMMATORY MARKERS TO SCREEN FOR INFLAMMATORY DISORDERS

Sometimes Recommended

Erythrocyte sedimentation rate, C-reactive protein (CRP), and other inflammatory markers are selectively recommended for screening for signs of systemic inflammation in patients with peripheral neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Patients with peripheral neuropathies without prior diagnostic evaluations, or with incomplete evaluations. Subsequent, additional tests may be needed, including rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits

Diagnosing an unknown condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.

Harms

Negligible

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale

Erythrocyte sedimentation rate is the most commonly used systemic marker for nonspecific, systemic inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with chronic neuropathic pain without clear definition of a diagnosis and/or with incomplete explanation of symptoms. However, test results should be interpreted cautiously as the specificity is not high. The ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended, as it the utility of such wide batteries of tests is dubious.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Non-specific inflammatory markers; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 3 articles, 54 in CINAHL, 9 in Cochrane Library, 7,360 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CYTOKINE TESTING

CYTOKINE TESTS FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Not Recommended

Routine cytokine testing is not recommended to diagnose chronic neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Cytokines purportedly determine whether a patient is experiencing pain or has suffered a toxicological insult. However, there are no quality studies that address this premise. Available studies suggest that these markers may be elevated in chronic pain conditions, but these studies did not have adequate control groups and did not control for potential confounders. The range of disorders in which cytokines may be elevated also needs definition, as the current range of conditions appears large (Taaffe et al., 2000, Martelletti et al., 1999, Perini et al., 2005, Covelli et al., 1991, Gratt et al., 2005, Alexander et al., 1998, Chen et al., 2004, Gur et al., 2002, Madson et al., 1994), suggesting they are not specifically isolated to patients with chronic pain. Thus, the specificity of these tests seems likely to be quite low.

A high-quality, 7-year study of 880 elderly subjects evaluated impacts of IL-6 and CRP on both cross-sectional associations with morbidity and long-term mortality (Taaffe et al., 2000). CRP and IL-6 were higher among smokers at baseline and those with higher body mass indexes (BMIs). IL-6 and CRP were also higher among those with hypertension, myocardial infarction, stroke, elevated glycosylated hemoglobin levels, HDL, and number of chronic conditions. Both IL-6 and CRP were inversely related to quartiles of moderate and strenuous physical activity. CRP and/or IL-6 were associated with incidence of hypertension, myocardial infarction, diabetes, and incident cases of chronic conditions. Physical performance measures of changes in grip strength, signature time, chair-rise and 6-m fast walk all were not significant for IL-6 or CRP.

Cytokines need to be rigorously studied to ascertain if there is a place for them in the evaluation and/or management of chronic pain conditions, including stratification for occupationally-relevant diseases. Documentation that the discovery of elevated cytokine levels results in changes in evaluation and/or clinical management would also be necessary. Alternatively, this testing may be useful if the absence of elevated cytokine levels would warrant concluding that a patient does not have a remediable physical cause of pain. While

cytokine testing is minimally invasive, and has a low risk of adverse effects, these tests are high cost, with no evidence that they alter the clinical management of patients with chronic neuropathic pain. Their place in the evaluation of patients with chronic neuropathic pain is yet to be determined and cytokine testing is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Cytokines, cytokine testing; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 441 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 441 articles, 37 in CINAHL, 102 in Cochrane Library, 17,600 in Google Scholar, and 0 from other sources†.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NEEDLE EMG AND NERVE CONDUCTION STUDIES

NEEDLE ELECTROMYOGRAPHY (EMG) AND NERVE CONDUCTION STUDIES TO EVALUATE NEUROPATHIC PAIN

Sometimes Recommended

Needle electromyography (EMG) and nerve conduction studies are selectively recommended for the evaluation of chronic neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Indications include the evaluation of symptoms that are either in one limb or are widespread. Includes the evaluation of potential radicular pain. Also includes the postsurgical population to evaluate the potential for a nerve conduction delay identifiable by NCS with inching/segmental technique. Generally not performed until there is failure to resolve after waiting 4 to 6 weeks to provide for sufficient time to develop EMG abnormalities (usually a minimum of 3 weeks to begin to show significant changes). When there is a clear diagnosis for which EMG will not change the diagnosis and/or management, EMG is not indicated.

Benefits

Diagnosing an unknown condition. Identification of a neurological conduction delay caused by a scar that is remediable.

Harms

Negligible. Modest pain from the procedure

Frequency/Dose/Duration

One evaluation. A second evaluation may be indicated when there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale

Needle electromyography (EMG) and nerve conduction studies (NCS) are often helpful to define the location and extent of neurological impairments, as well as to identify affected nerves and measure the amount of abnormalities (Kural et al., 2017, Rabbi et al., 2019). However, EMG in patients with small fiber neuropathy will have a normal EMG; .small fiber neuropathy may be assisted in diagnosis by a skin biopsy (Lauria, 2007). EMG/NCS is minimally invasive, has minimal adverse effects, is moderately costly, has been found to be diagnostically helpful, and is thus recommended for diagnosis in select patients with neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Needle EMG, nerve conduction, electromyography; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 601 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 601 articles, 67 in CINAHL, 87 in Cochrane Library, 9,730 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SURFACE EMG

SURFACE ELECTROMYOGRAPHY (EMG) FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Not Recommended

Surface electromyography (EMG) is not recommended for aiding in the differential diagnosis of chronic neuropathic pain. There are selective indications for use with biofeedback.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Surface EMG has been used for the treatment of neuropathic pain (Rabbi, 2019). Surface EMG has no clearly demonstrated value in the clinical evaluation or treatment of neuropathic pain with resultant altered management or improved clinical outcomes (Spolaor et al., 2016). Surface EMG may be of use in biofeedback training or gait analysis for musculoskeletal and/or neurologic disorders, but it has no established use in the management of chronic neuropathic pain and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Surface EMG, surface electromyography, electromyography; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 575 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 575 articles, 37 in CINAHL, 106 in Cochrane Library, 9,460 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL MRI

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Not Recommended

Functional magnetic resonance imaging (fMRI) is not recommended for diagnosing chronic neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Functional MRI has been used for the treatment of neuropathic pain (Peeters, 2020). There are no quality studies indicating that the findings on fMRIs are of sufficient sensitivity and specificity to permit identification of the presence or absence of chronic neuropathic pain or to distinguish between different types of chronic pain states. The clinical applications of the test have not been defined. Functional MRI is minimally invasive and has low adverse effects, is high cost, but has no quality evidence of efficacy, and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Magnetic Resonance Imaging, functional MRI; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 3,005 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 3,005 articles, 108 in CINAHL, 280 in Cochrane Library, 17,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 6 diagnostic studies and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LOCAL ANESTHETIC INJECTIONS

LOCAL ANESTHETIC INJECTIONS FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Sometimes Recommended

Local anesthetic injections are selectively recommended for diagnosing chronic neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Chronic neuropathic pain in a specific nerve distribution (e.g., ilioinguinal, genitofemoral) that is otherwise unexplained by other investigation, including imaging or EMG/NCS.

Benefits

Potential to identify a potentially treatable lesion.

Harms

Medicalization, nerve trauma, and continuing a search for a fixable lesion if one is not to be found.

Frequency/Dose/Duration

Once.

Rationale

Local injections (e.g., ilioinguinal, genitofemoral nerve blocks) have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes, although they may assist with diagnosis and consideration of potential treatment options and are thus recommended. However, corticosteroid or neuroablative injections/procedures for localized pain for these nerve blocks are not recommended as the risk of increased pain, local tissue reaction, and neuroma outweigh documented benefits (see Table 6).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Local anesthetic injections; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 1,264 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 1,264 articles, 20 in CINAHL, 866 in Cochrane Library, 18,300 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET) FOR DIAGNOSING CHRONIC NEUROPATHIC PAIN

Not Recommended

Single-photon emission computed tomography (SPECT) is not recommended to evaluate patients with chronic neuropathic pain (aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests). The use of positron emission tomography (PET) is also not recommended to evaluate patients with chronic neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

SPECT/PET have been used for the treatment of neuropathic pain (Alomar, 2018). SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions, but aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with chronic neuropathic pain (Alomar et al., 2018). SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. SPECT and PET scanning are minimally invasive, have negligible adverse effects, are high cost, have no quality evidence of efficacy for diagnosis of neuropathic pain, and therefore are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Tomography, Emission-Computed, Single-Photon, SPECT, Positron Emission Tomography Computed Tomography, PET; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 150 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 150 articles, 12 in CINAHL, 13 in Cochrane Library, 2,560 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term

algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

FUNCTIONAL CAPACITY EVALUATIONS

FUNCTIONAL CAPACITY EVALUATIONS FOR CHRONIC NEUROPATHIC PAIN

Sometimes Recommended

Functional capacity evaluations (FCEs) are selectively recommended for patients with chronic neuropathic pain. FCEs are typically used at the end of treatment or attainment of a healing plateau to attempt to objectify a worker's capability for their job requirements.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Need to objectify worker capabilities compared with either job-specific or general job requirements. Should generally be performed only after treatment options have been utilized, implemented, and stability has been reached with apparent residual deficits.

Benefits

Assess functional abilities and may facilitate greater confidence in return to work.

Harms

Medicalization, worsening of pain with testing. May have misleading results that understate capabilities.

Frequency/Dose/Duration

Generally only once unless there is significant passage of time or apparent change in function.

Rationale

FCEs are one of the few means to attempt to objectify limitations and are frequently used in the workers' compensation system. Because their reliability and validity have not been proven and there are issues with suboptimal efforts that are not necessarily captured, they should be considered as one set of data about what a patient was willing to do on a given day. They should not be used to override the clinical judgment about the work ability of a patient. They particularly should not be viewed as providing objective evidence when there is other corroborating evidence of subjective-objective mismatch(es) or evidence the

patient is able to accomplish more than was demonstrated at the time of the FCE. Most patients will not require an FCE, particularly where the patient is able to articulate a desire to return to work, along with stated capabilities that appear to match the clinical impression. An FCE may be helpful in identifying capabilities at an end of healing for purposes of attempting to support work limitations that are used to assign "permanent" restrictions and disability applications. However, clinicians should be particularly aware of major secondary gain issues when FCEs are performed for these purposes and be particularly vigilant about test-retest reliability, test validity measures, and the need to unequivocally report all measures as well as any evidence of subjective-objective mismatches.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Functional capacity evaluation, FCE; neuralgia, neuropathic pain, nerve pain; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 73 articles in PubMed using Most Recent tab, and we did a secondary search in PubMed using Best Match tab to find and review 73 articles, 1 in CINAHL, 168 in Cochrane Library, 17,400 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TREATMENT RECOMMENDATIONS

ACTIVITY MODIFICATION AND EXERCISE

BED REST FOR NEUROPATHIC PAIN

Not Recommended

Bed rest is not recommended for patients with neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

There is no evidence that bed rest is helpful for neuropathic pain. It has been found to be unhelpful for patients with low back pain (LBP) and other conditions. There are potential adverse effects that reportedly have included venous thromboses and pulmonary emboli

(see Low Back Disorders guideline). Bed rest, although not invasive, has potential for major adverse effects, is costly, has no documented benefits, and thus it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bed rest; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 8,829 articles in PubMed, 14 in CINAHL, 175 in Cochrane Library, 17,200 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AEROBIC EXERCISE FOR NEUROPATHIC PAIN

Sometimes Recommended

Aerobic exercise is selectively recommended for treatment of neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Aerobic exercise has been used for treatment of neuropathic pain (Cooper, 2016; Hammond, 2019; Zhang, 2021; Leitzelar, 2021 & Toloui, 2023). Moderate to severe neuropathic pain; diabetes mellitus and/or significant de-conditioning . However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (Liguori G, 2020) with regard to health screening and risk stratification.

Benefits

Improved function, improved endurance, improved neuropathy control if diabetes is contributing.

Harms

Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Intolerance of weight bearing in severe lower extremity osteoarthrosis. Other musculoskeletal disorders possible (e.g., plantar heel pain).

Frequency/Dose/Duration

Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Transition to home exercise program. The most detailed program for low back pain was walking at least 4 times a week at 60% of predicted maximum heart rate (220-age = maximum heart rate) is recommended (Chatzitheodorou et al., 2007). Benchmarks were 20 minutes during Week 1, 30 minutes during Week 2, and 45 minutes after that point. Nearly all patients should be encouraged to maintain aerobic exercises on a long-term basis additionally to maintain optimal health.

Indications for discontinuation

Non-tolerance, failure to progress, development of another disorder, or reaching a 4 to 6 week timeframe.

Rationale

A trial of treatment for diabetic peripheral neuropathy suggests efficacy of exercise (Gholami et al., 2018). Another trial suggested some efficacy (Hwang et al., 2008), while another trial suggested exercise improved musculoskeletal pain but not neuropathic pain (Cox et al., 2020). There is one moderate quality trial with a combination of aerobic, strengthening and stretching compared with an education control that suggested a trend towards efficacy (Toth et al., 2014). Systematic reviews have also found a relative lack of evidence, while suggesting exercise is important for recovery (Bernetti et al., 2021, Zhang et al., 2021). Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong rationale for select indications, and thus is selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Aerobic exercise, aerobic training, physical activity, exercise, physical exercise; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 620 articles in PubMed, 126 in CINAHL, 177 in Cochrane Library, 16,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 4 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

STRENGTHENING EXERCISE FOR NEUROPATHIC PAIN

Sometimes Recommended

Strengthening exercise is selectively recommended for treatment of neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Moderate to severe neuropathic pain; diabetes mellitus and/or significant strength deficits. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (Liguori G, 2020) with regard to health screening and risk stratification.

Benefits

Improved function, improved strength, improved ability to perform strength-demanding job tasks.

Harms

Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Other musculoskeletal disorders possible (e.g., plantar heel pain).

Frequency/Dose/Duration

Typically start with 3 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises.

Indications for discontinuation

Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4- to 6-week timeframe.

Rationale

One trial suggested efficacy of strengthening exercises for both neuropathic pain and function (Dhawan et al., 2020), while another with three arms suggested all improved in terms of function (Khan et al., 2022). However, another trial suggested an exercise program was ineffective for treatment of post-operative pain (Ammitzbøll et al., 2020). There is one moderate-quality trial with a combination of aerobic, strengthening and stretching compared with an education control that suggested a trend towards efficacy (Toth et al., 2014). There are no trials indicating stretching as a sole intervention is effective. Patients who have significant deconditioning with strength deficits, particularly with mismatches between abilities and job demands are strong candidates for strengthening exercises. Strengthening exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for select indications, and thus are selectively recommended. They may not affect pain, but are likely to improve functional measures.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Resistance Training, strength training, strength exercise; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 178 articles in PubMed, 15 in CINAHL, 252 in Cochrane Library, 17,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 9 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

AQUATIC THERAPY FOR NEUROPATHIC PAIN

Recommended

A trial of aquatic therapy is selectively recommended for patients with neuropathic pain. Patients should meet the referral criteria for supervised exercise therapy and have co-morbidities (e.g., extreme obesity, significant degenerative joint disease, etc.) that preclude effective participation in a weight-bearing physical activity.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Moderate to severe neuropathic pain; non-weight bearing status or partial weight-bearing; diabetes mellitus and/or significant de-conditioning.

Benefits

Improved function, improved endurance, improved neuropathy control if diabetes is contributing.

Harms

Negligible.

Frequency/Dose/Duration

Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Program should include up to 4 weeks of aquatic therapy with progression to a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. For some patients with chronic neuropathic pain, aquatic exercise may be the preferred method. In these few cases, the program should become self-managed and if any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program.

Indications for discontinuation

Non-tolerance, failure to progress, or reaching a 4- to 6-week timeframe.

Rationale

One trial compared aquatic therapy with ambulatory therapy and found dynamic gait improvement in the aquatic group while the land group improved in functional ambulation (Zivi et al., 2018). There is no quality evidence that aquatic exercise is helpful for treatment of neuropathic pain. However, there are circumstances where aquatic exercise may be indicated for treatment of patients with neuropathic pain. These include patients who are either non-weight-bearing or limited weight-bearing, including due to other disorders, that is co-contributing to their neuropathic pain and others who have significant deconditioning due to neuropathic pain. Aquatic exercise is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, and thus is selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Aquatic therapy, swimming, balneotherapy, hydrotherapy, aquatic exercise, water exercise; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 33 articles in PubMed, 2 in CINAHL, 64 in Cochrane Library, 15,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PHYSICAL OR OCCUPATIONAL THERAPY FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of a specific profession (e.g., physical or occupational therapy) to treat neuropathic pain. (However, there are many individual treatments that are often administered by these professionals that are indicated. See specific treatments.)

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Indications

Physical and/or occupational therapy have been used for the treatment of neuropathic pain (de Souza, 2016; Bernetti, 2020, & Kannan, 2023). Studies are heterogeneous with numerous simultaneous interventions, thus sound conclusions cannot be drawn from them (Hurwitz et al., 2002, Hurwitz et al., 2006, Kjaersgaard-Andersen et al., 1990, Ylinen et al., 2007, Bronfort et al., 2001, Chiu et al., 2005, Critchley et al., 2007, Falla et al., 2007, Ginn et al., 1997, Helewa et al., 2007, Hoving et al., 2006, Jordan et al., 1998, Moseley, 2002, Persson et al., 2001, Gudavalli et al., 2006, Hurwitz et al., 2005, Kaapa et al., 2006, Ylinen et al., 2003). See individual treatment modalities to ascertain the available evidence on specific treatment interventions, including exercises and other treatments.

Rationale

Studies are heterogeneous with numerous simultaneous interventions, thus sound conclusions cannot be drawn from them (Hurwitz et al., 2002, Hurwitz et al., 2006, Kjaersgaard-Andersen et al., 1990, Ylinen et al., 2007, Bronfort et al., 2001, Chiu et al., 2005, Critchley et al., 2007, Falla et al., 2007, Ginn et al., 1997, Helewa et al., 2007, Hoving et al., 2006, Jordan et al., 1998, Moseley, 2002, Persson et al., 2001, Gudavalli et al., 2006, Hurwitz et al., 2005, Kaapa et al., 2006, Ylinen et al., 2003). See individual treatment modalities to ascertain the available evidence on specific treatment interventions, including exercises and other treatments that are often provided by occupational and physical therapists.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Physical therapy, occupational therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 2,893 articles in PubMed, 264 in CINAHL, 1,696 in Cochrane Library, 17,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MEDICATIONS

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) FOR CHRONIC NEUROPATHIC PAIN

Recommended

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended for treatment of chronic neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Neuropathic pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as second-line medications,

often after tricyclic or SNRI anti-depressants are utilized which have considerably greater evidence of efficacy. In some patients, NSAIDs may be the preferred initial therapy due to the low adverse effect profile in working age adults. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. Generally, generic ibuprofen, naproxen, or other older-generation NSAIDs are recommended as second-line medications. Third-line medications should include one of the other generic medications. COX-2 selective agents are recommended when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety-critical workers.

Harms

Gastrointestinal adverse effects are especially prominent in those with a past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Individuals who are elderly, have diabetes mellitus, or have rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the highly and more-selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders). It appears that despite widespread usage, diclofenac does not have clear superiority (at least for LBP where it has been trialed), and it may have increased risks of adverse cardiovascular events (McGettigan et al., 2006), thus diclofenac is not recommended.

Frequency/Dose/Duration

For most patients, scheduled dosage, rather than as needed, is preferred to avoid adverse effects of other treatment options, but prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities may require more frequent monitoring. Use of an adjunctive cytoprotective agent may also be warranted. Topical NSAIDs are another viable option, especially for those with more localized pain (Ahmed et al., 2015).

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

NSAIDS have been used for treatment of neuropathic pain (Rasmussen-Barr, 2016). One randomized crossover trial of topical diclofenac for treatment of either post-herpetic neuralgia or CRPS found evidence of efficacy (Ahmed et al., 2015). There also is one moderate-quality trial with trend towards efficacy of a Cox-2 inhibitor (Shackelford et al., 2009). There is another moderate-quality trial of topical diclofenac for treatment of neuropathic pain (Ahmed et al., 2015). NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for radicular pain (and thus is inferred for other neuropathic pain), and therefore are recommended. However, diclofenac is not recommended due to apparent increased adverse cardiovascular events, thus other NSAIDs are recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Anti-Inflammatory Agents Non-Steroidal, NSAIDs, non-steroidal anti-inflammatory drugs; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 476 articles in PubMed, 27 in CINAHL, 270 in Cochrane Library, 16,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACETAMINOPHEN FOR NEUROPATHIC PAIN

Recommended

Acetaminophen is recommended for treatment of chronic neuropathic pain, particularly in patients with contraindications for NSAIDs.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Neuropathic pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen, or other older-generation NSAIDs are recommended before acetaminophen. Acetaminophen is a reasonable alternative or can be used as an adjunct, although evidence suggests it is modestly less efficacious.

Benefits

Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.

Harms

Negligible if used as prescribed. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.

Frequency/Dose/Duration

Generally prescribed up to 3.5g/day in divided doses, usually QID dosing.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There are no quality trials of acetaminophen for treatment of neuropathic pain. This drug does have evidence of efficacy for treatment of LBP, although not as successful as diflunisal (Hickey, 1982), mefenamic acid (Evans et al., 1980), indomethacin (Evans et al., 1980), or aspirin (Evans et al., 1980). Thus, while the evidence suggests efficacy of acetaminophen (also called paracetamol), it appears these medications are modestly less efficacious than NSAIDs (although generally safer) at least for LBP. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of LBP, and is thought to have modest efficacy. Therefore, it is recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Acetaminophen; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 118 articles in PubMed, 31 in

CINAHL, 210 in Cochrane Library, 15,900 in Google Scholar, and 0 from other sources†.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRICYCLIC, TETRACYCLIC, AND SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR ANTIDEPRESSANTS FOR NEUROPATHIC PAIN

Recommended

Tricyclic, tetracyclic, and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants are recommended for treatment of neuropathic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Neuropathic pain sufficiently severe to require medication. Anti-depressants are considered among the first-line agents to treat neuropathic pain. Several of the anti-depressants may also be used to take advantage of the sedating properties for nocturnal sleep disturbance due the neuropathic pain. One trial suggested superiority of combination therapy of nortriptyline with gabapentin compared to each drug alone (O'Connor, 2009), while another suggested superiority of combining amitriptyline 25mg/day with pregabalin 75mg BID (Achar et al., 2010).

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Dry mouth, constipation, suicide risk, urinary retention, glaucoma, QT prolongation, sinus tachycardia, dizziness, weight gain. Cardiotoxicity.

Frequency/Dose/Duration

Prescribe at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until a sub-maximal or maximal dose is achieved, sufficient effects are achieved, or adverse effects occur. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment,

particularly if they are compliant with the elements of a functional restoration program. One reportedly efficacious combination was nortriptyline 100 mg with gabapentin 3600 mg per day (O'Connor, 2009), while another was amitriptyline 25mg/day with pregabalin 75mg BID (Achar et al., 2010).

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

There are multiple moderate-quality trials of tricyclic/tetracyclic and SNRI antidepressants that included desipramine, amitriptyline, maprotiline, nortriptyline, clomipramine, duloxetine, venlafaxine (Gilron et al., 2009, Bowsher D, 1997, Achar et al., 2010)(Watson CP, 1982, Watson PNC, 1992, Carasso et al., 1979)(Hall et al., 2010, Kajdasz et al., 2007, Sindrup et al., 2003)(Watson, 1998). Quality data suggest modest efficacy against placebo (Matsuoka et al., 2019, Rowbotham et al., 2004, Schukro et al., 2016, Vrethem et al., 1997, Max et al., 1992, Yasuda et al., 2011, Gao et al., 2015, Sindrup et al., 2003, Kajdasz et al., 2007, Hammack et al., 2002, Watson et al., 1982); however, magnitudes of benefit are not large. Cochrane reviews found more evidence for amitriptyline than nortriptyline (Moore et al., 2015, Derry et al., 2015) and limited evidence regarding duloxetine (Gallagher et al., 2015) with concerns for biases in many studies.

Comparable efficacy was been shown between amitriptyline and duloxetine, as well as between amitriptyline and nortriptyline (Watson et al., 1998). Superiority of venlafaxine to carbamzepine has been shown (Jia HY, 2006). Data suggest mostly comparable efficacy comparing duloxetine and gabapentin (Khasbage et al., 2021, Tesfaye et al., 2013, Majdinasab et al., 2019). Comparable efficacy was shown between lamotrigine and amitriptyline (Jose et al., 2007) and between capsaicin and amitriptyline (Biesbroeck et al., 1995). One trial suggested pregabalin was superior to either venlafaxine or carbamazepine (Razazian et al., 2014). One trial suggested combination therapy of nortriptyline with gabapentin was superior to single drug arms and another trial suggested superiority of a combination of amitriptyline and pregabalin (Achar et al., 2010). One study suggested amitriptyline was more effective than maprotiline (Watson et al., 1992).

Tricyclic, tetracyclic, and SNRI antidepressants are not invasive, have adverse effects that range from modest to intolerable, are low cost, have consistent evidence of modest efficacy for treatment of neuropathic pain, and are thus recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms:

Antidepressive Agents Tricyclic, Serotonin and Noradrenaline Reuptake Inhibitors, TCA, SNRI; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 131 articles in PubMed, 111 in CINAHL, 49 in Cochrane Library, 8,470 in Google Scholar, and 0 from other sources†. We considered for inclusion 11 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 25 articles considered for inclusion, 5 randomized trials and 9 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) AND NOREPINEPHRINE-DOPAMINE REUPTAKE INHIBITORS (NDRIS) FOR NEUROPATHIC PAIN

Sometimes Recommended

Selective serotonin reuptake inhibitors (SSRIs) and norepinephrine-dopamine reuptake inhibitors (NDRIs) are selectively recommended for the treatment of neuropathic pain.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Neuropathic pain sufficiently severe to require medication. Tricyclic, tetracyclic, and SNRI anti-depressants are considered among the first-line agents to treat neuropathic pain. SSRI antidepressants have substantially less evidence of efficacy and thus should generally be considered second- or third-line agents.

Benefits

Modestly improved pain control.

Harms

QT prolongation, increased suicide risk, dry mouth, trouble sleeping. Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Serotonin syndrome.

Frequency/Dose/Duration

Regimens used in the quality trials include escitalopram 20mg/day (Otto M, 2008, Brasch-Andersen C, 2011), bupropion SR 150mg/day (Semenchuk MR, 2001), and up to 60mg/day of fluoxetine. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program.

Indications for discontinuation

Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale

Studies evaluating SSRIs for neuropathic pain suggest modest efficacy, including with escitalopram (Otto M, 2008, Arnold P, 2008). Another trial found desipramine superior to fluoxetine (Rowbotham MC, 2005). Because SSRI antidepressants have evidence of efficacy for treatment of fibromyalgia but have little evidence of efficacy for treatment of nociceptive chronic pain conditions (see Low Back Disorders Guideline), the mechanism of potential efficacy for peripheral neuropathic pain is unclear. As one trial suggested potentially superior results with desipramine (Rowbotham MC, 2005), and evidence is more robust for the other antidepressants, treatment with tricyclics and SNRIs as initial prescriptions is generally recommended before SSRIs.

Selective serotonin reuptake inhibitors (e.g., escitalopram, fluoxetine), bupropion, mirtazapine, and trazodone are not invasive, have moderate adverse effects, are low to moderate cost, have limited evidence of efficacy, and are thus selectively recommended for treatment of neuropathic pain. SSRIs and these other agents may separately be indicated for the treatment of depression, although an agent that also has greater evidence of efficacy against chronic neuropathic pain may be a better option. There is currently no quality evidence for norepinephrine-dopamine reuptake inhibitors, and thus they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Selective Serotonin Reuptake Inhibitors, SSRI; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 16 articles in PubMed, 31 in CINAHL, 66 in Cochrane Library, 16,800 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are

reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTIPSYCHOTIC MEDICATIONS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of antipsychotic medications for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of antipsychotic medications for the treatment of neuropathic pain. Antipsychotic medications are not invasive, have adverse effects, and are low to moderate cost. In the absence of evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antipsychotic agents, ; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 8 articles in PubMed, 3 in CINAHL, 13 in Cochrane Library, 11,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTICONVULSANT MEDICATIONS FOR NEUROPATHIC PAIN

Recommended

Anticonvulsant medications are moderately recommended for treatment of neuropathic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence High

Indications

Moderate to severe painful neuropathic pain sufficient neuropathic pain to require medication. Generally, anti-convulsants are considered a potential adjunct as a second- or third-line treatment for chronic neuropathic pain, after attempting other treatments (e.g., antidepressants, aerobic exercise, other exercise).

Benefits

Modest pain reduction. May include reduced sleep disturbance.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also may have adverse effects including nausea, vomiting, dizziness, confusion, somnolence and weight gain. Carbamazepine may be associated with fluid and electrolyte abnormalities. Topiramate may cause kidney stones and ocular toxicity.

Frequency/Dose/Duration

Frequency and dosing are based on the medication prescribed. Duration of use for neuropathic pain patients may be indefinite, although many of these patients do not require indefinite treatment as the condition usually often resolves or improves. Gabapentin dose is initiated usually at 300mg/day and gradually raised.

Indications for discontinuation

Resolution of pain, lack of efficacy, intolerance, or development of adverse effects. Monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.

Rationale

There is high- and moderate-quality evidence of efficacy for multiple anticonvulsants (gabapentin, pregabalin, lamotrigine, carbamzepine, and topiramate) for treatment of peripheral neuropathic pain in comparison with placebo (Vinik et al., 2007, Silver et al., 2007, Harke H, 2001, Eisenberg E, 2001, Raskin et al., 2004, Backonja et al., 1998, Lesser et al., 2004, Richter et al., 2005, Dworkin et al., 2003). Although not all studies are positive (Thienel et al., 2004, Grosskopf et al., 2006, Wallace et al., 2010, Holbech JV, 2011), the highest quality studies and those with larger sample sizes suggest efficacy, although magnitudes of benefit are modest. Most quality evidence is of peripheral neuropathic pain, although at least one quality trial included patients with multiple sclerosis (Silver et al., 2007).

Superiority of venlafaxine to carbamzepine has been shown (Jia HY, 2006). Data suggest mostly comparable efficacy comparing duloxetine and gabapentin (Khasbage et al., 2021, Tesfaye et al., 2013, Majdinasab et al., 2019). Comparable efficacy was shown between lamotrigine and amitriptyline (Jose et al., 2007). One trial suggested pregabalin was superior to either venlafaxine or carbamazepine (Razazian et al., 2014).

There is not evidence that adding lamotrigine to gabapentin is efficacious (Silver et al., 2007). Comparable efficacy has been suggested when comparing gabapentin and nortriptyline (Chandra et al., 2006). Valproic acid did not prove efficacious in one study (Otto M, 2004); however, in another study, divalproex showed efficacy for post-herpetic neuralgia when compared to placebo at 8 weeks (Kocher, 2005). Anticonvulsants are not invasive, have some adverse effects, are moderate cost, have some quality evidence of modest efficacy for treatment of neuropathic pain, and are recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Anticonvulsants; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 92 articles in PubMed, 57 in CINAHL, 96 in Cochrane Library, 18,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 21 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 19 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ANTIVIRAL MEDICATIONS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of antiviral medications to treat neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Antivirals have been used for treatment of neuropathic pain (Zhang, 2022). Two moderate-quality placebo-controlled trials conflict regarding efficacy of acyclovir and included 9-year follow-up data. One trial found comparable results between valacyclovir and famciclovir, but lacked placebo control (Tyring et al., 2000). In a study with oral acyclovir, the incidence of postherpetic neuralgia was not reduced (Mondelli et al., 1996)(Acosta et al., 2001); only 10% of study participants reported pain reduction. In another study (Huff et al., 1988, Huff et al., 1993), median pain duration was 20 days in acyclovir treated individuals vs. 62 days in placebo; however, the authors also noted that the absence of pain at the onset of cutaneous herpes zoster did not preclude later development of the disease. A study using amantadine was inconclusive (Galbraith, 1983). It has been suggested that the medication needs to be administered within 2 days to be effective. Antiviral medications are not usually invasive, have low adverse effects, and are moderate cost. However, in the absence of evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antiviral Agents; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 52 articles in PubMed, 15 in CINAHL, 67 in Cochrane Library, 16,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CLONIDINE FOR NEUROPATHIC PAIN

Recommended

Topical clonidine is recommended for treatment of neuropathic pain.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Neuropathic pain of sufficient severity to warrant medication. May be more helpful when the surface area is more limited than generalized.

Benefits

Reduction in pain.

Harms

Itching, redness, skin irritation, blurred vision, chest pain, palpitations, fatigue, dizziness, lightheadedness, irregular breathing, headache, seizures, swelling.

Frequency/Dose/Duration

Clonidine gel 0.1% applied to affected areas TID.

Indications for discontinuation

Intolerance, adverse effects, lack of efficacy, non-compliance and/or sufficient resolution of pain.

Rationale

One placebo-controlled trial found reduced pain with topical clonidine (Campbell et al., 2012). Another trial found comparable efficacy of topical clonidine compared to topical capsicum (Kiani et al., 2015), which elsewhere has evidence of efficacy. A low-quality trial found clonidine had additive benefit in addition to gabapentin (Hassanzadeh et al., 2023). A Cochrane review found topical clonidine may provide some benefit; however, the "evidence is very uncertain" (Serednicki et al., 2022). Clonidine is not invasive, has adverse effects, and is low to moderate cost cumulatively, and has some evidence of efficacy and is thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Clonidine; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 61 articles in PubMed, 28 in CINAHL, 169 in Cochrane Library, 7,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DEXTROMETHORPHAN FOR NEUROPATHIC PAIN

Sometimes Recommended

Dextromethorphan is selectively recommended for the treatment of patients with neuropathic pain.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients with peripheral neuropathies who have failed to sufficiently respond to NSAIDs, TCAs, and anticonvulsant agents, including gabapentin and pregabalin.

Benefits

Improved pain control, may include reduced sleep disturbance.

Harms

Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety-sensitive jobs.

Frequency/Dose/Duration

Doses range widely. In the successful trial, an average daily dose of 400mg was utilized. Dextromethorphan is recommended in doses that are on average at least 3 times higher than the antitussive dose, and carefully titrated to therapeutic effect. Duration for patients with chronic neuropathic pain generally be limited to 2 or 3 months as there is no evidence of long-term safety, although longer periods of use may be reasonable.

Indications for discontinuation

Resolution of neuropathic pain, lack of efficacy, development of adverse effects.

Rationale

There are few quality studies evaluating NMDA receptor/antagonists other than dextromethorphan (Galer BS, 2005, Grace RF, 1998, Wu CT, 1999). However, the quality studies of dextromethorphan involve many different patient populations and, in aggregate, somewhat conflict but on balance suggest some modest benefit. One trial suggested differences based on diagnoses, with diabetic neuropathy patients, but not postherpetic neuralgia patients, responding (Sang et al., 2002). A trial of largely central neuropathic pain was negative (McQuay HJ, 1994). Some evidence suggests that dextromethorphan may have modest morphine-sparing effects in limited circumstances, while memantine appears inferior to dextromethorphan (Sang et al., 2002, Martin et al., 2019). One trial suggested dextromethorphan was associated with reduced pain after ketamine infusion for up to 3 months compared with placebo or memantine (Martin et al., 2019). There is evidence that dextromethorphan reduces pain in diabetic neuropathy patients. An experimental model of pain in healthy subjects also has reportedly failed to confirm dextromethorphan's additional benefits beyond morphine (Frymoyer et al., 2007).

There is insufficient evidence to support the use of amantadine and memantine and of low doses of dextromethorphan. Published studies of high doses of dextromethorphan show relief in painful diabetic neuropathy, but not in postherpetic neuralgia. The basic concept of NMDA antagonism in neuropathic pain appears sound, but these agents also have high adverse effects. Thus, there is a need for quality studies and perhaps development of newer agents with fewer CNS adverse effects.

Dextromethorphan is not invasive, has high adverse effects, has limited evidence of modest efficacy in some patient populations with neuropathic pain, and thus is selectively recommended after failure of multiple other medications.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Dextromethorphan; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 10 in CINAHL, 21 in Cochrane Library, 2770 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MUSCLE RELAXANTS FOR ACUTE EXACERBATIONS OF NEUROPATHIC PAIN

Sometimes Recommended

Muscle relaxants are selectively recommended for brief use as a second- or third-line agent in acute exacerbations of neuropathic pain with muscle spasms.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Moderate to severe neuropathic pain with musculoskeletal manifestations, especially muscle spasm. (See Low Back Disorders Guideline for other detailed indications.) Not indicated for ongoing chronic pain treatment.

Benefits

Improvement in muscle spasm and pain related to muscle spasm

Harms

Sedation, intolerance, medicalization

Frequency/Dose/Duration

Due to the potential for misuse, carisoprodol is not recommended. Chlorzoxazone and chlormezanone are also not indicated due to incidence of adverse effects. Otherwise initial dose in evening (not during workdays or if patient operates a motor vehicle, though daytime use acceptable if minimal CNS-sedating effects). If significant daytime somnolence results, particularly if it interferes with performance of conditioning exercises and other components of the rehabilitation process or treatment plan, discontinue or prescribe a reduced dose. Duration for exacerbations of chronic pain is limited to a couple weeks. Longer-term treatment is generally not indicated.

Indications for discontinuation

Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, other adverse effects.

Rationale

There are no quality studies evaluating muscle relaxants for treatment of neuropathic pain. However, they have been evaluated in quality studies evaluating chronic back and neck pain (Bercel, 1977, Brown et al., 1978, Hingorani, 1971), although there are far more studies on

acute LBP (see Low Back Disorders guideline/Salzmann et al., 1992). The quality of the studies comparing these agents to placebo are likely overstated due to the unblinding that would be inherent in taking a drug with substantial CNS-sedating effects. The adverse effect profile is concerning (Lofland et al., 2001).

Most concerning is the significant potential for CNS sedation, which has typically ranged between 25 to 50%. There are some studies indicating more than 50% of the patients are affected by CNS sedation. Thus, prescriptions for skeletal muscle relaxants for daytime use should be carefully weighed against the patient's need to drive vehicles, operate machinery, or otherwise engage in occupations where mistakes in judgment may have serious consequences. Skeletal muscle relaxants also have a modest, but significant, potential for misuse (Elder, 1991). They should be used cautiously in patients with a history of any substance use disorder should be with caution.

Skeletal muscle relaxants are not recommended for continuous management of subacute or chronic spine pain or other chronic musculoskeletal disorders, although they may be reasonable options for select acute pain exacerbations or for a limited trial as a third- or fourth-line agent in more severely affected patients in whom NSAIDs and exercise have failed to control symptoms.

Diazepam appears to be inferior to other skeletal muscle relaxants (Brown et al., 1978, Basmajian, 1978), has a higher incidence rate of adverse effects, and is addictive. Therefore, diazepam is not recommended for use as a skeletal muscle relaxant. Evidence suggests that carisoprodol is comparable to cyclobenzaprine. Chlorzoxazone has been associated with hepatocellular toxicity. Chlormezanone has been implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis. Carisoprodol is particularly prone to misuse; thus, carisoprodol, chlorzoxazone, and chlormezanone are not recommended.

Muscle relaxants are not invasive, have significant adverse effects, are low to moderately costly and do not have evidence of efficacy to treat neuropathic pain. However, they have indications for short-term treatment of muscle spasms and exacerbations and are selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: muscle relaxants; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 74 articles in PubMed, 16 in CINAHL, 102 in Cochrane Library, 9990 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MAGNESIUM FOR NEUROPATHIC PAIN

Not Recommended

Magnesium is not recommended for the treatment of neuropathic pain.

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Low

Rationale

There are three moderate-quality studies of magnesium for treatment of neuropathic pain, with all suggesting lack of efficacy (Kim YH, 2015, Pickering et al., 2011, Pickering et al., 2020). Magnesium is noninvasive when administered orally (or minimally invasive if intravenous), has low to moderate adverse effects, and is low to moderate cost. However, with evidence of inefficacy, magnesium is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Magnesium; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 14 articles in PubMed, 9 in CINAHL, 16 in Cochrane Library, 12,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TUMOR NECROSIS FACTOR-ALPHA BLOCKERS FOR NEUROPATHIC PAIN

Not Recommended

TNF-alpha blockers are not recommended for treatment of chronic neuropathic pain.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Tumor necrosis factor-alpha blockers have been used for treatment of neuropathic pain (Jing, 2017). TNF-alpha blockers have been evaluated in a small but high-quality study and found to be ineffective (Nguyen et al., 2015). They have been found in another study to be ineffective (Korhonen et al., 2006, Korhonen et al., 2005). TNF-alpha blockers are minimally invasive, have adverse effects, and are high cost. Due to their lack of efficacy, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Tumor necrosis factor-alpha blockers, Etanercept, Infliximab, Adalimumab, certolizumab pegol, golimumab; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 21 articles in PubMed, 5 in CINAHL, 64 in Cochrane Library, 245 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TOPICAL NSAIDS FOR CHRONIC PAIN

Sometimes Recommended

Topical NSAIDs are selectively recommended for treatment of neuropathic pain (where target tissue is superficially located).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia,Ahmed et al., 2015), peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation.

Benefits

Improved pain control

Harms

Dry skin, erythema, pruritus, irritation, paresthesias. Allergies to adhesives in patches may occur.

Frequency/Dose/Duration

Diclofenac 1.5% lotion TID was used in the one quality trial.

Indications for discontinuation

Adverse effects, intolerance, sufficient improvement to no longer require treatment.

Rationale

Topical NSAIDs have been used for treatment of neuropathic pain (Casale, 2017). There is one moderate-quality trial showing efficacy of diclofenac lotion 1.5% for treatment of neuropathic pain from post-herpetic neuralgia and CRPS (Letz et al., 2000). Another moderate-quality trial suggested efficacy of topical aspirin. Yet one moderate-quality trial suggested aspirin superiority but not for diclofenac or indomethacin. However, the target tissue for neuropathic pain is often too deep for clear justification of use of topical NSAIDs. Topical NSAIDs are not invasive, have low adverse effects, are high cost for a typical treatment regimen, have evidence of efficacy for post-herpetic neuralgia, and therefore are recommended for neuropathic pain with superficial pain generation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Topical NSAIDs; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 20 articles in PubMed, 5 in CINAHL, 84 in Cochrane Library, 11,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from

Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TOPICAL KETAMINE AND AMITRIPTYLINE (ALONE OR IN COMBINATION) FOR NEUROPATHIC PAIN

Not Recommended

Topical ketamine and amitriptyline (alone or in combination) are not recommended for the treatment of neuropathic pain.

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Moderate

Rationale

Topical creams (ketamine, amitriptyline) have been used for treatment of neuropathic pain (Thompson, 2015; Kocot-Kepska, 2017; & Crul, 2020). Studies that compared ketamine cream with topical amitriptyline for patients with diabetic neuropathy (Razmjou et al., 2015) and chemotherapy-induced peripheral neuropathy (Gewandter et al., 2014) found a lack of efficacy. Another study was also negative that used 2% amitriptyline, 1% ketamine, or a combination of 1% ketamine and 2% amitriptyline for patients with post-herpetic neuralgia (Beyaz et al., 2016). These creams are non-invasive, have relatively moderate cost, but are not recommended due to their lack of efficacy.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Topical creams, topical ketamine, topical amitriptyline; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 69 articles in PubMed, 21 in CINAHL, 261 in Cochrane Library, 5,580 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 7 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CAPSAICIN PATCHES FOR NEUROPATHIC PAIN

Recommended

Topical capsaicin is moderately recommended for treatment of neuropathic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia), peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation. Most data suggest lack of efficacy for diabetic neuropathy and painful polyneuropathy (Kulkantrakorn K, 2013, Low PA, 1995).

Benefits

Improved pain control.

Harms

Erythema, burning, pain, pruritus, irritation.

Frequency/Dose/Duration

One capsaicin patch applied for 60 minutes, with improvements lasting up to 12 weeks (Backonja et al., 2008, Backonja et al., 2010, Irving et al., 2011, Webster et al., 2010). One open-label extension suggested the benefits may last to 12 months (Backonja et al., 2010). One trial also suggested efficacy of capsaicin cream 0.075% TID to QID for 6 weeks for post-herpetic neuralgia (Bernstein et al., 1989).

Indications for discontinuation

Adverse effects, intolerance, sufficient improvement to no longer require treatment.

Rationale

Capsaicin patches have been used for treatment of neuropathic pain (Burness, 2016; van Nooten, 2017; Yong, 2017; BLair, 2018; Sultana, 2020; & Giaccari, 2021). Multiple moderate-quality trials suggest efficacy of capsaicin for treatment of post-herpetic neuralgia and other neuropathic pain (Backonja et al., 2008, Irving et al., 2011)(Webster et al., 2010, Irving et al., 2012, Clifford et al., 2012, Haanpaa et al., 2016)(Simpson et al., 2017, Hussain et al., 2021, Jensen et al., 2014, Olusanya et al., 2023, Vinik et al., 2016). One trial found efficacy at 1 year (Backonja et al., 2010). One trial found capsaicin superior to gabapentin (Haanpaa et al., 2016, Cruccu et al., 2018). A Cochrane review also found evidence of efficacy, especially with high concentrations (>5%) of capsaicin (Derry et al., 2017). However, two trials of capsaicin cream for treatment of neuropathic pain were negative (Kulkantrakorn K, 2013, Low PA, 1995). Capsaicin is not invasive, has low adverse effects, is high cost, has evidence of efficacy for treatment of peripheral neuropathic pain, and thus is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Capsaicin, capsaicin patch; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 107 articles in PubMed, 106 in CINAHL, 226 in Cochrane Library, 6,450 in Google Scholar, and 0 from other sources†. We considered for inclusion 19 from PubMed, 2 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 24 articles considered for inclusion, 11 randomized trials and 6 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LIDOCAINE PATCHES FOR NEUROPATHIC PAIN

Recommended

Lidocaine patches are moderately recommended for treatment of peripheral neuropathic pain when there is localized pain amenable to topical treatment.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Moderate to severe peripheral neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia), peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation (Demant et al., 2015, Meier et al., 2003, Rowbotham MC, 1996). One quality trial (Galer et al., 1999) evaluated treatment of CTS with pain as a central complaint when other treatable causes of the pain have been eliminated and after more efficacious treatment strategies, such as splinting and glucocorticosteroid injection(s), have been attempted.

Benefits

Modest improvements in pain.

Harms

Dermal irritation and intolerance; may have adverse systemic effects if widespread applications of numerous patches.

Frequency/Dose/Duration

Lidocaine patch 5%, up to 4 patches applied up to 12 hrs/day. Duration of use may be ongoing for chronic, localized pain, although most patients do not require indefinite treatment. Caution is warranted regarding widespread use of topical anesthetics for potential systemic effects from widespread administration (Nalamachu et al., 2006). Topical 5% lidocaine medicated plaster has also been used (Binder et al., 2009, Baron et al., 2009, Baron et al., 2009, Baron et al., 2009), as well as lidocaine spray (Kanai et al., 2009).

Indications for discontinuation

Resolution, intolerance, adverse effects, lack of benefits, or failure to progress over a trial of at least 2 weeks.

Rationale

Lidocaine patches have been reportedly effective for treatment of localized peripheral neuropathic pain (Wang et al., 2023, Hussain et al., 2021, Rowbotham MC, 1996, Meier et al., 2003, Demant et al., 2015). Topical lidocaine has been suggested to improve pain associated with CTS and appears to be somewhat more effective than naproxen (Nalamachu et al., 2006). This provides some basis for a consensus recommendation for treatment of peripheral neuropathic pain. Lidocaine patches are not invasive, generally have a low adverse effect profile, are moderately costly, have some evidence of efficacy for treatment of carpal tunnel syndrome, and thus are recommended for treatment of peripheral neuropathic pain. They are not recommended for central neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms:

Lidocaine, Lidocaine patches; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 549 articles in PubMed, 105 in CINAHL, 1132 in Cochrane Library, 9,490 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MEMANTINE FOR NEUROPATHIC PAIN

Not Recommended

Memantine is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Some evidence suggests that dextromethorphan may have modest morphine-sparing effects in limited circumstances, while memantine appears inferior to dextromethorphan (Sang et al., 2002, Martin et al., 2019). One trial suggested dextromethorphan was associated with reduced pain after ketamine infusion for up to 3 months compared with placebo or memantine (Martin et al., 2019). Memantine is not invasive, has high adverse effects, has evidence suggesting lack of efficacy, and is thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Memantine; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 6 articles in PubMed, 2 in CINAHL, 2 in Cochrane Library, 1,460 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

VITAMIN B FOR NEUROPATHIC PAIN

Not Recommended

Vitamin B is not recommended for treatment of neuropathic pain. However, treatment of those with vitamin B deficiencies is indicated.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

B vitamins have been used for treatment of neuropathic pain (Fonseca, 2012; Schloss, 2016; Xu, 2016; Ozen, 2017; Sil, 2018; Xu, 2020; Didangelos, 2020; Didangelos, 2021; Khalil, 2021; Karaganis, 2021 & Farah, 2022). There are many randomized trials of various vitamin B compound(s). Most of the quality, placebo-controlled trials suggest a lack of efficacy of vitamin(s) B for either treatment or prevention of neuropathy (Rostock et al., 2013, Schloss et al., 2017, Stracke et al., 2008, Farvid et al., 2011, Fraser et al., 2012) while a few suggest some efficacy (Haupt et al., 2005, Didangelos et al., 2021, Fonseca et al., 2013). Vitamin B compounds have no to low adverse effects, and are low cost. As most placebo-controlled trials showed a lack of efficacy, they are not recommended. However, those with documented vitamin B deficiency should be treated and there is a low threshold for treatment of those with suspected vitamin B deficiencies.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Vitamin B Complex, B vitamins; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 82 articles in PubMed, 11 in CINAHL, 22 in Cochrane Library, 17,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 12 from PubMed, 3 from CINAHL, 0 from Cochrane Library, 15 from Google Scholar, and 0 from other sources. Of the 30 articles considered for inclusion, 25 randomized trials and 5 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HOT AND COLD THERAPIES

CRYOTHERAPY (SELF-APPLICATION OR IN-OFFICE) FOR NEUROPATHIC PAIN

Not Recommended

Cryotherapies are not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

This literature base is weak with many potential biases. Cryotherapies have been shown to be ineffective in multiple studies (Ng et al., 2020, Simsek et al., 2021, Ruddy et al., 2019). One study found exercise to be superior (Simsek et al., 2021), whereas cryotherapies were suggested to be weakly effective in another study (Beijers et al., 2020). Cryotherapies were superior to TENS (Elshinnawy et al., 2024) in one trial, even though TENS does not appear to be an effective treatment. Cryotherapies are not invasive, have minimal adverse effects, and are low to moderate cost depending on mode and length of treatment. Because most evidence suggests lack of efficacy, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Cryotherapy, cold therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 182 articles in PubMed, 16 in CINAHL, 486 in Cochrane Library, 6,720 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 2 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 0 from other sources. Of the 14 articles considered for inclusion, 7 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DIATHERMY FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against diathermy for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Diathermy has not been shown effective in quality studies for the treatment of chronic neuropathic pain. A low-quality study suggested a lack of efficacy (Lindblad et al., 2016). Diathermy is not invasive, has minimal adverse effects, is moderate cost depending on length of treatment, and has no evidence of efficacy. Thus, there is no recommendation regarding peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: dyathermy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 79 articles in PubMed, 0 in CINAHL, 2 in Cochrane Library, 1,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ULTRASOUND FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of ultrasound for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Ultrasound has been used for treatment of neuropathic pain (Perez-Neri, 2021). There are no quality studies of ultrasound for the treatment of neuropathic pain. Ultrasound is not invasive, has few adverse effects, but is moderately costly. In the absence of quality evidence, there is no recommendation for or against ultrasound for treating neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Ultrasonography, Ultrasound ultrasound therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3,954 articles in PubMed, 20 in CINAHL, 5,066 in Cochrane Library, 18,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ALLIED HEALTH INTERVENTIONS

HOMEOPATHIC AND HERBAL TREATMENTS FOR NEUROPATHIC PAIN

Not Recommended

Homeopathic and herbal treatments, such as harpagoside, willow bark (Salix), Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica montana, Curcuma longa, Tanacetum parthenium, St. John’s wort, nutmeg, vitamin E, and Zingiber officinale, are not recommended for treatment of chronic neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Multiple RCTs suggest lack of efficacy of alpha-lipoic acid for treatment of neuropathic pain (Ziegler et al., 1999, Ziegler et al., 2011, Reljanovic et al., 1999). One moderate-quality trial of topical sprays of nutmeg added to methyl salicylate, menthol, and coconut oil found lack of efficacy (Motilal et al., 2013). Another trial found lack of efficacy for St. John's wort (Sindrup et al., 2001). An experimental study of Neuragen PN suggested ultra-short-term efficacy (Li Z, 2010), but there were no clinical trial results of short- or long-term results. A Cochrane review of alpha-lipoic acid for diabetic neuropathy concluded it "probably has little or no effect on neuropathy symptoms" (Baicus et al., 2024). Another Cochrane review of herbal medicinal products for neuropathic pain concluded, "There was insufficient evidence to determine whether nutmeg or St. John's wort has any meaningful efficacy in neuropathic pain conditions." (Boyd et al., 2019). A third Cochrane review of acetyl-L-carnitine for treatment of diabetic peripheral neuropathy concluded, "We are very uncertain whether ALC causes a reduction in pain after 6 to 12 months' treatment..when compared with placebo" (Rolim et al., 2019). Homeopathic and complementary medications are not invasive, have generally low adverse effects, and are low to moderate cost. However, in the absence of quality evidence of efficacy, they are not recommended. They also may have interactions with other prescribed medications.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ("homeopathy s"[All Fields] OR "homoeopathy"[All Fields] OR "homeopathy"[MeSH Terms] OR "homeopathy"[All Fields]) AND ("complementary therapies"[MeSH Terms] OR ("complementary"[All Fields] AND "therapies"[All Fields]) OR "complementary therapies"[All Fields] OR ("complementary"[All Fields] AND "medicine"[All Fields]) OR "complementary medicine"[All Fields]) ; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 3626 in CINAHL, 685 in Cochrane Library, 2370 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 6 from Cochrane Library, 11 from Google Scholar, and 0 from other sources. Of the 17 articles considered for inclusion, 6 randomized trials and 11 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MAGNETS AND MAGNETIC STIMULATION FOR NEUROPATHIC PAIN

Not Recommended

Magnets and magnetic stimulation are not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence High

Rationale

There is no significant evidence base from which to draw conclusions on the utility of magnets as a treatment modality for neuropathic pain, although quality studies of other musculoskeletal disorders have not shown any indication for use of magnets for treatment. One trial was suggestive of difference but the markedly higher dropout rate in the placebo group suggests unblinding (Rick et al., 2017). A large trial of magnetic insoles suggested lack of efficacy (Weintraub et al., 2004, Weintraub et al., 2009, Weintraub et al., 2003). Another pilot study suggested lack of efficacy (Collacott EA, 2000). A trial of pulsed electromagnetic fields found lack of efficacy (Weintraub et al., 2009). One trial suggested efficacy (Nazeri et al., 2023). Magnets are not invasive, have no adverse effects, are low cost, have no quality evidence of efficacy, and are thus not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Magnets, magnet stimulation, magnetic stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 269 articles in PubMed, 64 in CINAHL, 614 in Cochrane Library, 17,800 in Google Scholar, and from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 8 articles considered for inclusion, 6 randomized trial, and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TAPING AND KINESIOTAPING FOR NEUROPATHIC PAIN

Not Recommended

Taping and kinesiotaping are not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Taping and kinesiotaping have not been shown effective in quality studies for the treatment of chronic neuropathic pain. Taping and kinesiotaping are not invasive, have some adverse effects, are moderate cost to high cost depending on length of treatment, and have no evidence of efficacy. Thus, they are not recommended for neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: athletic tape, kinesiotaping, kinesio tape, taping; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 19 articles in PubMed, 8 in CINAHL, 0 in Cochrane Library, 3,330 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MANIPULATION FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against manipulation in the treatment of neuropathic pain. There may be other indications for manipulation (e.g., see Low Back Disorders Guideline, including for radicular pain).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of manipulation for treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine

Disorders Guidelines. Manipulation is not invasive, has some adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, and thus there is no recommendation for or against manipulation for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Manipulation Osteopathic, Musculoskeletal Manipulations, Manipulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 243 articles in PubMed, 21 in CINAHL, 576 in Cochrane Library, 18,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INFRARED THERAPY (CLINICIAN-BASED OR SELF-APPLICATION) FOR NEUROPATHIC PAIN

Not Recommended

Infrared therapy (either clinician-based or self-application) is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Infrared has been used for treatment of neuropathic pain (Robinson, 2017). Infrared therapy was reportedly ineffective in two moderate-quality trials for the treatment of chronic diabetic neuropathic pain (Nawfar et al., 2011, Lavery et al., 2008), while one trial suggested some efficacy (Liao et al., 2017). Infrared therapy is not invasive, has minimal adverse effects, and is moderate cost depending on length of treatment. Because most evidence suggests a lack of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Infrared Rays, Infrared therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 41 articles in PubMed, 9 in CINAHL, 148 in Cochrane Library, 18,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MASSAGE FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of massage for patients with neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of massage for treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Massage is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against massage for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Massage therapy, Massage; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 35 articles in PubMed, 18 in CINAHL, 6 in Cochrane Library, 13,900 in Google Scholar, and 0 from other sources†. We

considered for inclusion 1 from PubMed, 0 from CINAHL, 2 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MECHANICAL MASSAGE DEVICES FOR NEUROPATHIC PAIN

Not Recommended

The use of mechanical massage devices by rehabilitation service clinicians or massage therapists is not recommended for neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of massage devices for treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. There is evidence reviewed that suggests devices are less effective than traditional massage. Massage devices are not invasive, have minimal adverse effects, are moderately costly, have no quality evidence of efficacy, and thus are not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Mechanical massage devices; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 1 in CINAHL, 27 in Cochrane Library, 5120 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MYOFASCIAL RELEASE FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for myofascial release for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There is no quality evidence of efficacy of myofascial release for treatment of neuropathic pain. Myofascial release is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, and thus there is no recommendation for or against myofascial release for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Myofascial release, myofascial release therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 14 articles in PubMed, 3 in CINAHL, 101 in Cochrane Library, 15,700 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ACUPUNCTURE/ELECTROACUPUNCTURE FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for acupuncture or electroacupuncture to treat neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Acupuncture and electroacupuncture have been used for treatment of neuropathic pain (Dimitrova, 2017; Ho-Choi, 2019; Yun, 2020; Zhao, 2021; He, 2022, Pei, 2023, Li, 2023). The RCTs significantly conflict and are many of them are subject to significant biases. Some of the trials show lack of efficacy for either acupuncture of electroacupuncture for treatment of neuropathic pain (Penza et al., 2011, Lewith et al., 1983, Garrow et al., 2014, Rostock et al., 2013, Elizabeth Andersen Hammond, 2022), although one of the three studies showed a trend towards efficacy (Garrow et al., 2014). Other trials have suggested benefits, although most have major biases (Gao et al., 2019, Iravani et al., 2020, Molassiotis et al., 2019, Friedemann et al., 2022, Lu et al., 2020, Chao et al., 2019, D'Alessandro et al., 2019). Acupuncture is minimally invasive, has minimal adverse effects, and is moderately costly. In the absence of quality evidence of efficacy, and with a significantly conflicting body of evidence that includes many major biases, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Electroacupuncture, acupuncture; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 97 articles in PubMed, 87 in CINAHL, 91 in Cochrane Library, 17,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 6 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 5 from other sources. Of the 21 articles considered for inclusion, 15 randomized trials and 6 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REFLEXOLOGY FOR NEUROPATHIC PAIN

Not Recommended

Reflexology is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Reflexology has been used for treatment of neuropathic pain (Paju, 2022). There are no quality studies of reflexology for treatment of neuropathic pain. Reflexology has not been

shown to be beneficial for the treatment of chronic neuropathic pain. It also has not been shown to be beneficial for treatment of low back pain in a moderate-quality study (Poole et al., 2007). Reflexology is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality evidence of efficacy for any condition. Thus, reflexology is not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Reflexology; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 147 articles in PubMed, 3 in CINAHL, 61 in Cochrane Library, 925 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

ELECTRICAL THERAPIES

LOW-LEVEL LASER THERAPY FOR NEUROPATHIC PAIN

Not Recommended

Low-level laser therapy is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality sham-controlled trial for treatment of neuropathic pain from diabetic sensorimotor polyneuropathy found a trend but statistical lack of efficacy (Zinman et al., 2004). A trial found comparable (in)efficacy with rTMS (Bonifácio de Assis et al., 2022). A trial comparing electromagnetic therapy with LLLT for treatment of trigeminal neuralgia found LLLT was superior (Al-Azab et al., 2023). A trial of photon stimulation found lack of efficacy (Swislocki et al., 2010). Low-level laser therapy has been suggested to be ineffective in one quality sham-controlled trial for the treatment of chronic neuropathic pain. Low-level laser therapy is not invasive, has minimal adverse effects, is high cost depending on length

of treatment, has no clear evidence of efficacy, and thus is not recommended for the treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Low-Level Light Therapy, Low level laser therapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 104 articles in PubMed, 7 in CINAHL, 51 in Cochrane Library, 17,700 in Google Scholar, and 0 from other sources†. We considered for inclusion 19 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 5randomized trials and 7 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

HIGH-VOLTAGE GALVANIC THERAPY FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against high-voltage galvanic therapy for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of high-voltage galvanic therapy for treatment of neuropathic pain. High-voltage galvanic therapy is not proven efficacious for the treatment of chronic low back pain or other chronic pain conditions. The single quality study suggests possible minimal, brief improvement for neck pain (Foley-Nolan et al., 1990). High-voltage galvanic therapy is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality evidence of efficacy. Thus, there is no recommendation for or against high-voltage galvanic therapy for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: High Voltage Pulsed Galvanic Stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 0 articles in PubMed, 0 in CINAHL, 0 in Cochrane Library, 1,960 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

H-WAVE® DEVICE STIMULATION FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for H-Wave® Device Stimulation for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of H-Wave® Device Stimulation for treatment of neuropathic pain. H-Wave® Device Stimulation is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality evidence of efficacy. Thus, there is no recommendation for or against H-Wave® Device Stimulation for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TREATMENT TERMS; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 3 articles in PubMed, 0 in CINAHL, 1 in Cochrane Library, 215 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTERFERENTIAL THERAPY FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against interferential therapy for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of interferential for treatment of neuropathic pain. One low-quality comparative trial suggested equivalent (in)efficacy with diathermy (Lindblad et al., 2016). Interferential is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality evidence of efficacy. Thus, there is no recommendation for or against interferential for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Interferential therapy, IFT; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 38 articles in PubMed, 0 in CINAHL, 121 in Cochrane Library, 759 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

IONTOPHORESIS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against iontophoresis for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality study of iontophoresis with vincristine suggested a lack of efficacy (Layman et al., 1986). One comparative trial of iontophoresis with lidocaine vs. lidocaine patch for treatment of post-mastectomy intercostobrachial neuralgia found greater pain reduction with the iontophoresis group (Aboelnour et al., 2019); however, no data on a durable difference were provided. There are no quality studies of iontophoresis with other medications for treatment of neuropathic pain. Iontophoresis is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality evidence of a significant and durable efficacy. Thus, there is no recommendation for or against iontophoresis for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: iontophoresis, electrophoresis; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 11 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 2,170 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MICROCURRENT ELECTRICAL STIMULATION FOR NEUROPATHIC PAIN

No Recommendation

This is no recommendation for or against microcurrent electrical simulation for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Microcurrent is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence and thus there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Microcurrent electrical stimulation, electrical stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 118 articles in PubMed, 218 in CINAHL, 2 in Cochrane Library, 352 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against percutaneous electrical nerve stimulation (PENS) for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality experimental trial of PENS included only one treatment and suggested some efficacy, but included no intermediate- to long-term outcomes and suggested it required additional trials to ascertain clinical efficacy (Raphael et al., 2011). Another low quality trial suggested some potential efficacy (Hamza et al., 2000). PENS is minimally invasive, has minimal adverse effects, is moderate to high cost in aggregate, and

has no quality evidence of clear clinical efficacy. Thus, there is no recommendation for or against PENS for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Percutaneous electrical nerve stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 32 articles in PubMed, 146 in CINAHL, 6 in Cochrane Library, 7,850 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against transcutaneous electrical nerve stimulation (TENS) for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

TENS have been used for treatment of neuropathic pain (Gibson et al., 2017, Mokhtari et al., 2020). There are few quality sham-controlled trials of TENS for treatment of neuropathic pain. A sham-controlled trial of microcurrent TENS suggested lack of efficacy (Gossrau et al., 2011). A trial comparing TENS with nortriptyline found superiority of nortriptyline (Zakerkish et al., 2019). A comparative trial of TENS vs. pulsed electromagnetic field therapy found evidence of equivalent (in)efficacy (Eid et al., 2022). There are mostly unblinded studies with some of them suggesting modest efficacy (Kumar et al., 1998, Kumar et al., 2008, Xu et al., 2014, Ing MR, 2015). A trial suggested additive benefit of TENS to physical therapy for pudendal neuralgia (Eid et al., 2021). A Cochrane review found very low evidence and "very limited confidence in the effect estimate" (Gibson et al., 2017). TENS is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, and has no quality sham-

controlled evidence of efficacy,. Thus, there is no recommendation for or against TENS for treatment of peripheral neuropathic pain. TENS may be a reasonable alternative for those who fail all other non-invasive interventions and continue to have symptoms sufficiently severe to require other treatment.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: TREATMENT TERMS; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 990 articles in PubMed, 547 in CINAHL, 23 in Cochrane Library, 17,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 2 from CINAHL, 2 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 8 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) FOR NEUROPATHIC PAIN

Recommended

Repetitive transcranial magnetic stimulation (rTMS) is recommended for treatment of neuropathic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

Moderate to severe, chronic neuropathic pain that is insufficiently responsive to other treatments including medications. The highest quality study required Visual Analog Scale (VAS) scores above 4, and having clear consciousness. Those with a personal or family history of epilepsy; history of craniocerebral surgery; intracranial implants; cardiac pacemakers; heart, liver, or kidney insufficiency; and coagulation disorders were excluded (Pei et al., 2019).

Benefits

Reduction in pain, while improving sleep quality and quality of life.

Harms

Dry mouth, headache, neck pain, dizziness (Pei et al., 2019).

Frequency/Dose/Duration

The highest quality study's most effective treatment arm used 15 consecutive daily treatments with 10-Hz, each stimulation session consisted of a series of 300 0.5-second pulses with a frequency of 10 Hz and an interval of 3 seconds between each train, giving a total of 1500 pulses per session, and the total time of stimulations was 17.5 minutes (Pei et al., 2019).

Indications for discontinuation

Failure to significantly benefit, adverse effects, non-compliance.

Rationale

Repetitive transcranial magnetic stimulation (rTMS) Mu, 2015; Gtzinsky, 2020; Attia, 2021; Zang, 2021; Jiang, 2022; Saleh, 2022; Li, 2022; & Diao, 2022). Of the 19 highest-quality sham-controlled trials, 18 trials suggested efficacy of repetitive transcrandial magnetic stimulation (Pei et al., 2019, Hosomi et al., 2020, Hosomi et al., 2013, Bonifácio de Assis et al., 2022, Attal et al., 2016, Attal et al., 2021, Wang et al., 2023, Dongyang et al., 2021, Onesti et al., 2013, Yang et al., 2022, Shimizu et al., 2018, Andre-Obadia et al., 2018, André-Obadia et al., 2011, Mori et al., 2022, Khedr et al., 2015, Zhao et al., 2020, Lindholm et al., 2015, Quesada et al., 2020), while one was negative (Galhardoni et al., 2015). The overall response rate has been suggested to be 47% (Quesada et al., 2020) and there are suggestions that higher doses are superior (Mori et al., 2022, Pei et al., 2019). There are several moderate- and low-quality studies using rTMS for the treatment of neuropathic pain (Slotty et al., 2015, Andre-Obadia et al., 2014, Galhardoni et al., 2015, Hosomi et al., 2013, Yilmaz et al., 2014, Saitoh et al., 2007) with no evidence of long-term efficacy and only some short term modest efficacy. rTMS is non-invasive, has some adverse effects, is moderate to high cost, and with many sham-controlled studies suggesting efficacy, is selectively recommended for those insufficiently managed with medications. However, durability is not well shown in available studies beyond 3 months.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Transcranial Magnetic Stimulation, repetitive transcranial magnetic stimulation, rTMS; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 187 articles in PubMed, 52 in CINAHL, 214 in

Cochrane Library, 9,020 in Google Scholar, and 0 from other sources†. We considered for inclusion 28 from PubMed, 3 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 34 articles considered for inclusion, 23 randomized trials and 8 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SYMPATHETIC ELECTROTHERAPY FOR NEUROPATHIC PAIN

Not Recommended

Sympathetic electrotherapy is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are no quality studies of sympathetic electrotherapy for treatment of neuropathic pain. Sympathetic electrotherapy is not invasive, likely has relatively minor adverse effects, but is costly. In the absence of quality evidence of efficacy, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Sympathetic Electrotherapy; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 32 articles in PubMed, 1 in CINAHL, 1 in Cochrane Library, 644 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

EXTERNAL RADIATION FOR SYMPATHETIC BLOCKADE FOR NEUROPATHIC PAIN

Not Recommended

External radiation for sympathetic blockade is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

While external radiation has been used to treat CRPS, available quality studies suggest it is not effective (Basford et al., 2003). There is no quality evidence of efficacy for external radiation for treatment of neuropathic pain. External radiation is not invasive, has adverse effects, moderate to high cost, and has no quality evidence of efficacy. Thus, it is not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 20 articles in PubMed, 1 in CINAHL, 0 in Cochrane Library, 6,110 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation regarding transcranial direct current stimulation (tDCS) for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Trials of tDCS are nearly all very short-term. Most of the sham-controlled trials suggest some very short-term efficacy of tDCS for treatment of neuropathic pain (Bonifácio de Assis et al., 2022, Attal et al., 2016, Kim et al., 2013, Li et al., 2018), although one trial found lack of efficacy (Lewis et al., 2018) and the overall magnitude of benefit across the studies is modest. However, data also suggest tDCS may be inferior to repetitive transcranial stimulation, as one trial documented inferiority (Attal et al., 2016), while another showed equivalency (André-Obadia et al., 2023) and a third trial suggested no additive benefit of fTMS top tDCS to rTMS (O'Neill et al., 2018). tDCS is not invasive, as low adverse effects, and is moderate to high cost. Because there are no intermediate or longer-term outcomes data, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Transcranial Direct Current Stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 123 articles in PubMed, 25 in CINAHL, 220 in Cochrane Library, 9,530 in Google Scholar, and 0 from other sources†. We considered for inclusion 18 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 17 articles considered for inclusion, 10 randomized trials and 6 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INJECTION THERAPIES

KETAMINE FOR NEUROPATHIC PAIN

Sometimes Recommended

Ketamine is selectively recommended for treatment of severe neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Severe neuropathic pain that is insufficiently managed with oral medications.

Benefits

Reduced pain that has been shown to last at least 30 days after treatment (Guimarães Pereira et al., 2022).

Harms

Psychedelic effects (including hallucinations), disorientation, confusion, loss of motor coordination, nausea, vomiting, loss of appetite, fatigue, dizziness, discomfort.

Frequency/Dose/Duration

The highest quality study used a treatment plan of 3 sessions every 4 days of ketamine 0.4mg/kg over 30-45min in 250mL 5% dextrose.

Indications for discontinuation

Adverse effects, achievement of sufficient recovery, non-compliance with other treatments.

Rationale

Most placebo-controlled trials have found some evidence of efficacy of ketamine (Kvarnstrom et al., 2003, Gottrup et al., 2006, Jorum, 2003), with durable improvements lasting up to 3 months (Mogahed, 2017). However, not all trials are positive, and the regimens vary. Multiple systematic reviews and metanalyses have reported some evidence of efficacy, but the overall evidence is very/low, and at the "expense of adverse outcomes" that include ~5-fold increased risk of psychedelic effects (Michelet et al., 2018, Guimarães Pereira et al., 2022). One trial found no benefit of ketamine infusions every 35 days and also found no additive benefit of magnesium (Pickering et al., 2020). Ketamine infusions are invasive, have significant adverse effects, are high cost, have some evidence of efficacy that lasts at least 30-120 days after infusion and thus are selectively recommended for treatment of severe neuropathic pain that is insufficiently managed with other treatments including medications.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ("esketamine"[Supplementary Concept] OR "esketamine"[All Fields] OR "ketamine"[All Fields] OR "ketamine"[MeSH Terms] OR "ketamin"[All Fields] OR "ketamine s"[All Fields] OR "ketamines"[All Fields]) AND ("infusate"[All Fields] OR "infusates"[All Fields] OR "infuse"[All Fields] OR "infused"[All Fields] OR "infuser"[All Fields] OR "infusers"[All Fields] OR "infuses"[All Fields] OR "infusing"[All Fields] OR "infusion"[All Fields] OR "infusions"[All Fields]); neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 62 articles in PubMed, 21 in CINAHL, 18 in

Cochrane Library, 17,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 15 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 9 randomized trials and 7 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRAPLEURAL BUPIVACAINE INFUSIONS FOR NEUROPATHIC PAIN

Not Recommended

Intrapleural bupivacaine infusions are not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

Intrapleural bupivacaine infusions have not been evaluated in sizable quality studies for diagnostic, prognostic, or treatment purposes regarding neuropathic pain. These infusions are invasive, have potential adverse effects, are costly, and have no evidence of efficacy. Thus, they are not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bupivacaine, intrapleural bupivacaine; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 771 articles in PubMed, 95 in CINAHL, 1681 in Cochrane Library, 348 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles,

we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

CORTICOSTEROIDS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for the use of corticosteroids for neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

One moderate-quality trial suggested a combination of methylprednisolone plus midazolam was superior to either agent alone for treatment of post-herpetic neuralgia (Dureja et al., 2010). However, because the steroid group was the least effective of the three arms, it raises questions about the utility of glucocorticoids for treatment of neuropathic pain. Another study showed only a slight trend favoring a single epidural injection of methylprednisolone plus bupivacaine over standard care (van Wijck et al., 2006). Epidural injections are invasive, have adverse effects, and are high cost. In the absence of clear evidence of efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Corticosteroids; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 406 articles in PubMed, 40 in CINAHL, 310 in Cochrane Library, 17,600 in Google Scholar, and 0 from other sources†. We considered for inclusion 10 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 0 randomized trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

IMMUNOGLOBULIN FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against immunoglobulin to treat neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

A high-quality trial for treatment of small-fiber neuropathy found lack of efficacy (Geerts et al., 2021). One trial for treatment of demyelinating polyneuropathy and diabetes found lack of efficacy (Breiner et al., 2019), while another found efficacy (Jann et al., 2020). One moderate-quality, unblinded trial suggested improved polyneuropathy pain with immunoglobulin at 4 weeks compared with standard care (Jann et al., 2012). A second moderate-quality trial suggested improved post-herpetic neuralgia pain at 4 weeks (Hugler et al., 2002). Immunoglobulin is invasive, has some adverse effects, and is high cost. In the absence of clear evidence of enduring efficacy, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Immunoglobulins, IVIG, Immunoglobulin; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 167 articles in PubMed, 27 in CINAHL, 112 in Cochrane Library, 14,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 3 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

LIDOCAINE INFUSION FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of lidocaine infusions for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are many high- or moderate-quality studies evaluating the short-term effectiveness of this treatment. Disorders studied principally included diabetic neuropathy (Galer et al., 1996, Kastrup J, 1986, Kastrup et al., 1986, Viola et al., 2006), CRPS (Tremont-Lukats et al., 2006), spinal cord injury (Kvarnström A, 2004), and post-operative pain (Kvarnstrom et al., 2003). The longest duration of follow-up with reported data appears to be 14 days (Kastrup J, 1987, Viola et al., 2006), with most studies reporting results for less than 1 day.

Most study results have been positive (Kastrup J, 1986, Kastrup J, 1987, Viola et al., 2006, Tremont-Lukats et al., 2006), but some have been negative (Kvarnström A, 2004, Kvarnstrom et al., 2003). Overall response rates among neuropathic pain patients reported are approximately 10 to 50% (Viola et al., 2006, Kvarnström A, 2004, Kvarnstrom et al., 2003). No intermediate or long-term quality studies on treatment efficacy have been reported. There is one pilot study that suggests a duration of improvement of 4 hours (Tremont-Lukats et al., 2006) and a few suggesting improvements for up to 14 days (Viola et al., 2006, Tremont-Lukats et al., 2006).The available data suggest duration of pain relief is proportionate to the dose administered (Viola et al., 2006, Tremont-Lukats et al., 2006). One cohort of 99 neuropathic pain patients reported 42% of patients had at least a 30% reduction in pain (Carroll, 2007). The same author recommended restriction of this procedure to those patients who could not take oral medications (Carroll et al., 2007). One trial found no long-term analgesic or quality-of-life benefits from lidocaine (Moulin et al., 2019). Other trials have also been negative (Ellemann et al., 1989, Rekatsina et al., 2022), while another had mixed results (Liu et al., 2018).

One study suggested ~32% less persistent neuropathic pain at 3 months after perioperative risk among breast cancer patients (Khan, 2019). Another trial suggested preventive use among taxane therapy patients (Aboulemagd, 2023). Another study suggested some preventive ability of lidocaine for chronic postoperative and neuropathic pain after gynecological surgery, although inferiority to dexmedetomidine (Rekatsina et al., 2022).

There is no quality evidence that these infusions result in a sustained decrease in pain medication requirements, reported pain, or an increase in overall function. Lidocaine infusions are invasive, have significant, dose-related adverse effects (Viola et al., 2006, Tremont-Lukats et al., 2006, Kvarnstrom et al., 2003), and are moderate to high cost depending on the number of treatments. While an adverse event would not be expected to be common, it could be serious or catastrophic. Thus, the intensity of monitoring required is unclear.

Duration of treatment success is neither demonstrated nor predicted to be intermediate to long term. Repeated infusions without objective evidence of prolonged efficacy and functional improvement are not recommended. There are no large, quality studies evaluating the safety and effectiveness of this treatment. Lidocaine infusions are invasive,

have adverse effects, are high cost, have conflicting evidence of efficacy, and have limited to no evidence of durability; thus, they are not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Lidocaine infusions; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 85 articles in PubMed, 18 in CINAHL, 92 in Cochrane Library, 8,560 in Google Scholar, and 0 from other sources†. We considered for inclusion 16 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 20 articles considered for inclusion, 12 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRAVENOUS ADENOSINE FOR NEUROPATHIC PAIN

Not Recommended

Intravenous adenosine is not recommended for the treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

No clear benefits have been found in two studies of adenosine infusion for the treatment of neuropathic pain (Sjolund et al., 2001, Gharehdaghi et al., 2018). Intrathecal adenosine was reported to be superior to intravenous adenosine for reducing tactile allodynia (Eisenach et al., 2003). Adenosine infusions are invasive, have potential adverse effects, are costly, and have no quality evidence of intermediate to longer-term efficacy. Thus, they are not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Intravenous adenosine, adenosine; neuralgia, neuropathic pain, nerve pain; controlled

clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 2 in CINAHL, 26 in Cochrane Library, 9,240 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MONOCLONAL ANTIBODY INJECTIONS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for monoclonal antibody injections for neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are few quality trials of monoclonal antibody infusions for treatment of neuropathic pain. One high-quality study using tanezumab showed some modest efficacy for neuropathic pain reduction at the highest doses (Bramson et al., 2015). In another study, fulranumab was trialed, but the study was terminated due to clinical concerns (Wang et al., 2014). Additionally, there are no long-term benefits yet identified from monoclonal antibody infusion for neuropathic pain (Eisenach et al., 2003), although intrathecal not intravenous adenosine was reportedly superior for reducing tactile allodynia. These treatments are invasive, have adverse effects, are costly, and have no quality evidence of intermediate to longer-term efficacy. Thus, there is no recommendation for treatment with monoclonal antibodies for neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Antibodies Monoclonal, monoclonal antibody injections; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 29 articles in PubMed, 6 in CINAHL, 102 in Cochrane Library, 13,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from

Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

DORSAL GANGLION DESTRUCTION FOR NEUROPATHIC PAIN

Not Recommended

Dorsal ganglion destruction is not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

There are no quality trials of dorsal ganglion destruction for treatment of neuropathic pain. These treatments are invasive, have potential adverse effects, are costly, have no quality evidence of efficacy, and thus are not recommended for treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Dorsal ganglion destruction; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 7 articles in PubMed, 60 in CINAHL, 5 in Cochrane Library, 18,300 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

NERVE BLOCKS FOR NEUROPATHIC PAIN

Sometimes Recommended

Nerve blocks are selectively recommended for treatment of neuropathic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Peripheral nerve entrapment with pain consistent with that one or two entrapped peripheral nerves, unresponsive to other treatments. One moderate-quality trial of intercostal neuralgia (Xiao et al., 2014) and another at the site of the nerve injury (Eker et al., 2012).

Benefits

Improvement in chronic pain .

Harms

Infection, bleeding, allergic reaction, lack of improvement.

Frequency/Dose/Duration

One trial used depo-methylprednisolone 80 mg plus lidocaine 0.5% (Eker et al., 2012). Another used weekly injections of betamethasone 1mL (dose unspecified) plus 5mL ropivacaine 0.75% plus vitamin B12 1mg (Xiao et al., 2014). Repeated injections should only occur if, and until there is incremental functional gain that continues to improve until reaching a plateau.

Rationale

One trial used depo-methylprednisolone 80 mg plus lidocaine 0.5% and found benefits persisting to 3 months (Eker et al., 2012). Steroid plus anesthetic injection nerve blocks are invasive, have adverse effects, are moderate to high cost, and have limited evidence that suggests some potential efficacy. Thus, they are selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Nerve block; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 4,848 articles in PubMed, 606 in CINAHL, 11,960 in Cochrane Library, 18,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 7 from CINAHL, 0 from Cochrane Library, 3 from

Google Scholar, and 0 from other sources. Of the 16 articles considered for inclusion, 6 randomized trials and 4 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

KINASE INHIBITORS FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation regarding kinase inhibitors for treatment of neuropathic pain.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

The available studies substantially conflict and thus there is no recommendation (Anand et al., 2011, Ostenfeld et al., 2013).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Protein kinase inhibitor, Kinase inhibitors, PKI; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 49 articles in PubMed, 7 in CINAHL, 39 in Cochrane Library, 18,900 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BOTULINUM INJECTIONS FOR NEUROPATHIC PAIN

Sometimes Recommended

Botulinum injections are selectively recommended for treatment of localized, peripheral neuropathic pain that is not sufficiently treated by other treatments. There is no recommendation regarding systemic neuropathies.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Severe, localized peripheral neuropathic pain that is insuffiiciently treated with other treatments including medication. There is no recommendation for systemic polyneuropathies.

Benefits

Short-to-intermediate reductions in pain, and improved quality of life for up to 24 weeks have been shown. Long-term benefits have not been shown.

Harms

Benign complications are typical of those of all injections (Witmanowski H, 2020). Adverse effects may also include headache, allergic reactions, anaphylaxis, paresthesia, dysesthesia, localized paresis, dysphasia, diplopia, or paralysis. Doses used and thus complications are higher in therapeutic than cosmetic use. Inappropriately high dosing may also be fatal (Witmanowski H, 2020).

Frequency/Dose/Duration

One set of injections in the affected area. Different doses have been used and there are no quality, comparative studies of doses.

Indications for discontinuation

Adverse effects, lack of efficacy or lack of durable effect lasting at least 3 months.

Rationale

Botox A has been used for treatment of neuropathic pain (see evidence table). Multiple quality trials have mostly reported efficacy and durability of up to 24 weeks for use of botulinum injections for treatment of localized peripheral neuropathic pain (Apalla et al., 2013, Ranoux et al., 2008, Shehata et al., 2013, Wu et al., 2019, Attal, 2016, Salehi et al., 2019, Taheri et al., 2020, Xiao et al., 2010), although one trial trended towards efficacy (Zuniga et al., 1998) and one trial was negative (Jamtøy, 2023). There are few trials addressing systemic disease and no clear evidence of significant effects that are also durable. Botulinum doses, numbers of injections per session, and whether series of

injections were used all varied widely. Botulinum injections are invasive, have potentially significant adverse effects, are high cost, and have evidence of efficacy particularly for localized peripheral neuropathic pain. Thus, botulinum injections are selectively recommended for treatment of localized, peripheral neuropathic pain that is not sufficiently treated by other treatments. These injections are not recommenced for systemic polyneuropathies as the supportive data have been insufficiently developed to weigh efficacy against potential harms and there are other effective treatments.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: ("botulinum toxins, type a"[MeSH Terms] OR "type a botulinum toxins"[All Fields] OR "botox"[All Fields]) ; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 97articles in PubMed, 44 in CINAHL, 20 in Cochrane Library, 11,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 21 from PubMed, 6 from CINAHL, 0 from Cochrane Library, 11 from Google Scholar, and 0 from other sources. Of the 38 articles considered for inclusion, 8 randomized trials and 29 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SURGICAL CONSIDERATIONS

SURGICAL DECOMPRESSION FOR NEUROPATHIC PAIN

Sometimes Recommended

Surgical decompression is selectively recommended for treatment of neuropathic pain. Surgical needs are based on the specific diagnosis that is able to be remedied by surgery. See other evidence-based guidelines for detailed review of these indications, such as Low Back Disorders, Hand, Wrist and Forearm Disorders, and Cervical and Thoracic Spine Disorders.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Pain consistent with peripheral nerve or spinal root/cord entrapment. Often this is consistent with a prior injury and scarring. Nerve conduction study is often helpful for peripheral entrapment neuropathies to confirm conduction delay at the same location as prior trauma. Prognosis is thought to be superior if the surgery is performed within 6 months of injury.

Benefits

Resolution of chronic pain.

Harms

Surgical risks without significant improvement.

Rationale

Aside from discrete entrapment and spinal cord/root entrapments reviewed in otherr evidence-based guidelines, there are no quality trials of surgical decompression of entrapped peripheral nerves. However, there are case series with evidence suggesting potential efficacy. Surgical decompression is invasive, has adverse effects, is high cost, but has a long history of efficacy in carefully selected cases, and thus is selectively recommended for those with clear, discrete indications (see other ACOEM evidence-based guidelines).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Surgical decompression; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 803 articles in PubMed, 24 in CINAHL, 1 in Cochrane Library, 4,310 in Google Scholar, and 0 from other sources†. Zero articles met the inclusion criteria .

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

SPINAL CORD STIMULATION FOR NEUROPATHIC PAIN

No Recommendation

There is no recommendation for or against the use of spinal cord stimulation (SCS) in the treatment of neuropathic pain. Peer-reviewed guidance for injured workers regarding CRPS and low back disorders is provided elsewhere.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

Use of spinal cord stimulators to treat complex regional pain syndrome and low back disorders are addressed in other ACOEM Guidelines. There are few quality sham-controlled trials for treatment of neuropathic pain aside from CRPS and spine disorders, precluding an assessment of efficacy of SCS for treatment of neuropathic pain.

There is one sham-controlled trial that was not well described and suggested some benefits of SCS (Parker, 2021). There are multiple open label and comparative trials which have suggested potential benefits (Sheng et al., 2022, Wan et al., 2021, van Beek et al., 2015, Petersen et al., 2021), although the active-comparative trials are naturally unable to define efficacy. There is one low-quality trial with a standard care bias suggesting potential benefit at up to 6 months (Duarte et al., 2014). There are trials amongst patients with spine and leg pain (see Low Back Disorders guideline) and others for CRPS (see CRPS guidance). One trial comparing usual care suggested superiority of SCS (de Vos et al., 2014). One small, low-quality experimental trial suggested preference for high-frequency to low-frequency stimulation (Reddy et al., 2016) and another experimental study evaluated subperception thresholds (Wolter et al., 2012).

Systematic reviews conflict regarding SCS's efficacy for neuropathic pain, including finding "limited evidence that SCS is effective in reducing pain intensity when compared with a placebo intervention" (Duarte et al., 2020). The European Federation of Neurological Sciences guideline concluded there was "weak" evidence in support of SCS for diabetic neuropathy (Cruccu G, 2016, Strand N, 2022).

SCS is invasive, has adverse effects, and is high cost. In the absence of significant evidence of efficacy, there is no recommendation for or against treatment of neuropathic pain.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Spinal Cord Stimulation; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 310 articles in PubMed, 110 in CINAHL, 85 in Cochrane Library, 18,000 in Google Scholar, and 0 from other sources†. We

considered for inclusion 32 from PubMed, 2 from CINAHL, 1 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 41 articles considered for inclusion, 7 randomized trials and 13 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

INTRATHECAL DRUG DELIVERY SYSTEMS FOR NEUROPATHIC PAIN

Not Recommended

Intrathecal drug delivery systems are not recommended for treatment of neuropathic pain.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Intrathecal drug delivery systems using opioids and anesthetics have been evaluated in few quality studies for treatment of neuropathic pain. Quality studies have both suggested efficacy (Kikuchi et al., 1999, Wallace et al., 2006) and have suggested lack of efficacy (Hayek et al., 2021, Rijsdijk M, 2013). Intrathecal drug delivery systems may be potentially beneficial in limited situations (e.g., those involving malignant pain conditions and terminal patients), but these situations are beyond the scope of this guideline. Intrathecal drug delivery systems are invasive, have significant adverse effects including fatalities, potential long-term sequelae from both implantation/retention of the devices, including granuloma formation, and those associated with the concurrent use of intrathecal opioids (Raffaeli et al., 2006). With evidence substantially conflicting, there is no recommendation for or against these devices. These systems could potentially be indicated in those who have failed multiple trials of different oral medications and other treatments and have undergone independent psychological consultation including psychometric testing that does not reveal a contraindication to implantation. Patients considered for implanted opioid delivery systems should be evaluated regarding their suitability for protracted use of systemic opioids. They should have documented compliance with all chronic oral opioids treatment criteria, previously shown to be responsive to oral opioids with documented improved function (but unmanageable adverse effects that use of these systems would be able to overcome).

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms:

TREATMENT TERMS; neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 402 articles in PubMed, 11 in CINAHL, 5 in Cochrane Library, 16,100 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 2 from CINAHL, 2 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 4 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

COMPLICATIONS AND COMORBIDITIES

Complications and comorbidities commonly include the following:

- Diabetes mellitus
- Alcohol
- Autoimmune disorders
- Nutritional deficiencies
- Pernicious anemia
- Herpes zoster/shingles

FOLLOW-UP CARE

It is recommended that patients with work-related neuropathic pain should have a follow-up visit every 1 to 2 weeks initially by a new clinician or while still out of work. Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. The initial appointments should focus on identify remediable causes of neuropathic pain and exposure elimination, if a neurotoxin is identified.

Initial visits should include an ongoing focus on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest or appliances. The clinician

should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is recommended to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is recommended. However, in the active rehabilitation phase for patients with neuropathic pain, follow-ups weekly for as much as 2 or 3 months is recommended to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

JOB ANALYSIS

The primary purpose of job analyses for patients with neuropathic pain is to identify and catalog all chemicals used in the workplace. This usually begins with a patient history, then supervisor interview, and subsequently obtaining Safety Data Sheets. This is followed by a careful evaluation of whether there is a known neurotoxin. In cases where a neurotoxin is identified, complete removal from exposure is indicated.

For radicular pain, see the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines.

REHABILITATION

OVERVIEW

There are numerous types of rehabilitation programs [604-609], with considerable heterogeneity even within one type of program. The WHO classified the interventions for chronic low back pain rehabilitation into the following categories: cognitive functions; pain management; exercise and fitness; activities of daily living; education and vocation; lifestyle modification; and self-management [610]. To help organize and present a hierarchical theoretical construct, rehabilitation is classified in this Guideline as primary, secondary, or tertiary based on both injury acuity and complexity. Primary rehabilitation is nearly entirely covered in other ACOEM Guidelines (e.g., Low Back Disorders Guideline). Specific interventions (e.g., medications, exercises, procedures, devices) used for chronic pain conditions are also covered in the other ACOEM Guidelines. However, the overarching rehabilitation programs are only covered in this guideline.

Primary rehabilitation includes the most widely encountered therapy, is most commonly ordered for acute and subacute pain disorders, and consists of a relatively minimal quantity(ies) of medical care coupled with physical therapy, occupational therapy or clinician directed exercises (i.e., a home exercise program). While there is much diversity, typical strategies commonly include teaching specific stretches, graded exercises, addressing fear avoidant beliefs (i.e., "kinesiophobia"), and advancing activity levels, generally in the acute to subacute phases, until recovery is complete. There are many quality trials evaluating these treatments and specific guidance for primary rehabilitation is included with each disorder (please see individual ACOEM Guidelines). Particularly when there are questions among clinicians regarding the worker's physical job demands and to

quantify the gap(s) between the job demands and patient's capabilities, there should delineation of the required work tasks through conversations with the patient and employer, and if needed, quantification of job physical activities/ergonomic analysis.

Secondary rehabilitation usually occurs after either failure of primary rehabilitation and/or a determination that the current healing course trajectory will not practically result in bridging a gap between current abilities and job physical demands. Secondary rehabilitation includes more advanced and contact time-intensive rehabilitative treatments and are most commonly termed Work Conditioning and Work Hardening. Back Schools are a specific type of program in this category. Early Intervention programs are another type of secondary rehabilitation program that are sometimes used. Work Conditioning usually emphasizes exercises and includes tasks to simulate work activities. Work Hardening typically includes progressive exercise but adds some limited psychological counseling and education. There are quality trials of Back Schools, but there is little quality literature supporting Work Conditioning and Work Hardening programs.

Tertiary rehabilitation involves interdisciplinary rehabilitation. There are many different terms and emphases of tertiary rehabilitation programs; however, they can generally be classified into pain programs and functional restoration programs. The more successful of these programs generally employ multiple disciplines using biopsychosocial approaches to address pain, function, work, and psychological distress. The less successful of these programs tend to be primarily procedure-oriented. By contrast, acute injuries are treated with acute care paradigms of utilizing specific treatment(s) for cure of a discrete diagnosis. There are some quality trials of tertiary rehabilitation programs.

Initiation of these programs may be considered in the subacute stage if disability is not adequately explained by physical findings and primary rehabilitation treatments have failed to significantly improve the functional status. Chronicity by itself is a major predictor of poor outcome [(148)]. The longer it takes to resolve the disability (delayed recovery), the higher the cost, the more likely patients are to never return to work, the greater the risk for costly medical care, and the greater the likelihood for costs to be shifted from the workers' compensation system to other payment systems (e.g., long-term disability, Social Security Disability Insurance). The increased costs of rehabilitation programs may be justifiable by cost benefit analysis of program outcomes of successful programs. Consistent with the above, earlier intervention programs may be reasonable.

Functional restoration is both a type of interdisciplinary pain management and rehabilitation program, as well as a general approach to medical care. Fundamental elements of a functional restoration approach include assessment of the patient's dynamic physical and functional status including traditional tests for strength, sensation, and range of motion. Psychosocial strengths and stressors must also be assessed (including a history of childhood abuse, anger, fear of reinjury, and a history of substance misuse), and the patient's support system, evidence of mood disorders, assessment of education and skills, medication use, presence of litigation, and work incapacity analyzed. Following this evaluation, the emphasis is on expectation management, directed conditioning and exercise, CBT, functional goal setting and decrease in medication use. An ongoing assessment of patient participation and compliance (with documentation of complicating problems and progress toward specific goals, including reduction in disability and medical utilization) is needed.

In functional restoration, the treatment team functions more as educators and coaches, not "treaters." Passive therapies and invasive interventions are de-emphasized in favor of home exercise/self-management techniques. There should be a shift of health, function, and well-being responsibility (locus of control) from physicians and therapists to the individual. A functional restoration approach may include the limited/adjunctive use of medications and interventional measures (where specifically indicated); however, these should not be viewed as ongoing solutions, and used to support the patient's active participation in rehabilitation. Rehabilitation should include instruction in preventive measures, education for relapse prevention, proper activity and work pacing, ergonomic accommodation, and when appropriate, recommend transitional return to employment.

Psychologically informed physical therapy may also be helpful and is an emerging practice where physical therapists purposefully incorporate techniques such as Motivation Interviewing, Cognitive Behavioral techniques including Acceptance and Commitment principles into their practice. In the Subgrouping for Targeted Treatment (STarT) model, the group identified of patients with low back pain identified as high risk of developing chronic pain was referred to specially trained therapist who were taught to integrate physical and psychosocial approaches [611-613]. Cognitive functional therapy is a program that uses a biopsychosocial framework to treat chronic back pain [614-628]. Although not standardized, psychologically informed physical therapy has been evaluated in multiple studies on different body areas where chronic pain tends to be most problematic [629-636]. A consortium of physical therapists from the United States has published a model to provide guidance on use of a biopsychosocial framework for physical therapists. The PRISM- Pain Recovery and Integrative Systems Model is a "salutogenic, integrative, process-based cognitive-behavioral model designed for physical therapist education and practice which was developed to align with national and international initiatives to better understand and manage pain."

The goal is a mitigation of a patient's suffering and his or her return to a productive life despite having a chronic pain problem. If an individual has risk factors for delayed recovery or fails to recover within the appropriate biological healing time frame, the acute care paradigms of specific diagnosis and treatment change to biopsychosocial approaches that address pain, function, work, and psychological factors impeding progress. Treatment programs focus on restoration of work-related function. These programs include work conditioning and work hardening, interdisciplinary pain rehabilitation programs and functional rehabilitation. Because functional restoration is an approach, not just a specific program, the approaches taken both overlap and are on a continuum.

TREATMENT RECOMMENDATIONS

WORK CONDITIONING, WORK HARDENING, EARLY INTERVENTION PROGRAMS, AND BACK SCHOOLS

WORK CONDITIONING, WORK HARDENING, EARLY INTERVENTION PROGRAMS, AND BACK SCHOOLS FOR CHRONIC PAIN

Sometimes Recommended

Work conditioning, work hardening, early intervention programs, and back schools are selectively recommended for the treatment of chronic pain. Both program-specific and patient-specific criteria must be met (see below).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Patients who:

- remain completely off work or are on modified duty for 6 to 12 weeks, whose job has moderate to high job physical demands, most commonly due to manual materials handling tasks;
- have not responded to less costly interventions including a 4- to 6-week physical (or occupational) therapy program or a graded therapy program of at least 6 to 8 weeks that includes aerobic and strengthening exercise components;
- have a stated strong interest and expectation to return to work;
- involve cooperation of the employer;
- are supervised by a qualified physician, physical therapist or occupational therapist;
- have had a careful assessment of their occupational demands;
- have had either inability to return to work or a FCE that indicated appropriate performance effort and consistency at a level of work lower than that to which they need or wish to return; and

Programs

A program must include: 1) a proven ability to return patients to work (i.e., at least 50% return-to-work rate), 2) a cognitive-behavioral approach with a focus on function rather than pain (Kool et al., 2005), 3) kinesiophobia/FABT, 4) a conditioning or aerobic exercise component, 4) simulated graded work tasks, and 5) tailoring to the worker's needs and specific gaps between current capabilities and job demands.

Benefits

Return to work and improved functional recovery with faster meeting of the gap between capabilities and job demands.

Harms

Negligible. Subjectively worse pain with exercises that usually improves or resolves with continued, but sometimes needing modestly reduced exercises. High cost and medicalization may occur.

Frequency/Dose/Duration

Work conditioning and early intervention programs 3 to 5 times a week; work hardening daily. Weekly evaluations demonstrating compliance with all program elements (e.g., CBT and exercises) and functionally significant progress towards the return-to-work goal must be documented to justify continuation. Program length and intensity should be dictated by each patient’s unique rehabilitation needs.

Indications for discontinuation

Program completion, return to usual work, non-compliance.

Rationale

While there is limited evidence that work conditioning, work hardening, early intervention programs and back schools are effective for chronic spinal pain, there is a longstanding belief and experience that they may be highly effective for select programs that have proven, high rates of durable return to work (at least 50% for at least 6 months).

Most of the quality evidence is heterogeneous, addresses back schools, and the programmatic components are generally not well described (Paolucci et al., 2016, Morone G, 2012, Paolucci et al., 2012, Jaromi M, 2012,Henchoz Y, 2010, Durmus D, 2014, Sundstrup, 2014,Costantino C, 2014,Hara et al., 2018, Rosenberg et al., 2021,Cecchi et al., 2010, Garcia et al., 2013,Poquet N, 2016, Parreira P, 2017), resulting in a reduction in the level of evidence to "I" Insufficient Evidence.

Other than use of a specific educational product, such as an educational booklet, the educational components in particular are poorly described. Descriptions of the ergonomics training are also meager, with concerns about the frequency of potentially inaccurate beliefs provided (e.g., failure to emphasize force and excessive attention to posture,Garg A, 2007, Garg A, 2014, Kapellusch JM, 2013, Rempel D, 2015). This large programmatic variability also leads to difficulties in comparing the results between many of the RCTs.

Variability in the quality of back schools appears to be problematic. The more successful programs appear to have greater reliance on graded, progressive aerobic exercise, progressive endurance exercises and include cognitive-behavioral principles rather than emphases on education, flexibility, and symptom-limited exercises (Garcia et al., 2013). There is moderate evidence suggesting that back schools have better short-term effects than other treatments for chronic LBP and that such schools are more effective in an occupational setting than in a non-occupational setting. Select subacute LBP patients (towards the end of the 3-month period of subacute LBP) may be candidates, but these are infrequent as other treatments should be given time to prove efficacious.

These programs are also believed to be effective for many other chronic pain syndromes, although there is no quality evidence of efficacy. While there is potential for overlap, work conditioning, work hardening, early intervention (see below) and back schools are distinct programs and are not intended for sequential use, although this may be appropriate in certain situations depending on program components. These programs are inappropriate for acute pain and most subacute pain patients. In subacute pain, there may be highly limited applicability, particularly if there is both 1) an early identification that the primary obstacle to RTW is inability to accomplish the job demands and 2) targeting those gaps through therapy has already proven insufficient. In select chronic cases, particularly with

pain and illness behavior and a high level of reported dysfunction, a more intense IPRP should be considered.

Although less costly, work conditioning, work-hardening and early intervention programs do not need to be attempted before moving to an IPRP as long as a quality interdisciplinary program with proven outcomes of at least 50% return to work success is accessible to the patient. Program choice depends on availability and matching patient needs to the services offered to provide the most cost-effective and beneficial outcome.

Hence, these programs may provide the greatest potential impact when used to manage patients during the late subacute phases of injury, although they may also be appropriate for use in those with chronic pain who do not, after evaluation, have significant psychosocial factors contributing to the patient's clinical presentation. These programs are not invasive and have low adverse effects, but are high cost and are selectively recommended.

Evidence

Work Conditioning, Hardening, Early Intervention:
A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: work conditioning, hardening, early intervention; chronic pain, neuralgia, neuropathic pain; chronic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 260 articles in PubMed, 57 in CINAHL, 1202 in Cochrane Library, 18,000 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 0 systematic reviews met the inclusion criteria.

Back Schools:
A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Bak shools; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 5 articles in PubMed, 4 in CINAHL, 0 in Cochrane Library, 20,600 in Google Scholar, and 0 from other sources†. We considered for inclusion from PubMed, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term

algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

BACK SCHOOLS

Back schools are a type of secondary rehabilitation and have been used for almost 40 years for the rehabilitation of LBP patients [497,637,638]. Components of back school programs are quite variable and may include any or all of the following components: physical training, exercise, behavior modification, stress management, lifestyle change, education on anatomy, biomechanics, and "optimal posture." [497,637,639] While the primary thrust of these programs is rehabilitation, a major secondary aim used to justify the costs of this intervention is the prevention of subsequent LBP episodes [638,640]. There are different methods of program delivery including video and classroom-style presentation by a clinician.

EARLY INTERVENTION (FUNCTIONAL RESTORATION) PROGRAMS

Early identification and appropriate management of patients exhibiting signs of delayed recovery is believed to decrease the likelihood that symptoms will become chronic [641]. Patients who are identified at risk for delayed recovery may benefit from a limited but intense program of physical restoration and education, including management of barriers to recovery and return to work. These patients may require an abbreviated early intervention interdisciplinary rehabilitation program (IPRP based on functional restoration principles, rather than a longer program utilized for more complex cases. Early intervention programs are an alternative to work conditioning and work hardening programs for subacute or early patients with chronic pain who have evidence for delayed recovery with an increased need for education and psychological assessment and intervention. These programs are usually begun when a significant gap is identified between functional abilities and job demands, ideally in the early subacute time (e.g., 30-60 days). An IPRP may also be justified earlier if risk factors for delayed recovery are identified. The interdisciplinary functional restoration program used for early intervention contains the features of a functional restoration program, but involves lower intensity and duration of services than a program used for patients with greater chronicity or intensity of disability. The type, intensity, and duration of services should be dictated by the patient's unique rehabilitation needs. The time frame of 3 to 6 months post-injury (or earlier if risk factors for delayed recovery are identified) is vital for intervening with the most effective treatment possible in order to avoid the negative sequelae that come with increasing duration of disability. During this time frame, normal musculoskeletal healing will generally have occurred, eliminating any remaining physical barriers to intensive rehabilitation. Such programs are appropriate for prevention, before the patient is entrenched in a chronic pain syndrome or before severe pain and illness behavior evolves.

WORK CONDITIONING AND WORK HARDENING

There is no unified agreement on definitions for work conditioning and work hardening, and sometimes the terms are used interchangeably.

Work conditioning has been defined by the American Physical Therapy Association (APTA) as "an intensive, work-related, goal-oriented conditioning program designed specifically to restore systemic neuromusculoskeletal functions (e.g., joint integrity and mobility, muscle performance (including strength, power, and endurance), motor function (motor control and motor learning), range of motion (including muscle length), and cardiovascular/pulmonary functions (e.g., aerobic capacity/endurance, circulation, and ventilation and respiration/gas exchange)." (642)

Work hardening has been defined by APTA as a "highly structured, goal-oriented, individualized intervention program designed to return the patient/client to work. Work Hardening programs, which are multidisciplinary in nature, use real or simulated work activities designed to restore physical, behavioral, and vocational functions. Work Hardening addresses the issues of productivity, safety, physical tolerances, and worker behaviors." Thus, work conditioning is classified as a single-discipline program and work hardening program as interdisciplinary.

The Commission on Accreditation of Rehabilitation Facilities (CARF) defines occupational rehabilitation as work conditioning, and comprehensive occupational rehabilitation as work hardening. Although not universally accepted, some physicians consider work conditioning as a generalized endurance and strengthening program that includes work simulation activities, whereas work hardening is a program where a specific job has been identified and stresses involvement in sets of occupationally-related tasks and functional activities that are directly related to a patient's work. Work conditioning programs in the U.S. are most often provided by a single-therapy discipline, either physical or occupational therapy.

TERTIARY PAIN PROGRAMS

TERTIARY PAIN PROGRAMS FOR TREATMENT OF CHRONIC PAIN (INTERDISCIPLINARY PAIN REHABILITATION, MULTIDISCIPLINARY REHABILITATION, CHRONIC PAIN MANAGEMENT, FUNCTIONAL RESTORATION)

Sometimes Recommended

Tertiary pain programs are selectively recommended for a minority of patients with chronic pain who have failed trials of evidence-based conventional treatments, lack other evidence-based treatment options, and remain significantly incapacitated. It is essential that both program-specific and patient-specific criteria be met prior to referring to and initiating such programs (below). Such programs include interdisciplinary pain rehabilitation programs, multidisciplinary rehabilitation programs, chronic pain management programs, and functional restoration programs.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Functional restoration programs are recommended for patients with chronic pain who have failed trials of evidence-based conservative treatments, lack other evidence-based treatment options, and remain significantly incapacitated. Both program-specific and patient-specific criteria should be met prior to referring the patient and initiating such a program. See the following section for details.

Benefits

Improvement in function, return to work, return to unrestricted duty. Improved functioning in home, work and community settings. May facilitate opioid and other addictive substances weaning processes.

Harms

High costs. Further medicalization. Some pain programs do not primarily concentrate on functional recovery, prescribe excessive opioids, or excessively utilize interventional techniques that inhibit self-efficacy and are avoidable through proper referrals.

Frequency/Dose/Duration

Tertiary pain program treatment is generally a minimum of 5 hours/day, 5 days/week; 4-6 weeks; 160 hours maximum. Any exceptions need to be negotiated with the payer with justification. See the following section for details.

Indications for discontinuation

Program completion, non-compliance, or lack of progress. Progress should be continuously measured. At any point where there is a plateau and/or lack of improvement in objective measures over not longer than 2-week intervals, the program should be discontinued.

Rationale

These programs have been used for treatment of chronic pain (Mehta et al., 2015, Fashler et al., 2016, Dosenovic et al., 2017, Elbers et al., 2022, Joypaul et al., 2019, Oosterhaven et al., 2019, Wegrzynek et al., 2020, Flegge et al., 2022, Almeida et al., 2022). There are several studies of various tertiary pain programs to treat musculoskeletal disorders and both the literature and clinics are both quite heterogeneous (Fashler et al., 2016), and judged to be at high risk of bias (Casey et al., 2020), making both assessments of efficacy and comparisons between programs difficult. There are some favorable data that have been published from some select programs (Kool et al., 2005, Nazzal, 2013, Becker N, 2000, Bair et al., 2015, Hutting, 2015, Oldenmenger, 2011, Roche-Leboucher et al., 2011, Monticone, 2013, Retracted - Monticone, 2016, Nazzal, 2013, Jay et al., 2016, Amris et al., 2014, Van der Maas et al., 2015). A study attempting to assess treatment of subgroups of chronic back pain patients failed to find efficacy of that approach (Verra et al., 2017). Another study found no efficacy of an integrated rehabilitation program compared with an existing program (Schmidt et al., 2020). A Cochrane review found evidence of efficacy of a multidisciplinary

psychosocial program for treatment of chronic LBP compared with usual care or physical treatment on pain and disability, but only "modest" effects on RTW status (Kamper SJ, 2014) and another Cochrane review and a second systematic review found no clear evidence of efficacy of a multidisciplinary psychosocial programs for treatment of subacute low back pain, as while there was superiority to usual care, there was no evidence of efficacy compared with any other treatment ((Marin TJ, 2017, Bernaers L, 2023). With the possible exception of the workplace-based interventions, most successful multidisciplinary programs appear to have either utilized a cognitive-behavioral approaches and/or significantly involved psychologists (Fairbank, 2005, Haldorsen, 2002, Newton-John et al., 1995, Taal et al., 2004).

Programs in the literature could be mostly segregated into two basic types:

- a program consisting of a limited number of disciplines in a combined behavioral-exercise approach (e.g., an occupational physician, physiotherapist, and psychologist); and
- a workplace focused program to facilitate return to work with a multidisciplinary, participatory ergonomics team approach (ergonomist, worker, supervisor, and others).

There is nascent, moderate quality evidence that a distance-based, multi-disciplinary program may be effective for those with chronic pain, although these results may be limited to less severely affected patients (Smith et al., 2019).

Importantly, there are no quality programs documenting efficacy of major outcomes measures that are invasive/interventional procedure-based and/or procedure-centric. Thus, there is a near total absence of quality studies that assess multidisciplinary programs that emphasize interventional approaches as are common in the U.S. In addition, the preponderance of the evidence is based on patients with LBP (Kool et al., 2005). Other conditions have not been systematically studied. Participation in a tertiary pain program has only been reported in one study of upper extremity MSDs (which may have issues of diagnostic and interventional considerations) and was not shown to be of benefit (Rodgers et al., 2003). These programs may be particularly helpful if there is medical need to wean the patient from opioids or other medications and/or the patient has shown demonstrable clinical progress with less intense rehabilitation but that “pain limitation” has impeded adequate recovery. It is typically essential to address commonly entrenched psychosocial barriers to recovery and a "chronic pain syndrome" as sequelae of the original physical components of the injury. Functional restoration may be appropriate, as well as vocational re-entry in positions not requiring the same job physical characteristics when all previous treatments have failed.

With the possible exception of workplace-based interventions, most successful multidisciplinary programs appear to have either utilized a cognitive-behavioral approach or involved psychologists (Haldorsen, 2002, Taal et al., 2004, Fairbank, 2005, Jensen IB, 2005). While exercise is a major focus in a number of these successful programs (Lindstrom et al., 1992, Haldorsen, 2002, Taal et al., 2004, Fairbank, 2005, Jensen IB, 2005), the one trial comparing a graded exercise approach with a participatory ergonomics approach found exercise was inferior (Anema, 2007). This suggests that of the various options available, the participatory ergonomics approach appears to be superior to the other approaches (Loisel P, 1997). These heterogeneous studies also suggest that multidisciplinary programs that focus on functional improvements are superior (Kool et al., 2005). These programs have also been

shown to be as effective as spinal fusion surgery (Mayer et al., 1985, Mayer et al., 1987, Fairbank, 2005).

Some U.S.-based programs involve significant interventions, but there is no documentation of superior outcomes from participation in such programs which can be expensive (>$20,000 to $80,000). Tertiary pain programs are indicated for select, more severely affected patients, including those who have failed appropriate conservative management (e.g., appropriate medications, active graded exercise program, behavioral interventions, etc.). Generally, these referrals are most indicated in the early chronic pain management timeframe (3 to 6 months). However, there are times when earlier referral in the mid- to late-subacute interval is indicated. One should be aware that there is a belief that earlier referral results in higher probability of successful treatment, but that supposition has not been rigorously tested and is prone to a strong spectrum bias (i.e., patients who have the condition for a shorter time are more likely to have returned to work/function and thus have been removed from the sample to test a theory that there is a difference in outcomes based on earlier referral). Referrals beyond 6 months may also be indicated if there has been failure to progress with numerous interventions, there is reasonable expectation for potential benefits, and indications are met. Referrals during the subacute phase best occur when there is a quality program with proven outcome efficacy available, the patient has documented delayed recovery, yet there is interdisciplinary assessment that the patient is likely to benefit from the program. Tertiary pain programs of the types described in the literature are not invasive, have few adverse effects, but are high cost. They are selectively recommended for highly select patients. The rating was downgraded from "C" to "I" in large part due to study heterogeneity.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Tertiary pain program, Interdisciplinary pain rehabilitation, Multidisciplinary pain; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 13,529 articles in PubMed, 136 in CINAHL, 410 in Cochrane Library, 16800 in Google Scholar, and 0 from other sources†. We considered for inclusion 33 from PubMed, 6 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 43 articles considered for inclusion, 4 randomized trials and 19 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

There are several types of tertiary pain management programs, including interdisciplinary pain rehabilitation programs, multidisciplinary rehabilitation programs, chronic pain management program, and functional restoration programs [643-654]. These programs are intended to manage the psychological, social, physical, and occupational factors associated with the chronic pain problem. Precise components and emphases of these programs may vary, however, all are intended for chronic pain/disability. Most typically use a biopsychosocial approach and emphasize improved function, reduced pain and illness behaviors, and mitigation of chronic pain associated disability.

All programs generally involve an interdisciplinary team consisting of a core group of physical therapists, occupational therapists, psychologists, nurses, and case managers providing individualized treatment in a structured setting. The components offered, the sequencing of programmatic components, and the relative importance and value of each therapeutic component frequently differ from program to program. There is also much variation in the intensity and duration of these programs.

Outcome monitoring is critical for documenting program efficacy, cost effectiveness, and decisions on whether or not to refer a patient to a given program. Multidisciplinary physician oversight should be provided in such programs. Most programs include progressive physical activity, which incorporates exercise intended to move the patient toward a home fitness maintenance program and a gradual increase in personal and occupational functional tasks.

INDICATIONS FOR FUNCTIONAL RESTORATION PROGRAMS

Functional restoration programs are recommended for patients with chronic pain who have failed conventional treatments and remain significantly incapacitated. Both program-specific and patient-specific criteria should be met prior to referring the patient and initiating such a program.

1. **First, determine if a functional restoration program should be used to facilitate recovery.**
It should be determined that “conventional” individualized non-interdisciplinary care (including medical management, psychological care, and physical or occupational therapy) has not resulted in the following:

a) Improvement and stabilization from a pain management medication use, functional (ADLs), and psychological standpoint.

b) Readiness to return to full duty or modified work, or a retirement decision.

c) Achieving maximal medical Improvement (MMI) status if but for a functional restoration program (in some states, also termed permanent & stationary [P&S]).

2. **Upon meeting the above criteria, the next step is a request for a multi-disciplinary evaluation (MDE). The MDE team (physician, psychologist, PT) then evaluates the individual and opines as to whether the clinical evaluation/data support that involvement in an FRP will result in 1a, 1b, 1c, with moderate to major improvement in (controlled) medication use, ADLs/functional abilities and psychological stabilization/improvement.**

To accomplish this, a patient must go through a thorough evaluation, which should comprise a record review and assessment by program personnel, including a pain physician for a medical history and physical, a comprehensive evaluation by a psychologist, and an evaluation by a therapist (PT and/or OT). The purpose of these assessments is to rule out treatable conditions, identify addiction issues (and refer elsewhere if needed), and establish patient appropriateness for a tertiary pain program. Psychological evaluation with psychometric testing is necessary to identify factors that contribute to disability and to develop potential intervention(s) for identified problems. These evaluations also should identify barriers to recovery that will need to be dealt with by the treatment team during the program, including fear avoidance beliefs ("kinesiophobia"), catastrophizing, fear of re-injury, and potential barriers to physical progress and assessment. The PT/OT evaluation should include baseline functional abilities testing to quantify capabilities (see Tables 9 and 10). Other evaluations (e.g., case management or nursing assessments) are done if additional information is necessary to specifically assess patient benefit and to help guide the treatment in the program.

There is no specific timeframe beyond 3 months which is required to elapse before attempting a tertiary pain program. Some patients may begin to demonstrate a chronic pain syndrome with significant disability within a few weeks of injury (during which time other interventions are indicated prior to a tertiary pain program, see other guidance). For others, 6 months or more may elapse before chronic pain syndrome changes occur and/or the above conditions are met. At this time, there is no quality evidence that a tertiary pain program is necessary to prevent the evolution of a chronic pain syndrome. Success in this regard is based on appropriate medical and functionally based care [(655)].

The admission of a patient to a tertiary pain program should be based on the above factors and meet all of the following patient-related criteria:

● The patient is either completely off work or on modified duty for at least 3 months and not trending towards functional recovery over the next 1-2 months.

● Other appropriate evidence-based medical and/or invasive care has been attempted (if indicated) and proved to be inadequate to restore functional status.

● The patient has appropriate rehabilitation potential (i.e., judged to be able to substantially benefit from the program).

● The patient is not responding to less costly interventions, including evidence-based individualized medical care, physical or occupational therapy (e.g., including active graded exercise program), and psychological/behavioral services.

● The patient has at least some behavioral or psychosocial issues affecting their recovery. For workers without behaviorally related issues and merely a physical gap between the current capabilities and future job requirements, work conditioning/work hardening programs are usually both more appropriate and cost-effective.

● The patient has measured, reproducible, and substantial gaps between current physical capabilities and actual or projected occupational demands.

● There are no known contraindications to the treatment program, e.g., certain unstable medical or orthopedic/neurosurgical conditions, primary substance use disorder, or

cognitive limitations which would prevent participation in physical rehabilitation and learning.

- There is an absence of other evidence-based medical, physical medicine, behavioral or interventional treatment options for the given disorder with potential to provide significant clinical improvement.
- The patient is committed to recovery.

A special consideration applies to patients with significant opioids and/or benzodiazepine and/or addictive substance(s) use. These patients may require significant involvement of an addiction specialist for success of a tertiary interdisciplinary or multi-disciplinary pain treatment program for that particular patient. In some cases, detoxification and/or treatment by an addiction specialist may be necessary before consideration of treatment by an inter- or multidisciplinary pain program.

3. **Although there are no absolute contraindications for a functional restoration program, determine whether the individual has any medical or personal issues that would prevent them from fully participating in and benefiting from the program, such as the following:**

- Unstable medical or psychiatric conditions.
- Focus on passive treatments, such as interventions or surgery.
- Lack of motivation or interest in actively participating in rehabilitation.
- Substance misuse issues.
- Cognitive limitations that would hinder learning and understanding.

4. **A functional restoration program should NOT be recommended in the following cases:**

- If the main goal alone is to improve physical strength and endurance to return to work (physical reconditioning).
- If the worker's mental health issues are the primary issue and can be managed with one-on-one counseling.
- If a less costly work conditioning/hardening program may help the worker stabilize the medical condition, return to work, or close the case.

In other words, an FRP might not be necessary if the worker's primary needs are physical reconditioning and manageable mental health issues, and a simpler, less costly program, or a few select and indicated intervention(s), can help achieve the goals.

5. **MMI/P&S status notification:**

- At the initial evaluation (MDE), the injured worker should be told that they will likely be considered to have reached MMI/P&S status by the end of the functional restoration program, assuming they have not previously been deemed MMI.
- The physician and FRP Team will explain this and provide a detailed final report at the conclusion of the FRP. If the patient does not RTW at the end of the program, reason(s) must be documented in the final report.

6. **The MDE should result in the identification of delayed recovery factors and strategies to overcome them as well as specific recovery goals and the process to achieve those goals which are agreed upon with the injured worker, and documented, at the time of the MDE and at the beginning of the FRP.**

7. **Employment plans/goals:**

● Pre-FRP: Unless the patient has fully retired from the workforce, the plan/goal should be to return to work in some capacity either at the same employer or for the individual to be ready to seek alternate employment.

● While a plan to return to work is not an absolute prerequisite for engaging in an FRP, the MDE team and the injured worker have the burden of clearly delineating the goals of FRP to justify FRP engagement in cases where the plan is not return to work.

8. **Physical function:**

● Clear documentation of goals set and met for significant physical functional improvement in ADLs and work capabilities should be documented weekly on the chart (see Table 9) in categories identified at the MDE and during the FRP. The patient should be part of the goal-setting and acknowledge the weekly status.

● If not entirely applicable, Table 9 should be modified (e.g., added categories) to accurately reflect the detailed plan/goals for the specific injured worker; however, this chart is designed for patients with low back pain and most other patients.

9. **Well-being/quality of life (QOL) and ADL function:**

● Clear documentation of improvement in physical and mental well-being and ADL function must be provided weekly to the concurred parties (payers, attorneys, etc.) in categories identified at the MDE and during the FRP. The report should include that the patient acknowledges and agrees the weekly status and goals to be achieved.

● If not entirely applicable, Table 10 should be modified (e.g., added categories) to accurately reflect the detailed plan/goals for the specific injured worker; however, this chart is designed for patients with low back pain and most other patients.

10. **Work restrictions:**

● Work restrictions should be updated weekly. The patient should acknowledge the weekly status.

11. **Functional restoration program continuation:**

● Authorization to continue the program based on functional and psychological gains, as noted above, should be requested at an agreed-upon schedule with the payer (typically every two weeks). Should the payer opt not to provide further authorization, payment should continue for the program, including the day the denial is documented/received.

● Daily and regular attendance is expected. Absences other than for documented illness or approved absence due to other issues shall be cause for program discharge.

12. **FRP timeframe expectation:**

● Minimum of 5 hours/day; 4-6 weeks; 160 hours maximum. Any exceptions need to be negotiated with the payer with justification.

13. **FRP costs:**

● Recommended charges are not part of the ACOEM Chronic Pain Guideline and, therefore, are not included.

14. **Patient participation agreement:**

● As noted above, admission and continuation in the FRP is contingent on the injured person being actively involved and knowledgeable about his or her program including goals set and progress made. This should be documented between the FRP Team and the individual.

15. **Other program criteria:**

The most important tertiary pain program criterion for approval is a proven track record of returning patients to work.

Chronic pain programs must assist the injured worker in overcoming disability while not involving unnecessary and excessive healthcare which can also result in increased iatrogenically caused disability. Programs with favorable outcomes tend to be those that emphasize principles of functional restoration and either minimize use of procedures or altogether eschew procedures. There is great variability in the quality of care in these programs, and familiarity with a program and its "track record" is necessary before referring a patient to a specific program. All medical and therapy services must be supervised by a physician who is directly involved with the program, who regularly interviews and examines the patient for relevant parameters.

Programs with quality evidence of efficacy could be mostly segregated into two basic types, both of which involve an integrated team-based approach involving either:

● a program consisting of a limited number of disciplines in a combined behavioral-exercise approach (e.g., an occupationally-oriented physician, physical therapist (and/or occupational therapist), and psychologist); and

● a workplace-focused program to facilitate return to work with a multidisciplinary, participatory ergonomics team approach (ergonomist, worker, supervisor, and others).

Thus, a program must fall into one of these two categories to be considered recommended by this evidence-based guideline, although quality evidence suggests a participatory ergonomics approach may be the superior option of these two types of programs [656,657]. Programs may involve a pain physician, physical therapist (and/or occupational therapist), and psychologist. It should generally also directly or indirectly include the ability to involve vocational counseling, nursing, and case management.

Programs must measure, track and emphasize:

● the development of a patient-centric mindset for recovery,

● tailoring of the program to target the worker's specific deficit(s), needs and focus on and return to function,

● return to work, including the development of measured gaps between the worker's abilities and that worker's specific job demands,

● cognitive-behavioral approaches (see Behavioral guidance),

● kinesiophobia/FABT and fear of re-injury interventions (i.e., actively assessing the presence of those beliefs and addressing any identified),

● progressive aerobic exercises,

● progressive strengthening exercises,

● simulated graded work tasks, and

● is tailored to specific gaps between current capabilities and job demands. When a specific prior job is no longer available, identification of reasonable goals to be met are identified for post-program job seeking.

● Programs must track overall program outcomes. While there is no current minimum return-to-work success rate for program eligibility for workers' compensation patients, it is projected that such guidance will naturally be developed.

FREQUENCY/DOSE/DURATION OF FUNCTIONAL RESTORATION PROGRAMS

Treatment program length may be influenced by the severity of deficits, gap(s) between current function and occupational demands, speed of progress, cessation of healing (or reaching a “plateau”), and thus are somewhat individualized. Complicating problems such as coordinating with part-time work, transportation, child care, extreme functional deficits, psychological disorders, high-dose opioids, or limitations imposed by comorbid medical conditions are considerations that may necessitate a slower approach to program participation and longer treatment duration.

The program's primary emphasis must be on progressive physical activity, which incorporates exercises intended to move the patient to fill gaps between current function and work tasks, as well as toward a home fitness maintenance program and a gradual increase in personal functional tasks. Emphasis on increased well-being and emotional stability occurs during the program.

In most effective tertiary pain programs, physical reconditioning, patient education, CBT, behavior modification, psychological interventions, activity fear avoidance (“kinesiophobia”), stress management, or biofeedback procedures are key components. Regular objective measurements, tracking and monitoring of progress, modification of treatment plans, and interdisciplinary team communications are required [(658)]. Outcome monitoring is critical for documenting program effectiveness and proving the program meets criteria for referral and treatment. The effectiveness of some of these programs has been documented, and well-designed programs are cost-effective with respect to direct healthcare expenditures, disability costs, and other economic indicators, although many US pain practices are procedure-centric and have no quality evidence of efficacy.

Inpatient Care. Nearly all patients can be treated on an ambulatory basis. In the rare circumstances where hospitalization is required, this should be under the control of or closely coordinated with a tertiary pain program physician [(659)]. Indications for inpatient care include any of the following:

● detoxification on an outpatient basis presents unacceptable medical risk(s);

● medical instability;

● the evaluation suggests that treatment may exacerbate pain/illness behavior to the extent that there is a risk of injury or render florid manifestation of a major psychiatric disorder;

● 24-hour nursing care is required;

● extreme pain behavior and dysfunction that makes outpatient care infeasible, and there is reasonable evidence presented by the evaluating pain team that a brief inpatient stay will enable transfer to an outpatient tertiary pain program.

When these conditions no longer apply, the patient should be discharged from an inpatient program.

Non-indicated Therapies. Therapies such as injections that do not have specific indications, have the distinct potential to reinforce pain/illness behavior, and therefore retard functional progress in a tertiary pain program (see ACOEM disorder-specific guidelines). There is no quality evidence that such procedures provide any incremental benefit in a tertiary pain program. There is also no empirical evidence that passive modalities (e.g., heat, cold, ultrasound, massage) provide additional benefit in a tertiary pain program. These should only be used for specific, limited indications and if they facilitate improvement in exercise or function (see ACOEM disorder-specific guidelines).

Other Functional Restoration. At times, patients may require functional restoration but find that either a formal program does not exist, or it is not appropriate due to medical or social issues. In such cases, functional restoration can sometimes be accomplished, provided the patient requires treatment for specific clinical indications with specific services to be provided. At a minimum, there should be appropriate indications for behavioral/psychological treatment, physical or occupational therapy, and at least one other rehabilitation-oriented discipline. Care must be coordinated by a physician appropriately qualified and experienced to provide and supervise rehabilitation services or functional restoration. Criteria for the provision of such services should include:

● satisfaction of the criteria for coordinated functional restoration care as appropriate to the case;

● a level of disability or dysfunction that does not require treatment in a formal program;

● no drug/substance dependence or problematic or significant opioid usage; and

● a clinical problem for which return to work can be anticipated upon completion of the services.

Follow-up. Regular or intensive formal treatment is not usually necessary after successful discharge from a tertiary pain program. However, it is important that patients continue a self-directed home program of physical restorative and psychological pain management

approaches learned during the tertiary pain program. Routine follow-up should be provided to assess the durability of the functional restoration achieved, with a long-term care plan established to facilitate management by the treating physician.

PARTICIPATORY ERGONOMICS

PARTICIPATORY ERGONOMICS PROGRAMS FOR CHRONIC PAIN

Sometimes Recommended

Participatory ergonomics programs are recommended for select patients with subacute and chronic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Indications

Patients with subacute and chronic pain who remain off work or on a different job, have apparent workplace barriers to return to work, and where there is managerial support and interest in analyzing and addressing barriers. This may be particularly beneficial in settings with low or no effective controls on lost time (e.g., there has been no attempt to develop modified or "light duty" positions). Primary preventive programs may be best indicated in high-risk jobs, especially those with high-force requirements.

Benefits

Earlier return to work. Primary, secondary, and tertiary prevention. Improved and earlier functional recovery through earlier return to work.

Harms

Negligible. Risk of managerial attention to a worker with subsequent workplace labeling of a ‘problem worker.’

Frequency/Dose/Duration

Generally only one evaluation of a job and workplace is needed. A second evaluation of potential interventions may occasionally be needed.

Indications for discontinuation

Workplace is unable to change the job, infeasibility, noncompliance, disinterest.

Rationale

Participatory ergonomic programs have been used for treatment of chronic pain (Russo et al., 2021). Quality evidence is available to assess the effects of a participatory ergonomics return to work program for subacute to chronic LBP. However, studies have largely been

performed in Europe where practices are far different, lost time may be more extensive and therefore, generalizability to the U.S. is somewhat unclear (Lambeek, 2010, Lambeek, 2010, Driessen, 2011). In addition, the return to work timeframe has likely shifted in the US to far earlier timeframes than in the past as the concept of “rest” for back pain has been shown to be unhelpful. One trial suggested a combination of participatory ergonomics, CBT and physical training resulted in improvement lifting and fear avoidance, but no change in sick leave days or improved work ability (Rasmussen, 2016). Return-to-work programs may be low cost relative to the lost time saved particularly where there are no other controls on lost time. These programs are not invasive, have low potential for adverse effects and are recommended. However, they do require willingness and interest among multiple parties to be successful. The rating is reduced from "C" to "I" due largely to study heterogeneity.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Participatory Ergonomic, participatory ergonomics; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 17,935 articles in PubMed, 3 in CINAHL, 1 in Cochrane Library, 16,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 7 randomized trials and 1 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Participatory ergonomics are usually work-site based and generally imply that the worker is engaged in the process of job design, organization, sequencing, or layout instead of merely working on a job designed by an engineer without input into how the job is accomplished. There are two major types of participatory ergonomics teams for purposes of this discussion. One involves a proactive job design and may involve engineering, management, health care, and particularly the worker in viewing, commenting, and critiquing proposed job designs prior to implementation. This ideally also includes the potential for modifications after implementation. The other main type of participatory ergonomics involves returning a worker to a job after an injury and particularly after a prolonged absence.

BEHAVIORAL INTERVENTIONS

OVERVIEW

Pain is a psychological phenomenon that is influenced by a myriad of biomedical and psychosocial factors. An approach to pain assessment that has shown considerable promise has been the assessment of cognitions related to pain, particularly the assessment of pain catastrophizing and fear avoidance (i.e. kinesiophobia) [(660)]. This approach naturally leads to behavioral interventions.

The traditional approach to assessing and treating pain uses an ordinal pain scale (0 to 10). Unfortunately, a patient's pain report may be confounded by a variety of variables including:

1. the perception of pain, and especially chronic pain has a low correlation with pathophysiology,
2. the perception of pain is influenced by psychological variables such as mood, arousal, attention and cognition, and
3. the patient may be incentivized to alter reports of pain.

Thus, there is increasing use of function-centered questionnaires to determine the degree to which pain impacts function, although these too are usually subjective. Advancing research using fMRI and similar technologies may develop into objective method(s) of identifying brain activity that corresponds and corroborates pain complaints [(661-664)]. However, these imaging techniques require further study in workers, as they may produce problematic findings (e.g. the patient's brain image suggests pain activity, although the patient does not report pain). These challenges present further problems as psychological and behavioral issues that impact pain and function may go unaddressed while being of critical importance.

When patients are assessed psychologically, pain problems are generally evaluated with various psychological instruments that provide qualitative and quantitative inferences about the patient's perceptions and related behaviors. Addressing pain-related dysfunction, psychological comorbidities (e.g., anxiety, fear, depression, anger, hopelessness, stress) and engaging in problem solving to address social roadblocks to recovery is usually more helpful than focusing on analgesia. One treatment approach with considerable evidence of success is cognitive behavioral therapy (CBT). CBT recognizes the pain, but works to change the patient's negative thoughts about the pain and its impacts, including the development of constructive skills, coping and behaviors related to the pain. Recognition of fear avoidant beliefs/kinesiophobia and catastrophization is primarily identified during vigilant history, physical examination, therapy appointments when advancing exercises, and observation of function rather than administration of questionnaires, although the Tampa Scale of Kinesiophobia is the most commonly used tool [(665,666)]; these issues require prompt addressing after patient vocalizations.

The way in which the clinician manages the patient with delayed recovery may affect the degree to which chronic pain behaviors develop. As pain is a biopsychosocial phenomenon, a formal psychological evaluation (which may include appropriate diagnostic psychological testing) may be helpful (see below). In addition to identifying psychological risk factors, the identification of any social risk factors is also important (see the Work Disability Prevention

and Management guideline). Social risk factors may include work-related issues such as job satisfaction or co-worker support, family reinforcement of pain behaviors or lack of support, and legal/financial incentives for poor recovery. Additionally, cultural beliefs regarding origins of disease and health care patterns may also influence presentation and recovery. These should be addressed in a positive, cooperative and sensitive manner to facilitate recovery and minimize the chance of physical debilitation and chronic or long-term disability [(182)].

Treating chronic pain syndromes requires specialized knowledge, substantial time, and access to multiple disciplines if not multidisciplinary care. Judicious involvement of other health care professionals (e.g., psychologists, occupational and physical therapists, etc.) who can offer diagnostic assessments and additional therapies where indicated, while the clinician continues to direct the therapeutic process to maximize functional restoration. Close communication between all treating professionals is essential.

TREATMENT RECOMMENDATIONS

PSYCHOLOGICAL EVALUATION

PSYCHOLOGICAL EVALUATION FOR CHRONIC PAIN

Sometimes Recommended

A psychological evaluation with psychometric testing is recommended as part of the evaluation and management of patients with chronic pain who are not at full work status. A psychological evaluation can identify psychosocial barriers that are contributing to disability and inhibiting function, as well as assess which psychological factor(s) should be considered and included as part of the overall treatment plan.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence High

Indications

Patients with moderate to severe chronic pain who meet one or more of the following conditions:

1. There is need to understand psychosocial factors contributing to the patient's pain reports and disability behaviors.
2. *Inadequate functional recovery:* This includes continued dysfunctional status despite a duration which exceeds the typical course of recovery; failure to benefit from indicated therapies or to return to work when medically indicated; or a persistent pain problem which is inadequately explained by the patient's physical findings.
3. *Medication issues and/or drug problems:* This includes any suspicion of drug overuse or misuse, aberrant drug behavior, substance use disorder, addiction, or use of illicit substance, or for consideration of chronic use of opioids (Henningsen et al., 2007, Kelly et al., 2008, Moretti et al., 2012, Almeida et al., 2003).
4. Significant psychosocial dysfunction that is observed or suspected.
5. Current or premorbid history of psychiatric symptoms or disorder.
6. *Problems with compliance/adherence with prescribed medical treatment or rehabilitation program:* For evaluation of candidacy for or potential benefit from a proposed

functional restoration program, e.g., comprehensive occupational rehabilitation or interdisciplinary pain rehabilitation (see Functional Restoration).
7. *Evidence of possible cognitive impairment which is associated with related significant ADL dysfunction:* This may be secondary to injury and/or possible adverse effects of medical therapies initiated for the chronic pain.
8. Catastrophic injuries with significant pain related or other dysfunction, e.g., spinal cord injury, and projected long-term rehabilitation to pre-identify issues (Sutbeyaz et al., 2009, Shupak et al., 2006, Maestu et al., 2013).
9. Certain procedures are contemplated, e.g., back surgery (see Low Back Disorders Guideline) or spinal cord stimulation.

See also the ACOEM Workplace Mental Health guidelines for recommendations regarding depressive disorders, anxiety disorders, and posttraumatic stress disorder.

Benefits

Identify psychological factors that may maintain chronic pain and disability, begin treating and remove barriers to rehabilitation, and facilitate recovery and restoration of function.

Harms

Negligible. The implications of requesting a psychological evaluation are often misconstrued to imply that the purpose is an accusation. Though such diagnoses may be rendered, this does not necessarily imply a “psychological” or “mental” cause for the symptoms and signs.

Frequency/Dose/Duration

One comprehensive psychological evaluation should be performed by an independently licensed psychologist, and may in some especially more complex cases include collaboration with other professions. Ongoing treatment as indicated by the results of the initial evaluation. Content follows (Thomas et al., 2007, Taylor et al., 2013)(Anderson JD, 2013, Taylor et al., 2013).

1. *Appropriate review of records:* The referring clinician should assist in providing medical record documentation. Other information is sometimes reviewed, as necessary, e.g., from a family assessment, job description, etc.
2. *Clinical interview with patient:* The following parameters should be described from this interaction and other data obtained: History (including mental health, physical health, work, educational, legal, and substance use history), description of the pain, disability and/or other clinical problem, analysis of medication usage, social history, mental status, and behavioral assessment (including, as necessary, ADL, functional issues, and operant parameters, e.g., pain/illness behavior and environmental influences). Common barriers and factors related to treatment success should be addressed, including patient expectations, self-efficacy, loss of control, pain acceptance, catastrophization, and kinesiophobia.
3. *Psychological testing:* A battery of appropriate diagnostic psychological tests should be administered and interpreted, as necessary. This should include instruments with evidence of validity and/or appropriate normative data for the condition or problems being

assessed and have known value in differential diagnosis or treatment planning (Hargrove et al., 2012). In selecting test instruments, the clinician should consider: 1) the appropriateness of the test(s) for the patient's presenting complaints and condition; 2) the appropriateness of a test(s) given the degree to which the patient's medical, gender, race/ethnicity, age, educational and other group status was represented during the test(s) development; 3) how a patient's performance in comparison to normative data will be useful in diagnosis or treatment planning; 4) the prognostic value of interpreted test data for certain treatments; and/or 5) whether the sensitivity and specificity will enhance the accuracy of a diagnosis (more specific test information is found in Appendix 1). Indications for psychological tests may include circumstances when:

- understanding factors contributing to the patient's pain reports and disability behaviors;
- a mental disorder is suspected;
- evaluating for a functional restoration program;
- the evaluation is part of a pre-surgical assessment;
- there is suspicion of cognitive impairment;
- the veracity of the complaint is at issue.

Standardized psychological testing should be done as a part of a comprehensive mental health evaluation, as properly performed psychological testing enhances the reliability and value of a psychological evaluation. Psychological testing is usually performed by a psychologist, but psychiatrists or other physicians also perform such assessments if it is within the scope of their training and experience (Hargrove et al., 2012, Fregni et al., 2006). Standards for the psychological assessment of patients with chronic pain have been reviewed elsewhere (Bruns, 2014). Additionally, both evidence and expert consensus regarding what variables should be assessed in these evaluations has also been reviewed (Bruns et al., 2009). The test battery for evaluation of patients with chronic nonmalignant pain includes, but is not limited to:

1. Test(s) for assessment of the presenting pain, and/or other related health complaints or dysfunction;
2. Test(s) of personality and psychopathology;
3. Brief cognitive testing, when there is suspicion of CNS impairment;
4. *Diagnostic impressions:* These should be inferred according to the ICD-10 (Madson et al., 1994).
5. *Summary:* The psychological evaluation should provide both cogent explanations for the identified complaints and dysfunction, and recommendations for management (see Appendix 1 for examples of tests).

Indications for discontinuation

Largely negative results from an evaluation, resolution, and/or treatment to a level of acceptable stability.

Rationale

There are no quality trials of psychological evaluations, although there are many trials of specific tests. Such assessments are routinely accomplished for the various purposes given above, including treatments for which various levels of evidence are provided herein, e.g.,

functional rehabilitation or interdisciplinary pain programs, candidacy for certain procedures, or chronic use of opioid medications.

Chronic pain problems are usually maintained by a variety of medical, physical, social, psychological, and occupational factors; the general purpose of a psychological evaluation regarding chronic pain is to comprehensively evaluate these influences and identify factors for intervention(s). However, most pain complaints and functional deficits arising from musculoskeletal injuries resolve spontaneously or respond adequately to initial conservative treatment. Psychological evaluation should be considered for patients with chronic pain, i.e., where the pain problem or dysfunction persists longer than typical for the associated condition. Notwithstanding the numerous risk factors for development of chronic nonmalignant pain, the prediction of chronicity based on psychological evaluation of a specific patient has not been reliably demonstrated. The general purpose of the psychological evaluation is to:

- describe and diagnose the current psychological and psychosocial dysfunctions;
- describe psychological strengths;
- elucidate the current psychological and behavioral factors which are salient in maintaining the complaints and dysfunction;
- assess the likely premorbid factors which may be contributory; and
- recommend treatment, management, and/or occupational/vocational options.

Psychological testing conducted outside the context of a qualified mental health evaluation has not been evaluated in quality studies and is believed to either provide little if any helpful information for the treating clinician, may be potentially misleading, and psychological test results outside settings comparable to those used for standardization may be uninterpretable. Tests used in isolation provide questionable clinically useful diagnoses or prognostic information for various procedures (see below).

The professional consensus is that the use of automated or computerized interpretation of standardized psychological instruments without adequate clinical correlation is inappropriate, although there are no large quality studies to evaluate that potential approach. Interpretation is best accomplished in the context of the individual patient mental health examination with corroboration of other clinical findings (Mendonca ME, 2011, Villamar et al., 2013). Ethically, it is always preferable to conduct psychological evaluation and standardized testing in a patient's preferred language and in consideration of unique cultural issues (Hargrove et al., 2012, Fregni et al., 2006, Mendonca ME, 2011). Where alternate language forms of specific psychological test instruments are utilized, there should be assurance of appropriate validity. Assessments performed via a translator should be avoided whenever possible. When done in this fashion, errors, distortions, and misevaluation of patients' mental status and other parameters may occur (Fagerlund et al., 2015, Fregni et al., 2006, Boyer et al., 2014, Mhalla et al., 2011). When performed in this manner, the increased potential for a distorted assessment of the patient should be taken into consideration and documented.

Psychological evaluations are not invasive, have negligible adverse effects, are moderate cost, have clinical evidence of efficacy and are thus selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Psycological evaluation; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 15,987 articles in PubMed, 15 in CINAHL, 32 in Cochrane Library, 18,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 2 from CINAHL, 2 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 1 randomized trials and 2 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Psychological and behavioral factors are key components of subacute and chronic pain conditions, such as the following:

- Risks of development of chronic pain (e.g., pre-existing anxiety [122,127,667,668,669], depression [122,667,668], catastrophizing, somatization [122], fear avoidant beliefs ("kinesiophobia") [166], fear of reinjury [166], job dissatisfaction, job instability, inadequate coping skills, familial social support, workplace social support; alcoholism [667,668]; and
- Risks from chronic pain (e.g., development of, or recurrence of anxiety [125,669], depression [668,669,670], catastrophizing, job instability, social estrangement, familial instability). (These issues are described in the Chronic Pain Guideline's Introduction and Basic Principles.)

Psychological evaluation and treatment should be strongly considered for patients with chronic pain. Since such patients often present difficulties in diagnosis, rehabilitation, appropriateness for invasive procedures, and return to work planning, consultation can be helpful in these areas. Additionally, through behavioral medicine even those with relatively low levels of formal psychopathology may learn better ways of self-managing symptoms and therefore optimize their pain outcomes. As well, those with subacute pain who are not improving as expected are also candidates for psychological evaluation to improve function and to develop a plan to avoid chronic pain behaviors.

COGNITIVE BEHAVIORAL THERAPY

COGNITIVE BEHAVIORAL THERAPY (CBT) FOR CHRONIC PAIN

Recommended

Cognitive behavioral therapy (CBT) is moderately recommended for the treatment of subacute and chronic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence High

Indications

CBT is indicated for all patients with chronic pain conditions.

Additional indications that further increase the need and potential benefits for the use of CBT in chronic pain conditions include one or more of the following:
1. Inadequate results from traditional physical (or occupational) therapy and exercise program;
2. clinically significant problems of noncompliance or non-adherence to prescribed medical or physical regimens;
3. Mood disorders that complicate the management of the pain condition;
4. planned vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work);
5. resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions;
6. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification; and
7. Sleep disturbance due to pain.

CBT is also indicated for many acute and subacute pain conditions (see ACOEM disorder-specific guidelines), as well as depressive disorders, anxiety disorders, and PTSD (see the ACOEM Workplace Mental Health guidelines).

Benefits

Improvements in management of pain, functioning in home, work, and community settings. Reduced disability (Linton, 2005). May improve success of return-to-work process. May ease opioid-weaning process. Reported reduced pain intensity and pain catastrophizing (Cherkin et al., 2016, Darnall et al., 2021), depressive symptoms (Cherkin et al., 2016, Darnall et al., 2021, Williams ACC, 2020), anxiety to 3 and 6 months post-treatment (Darnall et al., 2021), as well as improved sleep at 3 months post-treatment (Darnall et al., 2021). Reported volumetric increases measured by MRI in brain regions associated with the pain control that correlated with reductions in pain intensity immediately posttreatment.

Harms

Negligible.

Frequency/Dose/Duration

CBT provided either independently (Lamb SE, 2010) or as a component therapy integrated into a program that includes physical or occupational therapy, such as an interdisciplinary or other functional restoration program (Monticone et al., 2013), especially where the primary complaint is LBP. Established protocols for CBT range widely. The shortest successful program show to have durable results is a 2-hour "Empowered Relief" program (Darnall, 2024, Darnall et al., 2021, Darnall, 2019). Other programs require from 16 hours (Lamb SE, 2010, Monticone et al., 2013) to up to 24 hours to accomplish (Gyani et al., 2013). For select patients (e.g., ongoing medical procedures, serious complications, medication dependence, injuries associated with psychological trauma), longer supervised psychological/psychiatric treatment may be justified. Adjunctive treatment generally includes aerobic exercise and/or medication for concomitant mental health disorders (i.e., depressive disorders, anxiety disorders, PTSD; see the ACOEM Workplace Mental Health guidelines). CBT should normally be limited to 6 sessions or less initially. Additional appointments may be needed, especially for those with multiple complex problems to address and/or to sustain and reinforce progress. Provision of additional appointments should be contingent on compliance with the requirements from the initial set of appointments. When therapy is provided as a component of an interdisciplinary or functional restoration program, the number of sessions is based on the needs of the program to provide relevant treatment objectives.

Distance-based administration has been found effective (Ziadni et al., 2021, Buhrman et al., 2004), although there are no comparative trials to suggest comparative effectiveness.

Indications for discontinuation

Noncompliance, failure to obtain functional or behavioral improvement, cognitive impairment, or low literacy prevents the patient from benefiting from the CBT protocol.

Rationale

Cognitive behavioral therapy has been shown to be effective in most studies for the treatment of chronic pain (see evidence table). There are many moderate quality trials of CBT and combinations of CBT with physical therapy and other interventions. Efficacy of CBT and is suggested by a large majority of studies with improvements in pain and function (Linton, 2005, Linton, 2000, Kashikar-Zuck et al., 2012, Cherkin et al., 2016, Luciano et al., 2014, Wetherell, 2011, Vibe Fersum et al., 2013, Castel et al., 2012, Glombiewski, 2010, Thieme et al., 2006, Ang et al., 2010, Darnall et al., 2021). Two quality trials have shown multi-dimensional benefits for CBT months after treatment and across a range of outcomes, including reduced anxiety, depression, and pain catastrophizing (Cherkin et al., 2016, Darnall et al., 2021). One trial suggested significant reduction in disability attributed to a combination of CBT and physical therapy (Linton, 2005), and another trial suggested better development of muscles in the physical therapy exercises plus CBT group compared with physical therapy exercises alone (Bagheri et al., 2020). One trial suggested comparable effectiveness with MBSR (Cherkin et al., 2016). Some trials have not suggested efficacy, including one trial comparing medication optimization with CBT for chronic low back pain

(Bushey et al., 2022), and another adding cognitive patient education for low back pain (Werner et al., 2016).

A Cochrane review concluded there was sufficient evidence from a large evidence base that CBT had small or very small effects to improve pain, disability and distress from chronic pain (Williams et al., 2012). Another systematic review with meta-analysis of studies of combined pain and sleep disturbance concluded CBT for insomnia improved pain control, disability, depression and sleep (Enomoto et al., 2022).

There also is considerable evidence of efficacy of CBT for treatment of depressive disorders, anxiety disorders and PTSD. See the ACOEM Workplace Mental Health guidelines for the indications and recommendations for treatment of those conditions.

There is no quality evidence to support the use of psychotherapeutic techniques which are not primarily behavioral or cognitive-behavioral in nature in the treatment of patients with chronic nonmalignant pain. While CBT is sometimes used alone, its use in combination with other interventions is generally recommended (Linton et al., 2005, Linton et al., 2000, Kashikar-Zuck et al., 2012, Cherkin, 2016, Wetherell, 2011, Luciano et al., 2014, Vibe Fersum, 2013, Glombiewski, 2010, Castel et al., 2013, Ang et al., 2010). CBT is not invasive, has negligible adverse effects, is low to moderate cost in aggregate, has evidence of durable efficacy and thus is recommended for management of most, if not all patients with chronic pain conditions and many with subacute pain. Considering that there is evidence of enduring efficacy of only a one-time intervention, i.e., "Empowered Relief" (Darnall, 2024, Darnall et al., 2021), CBT has the potential to be particularly efficient in helping many patients while being potentially quite economical.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Cognitive Behavioral Therapy, CBT ; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 9,446 articles in PubMed, 254 in CINAHL, 49 in Cochrane Library, 35,200 in Google Scholar, and 0 from other sources†. We considered for inclusion 22 from PubMed, 7 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 35 articles considered for inclusion, 20 randomized trials and 11 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Psychological or behavioral treatments are commonly provided to patients with chronic pain syndromes. Patients who should be more strongly considered for these services include those with one or more of the following: delayed recovery, ineffective pain coping skills, psychological disorder(s), insomnia, stress-related psychophysiological responses such as muscular bracing, problematic medication use, excessive fear avoidant beliefs, and/or non-adherence with prior physical activity or other prescriptions. Where indicated, this has been typically provided with cognitive-behavior therapy (CBT). This is a type of psychotherapy which emphasizes the relationship of cognitions, behaviors, and mood to physical symptoms in an attempt to promote specific therapeutic goals. CBT techniques generally employ "homework" assignments in addition to direct psychotherapeutic treatment, and because of that CBT protocols have varying requirements for literacy. The provision of therapy does not generally require an ICD-10 diagnosis, though this is often obtained in patients with chronic pain syndromes, and many such patients *may* meet criteria for various diagnoses. Other diagnoses frequently include insomnia, posttraumatic stress disorder, somatoform disorders, depression and/or anxiety disorders. Note that CBT treatments for chronic pain, depression, insomnia etc. are distinct therapies with unique protocols.

FEAR AVOIDANCE BELIEF TRAINING

FEAR AVOIDANCE BELIEF TRAINING (FABT) AND KINESIOPHOBIA TRAINING FOR CHRONIC PAIN

Recommended

Fear avoidance belief training (FABT) and kinesiophobia training are recommended for the treatment of patients with acute, subacute, and chronic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Low

Indications

Patients with any fear-avoidant beliefs (i.e., kinesiophobia).

Benefits

Improvement in functional recovery, less pain, less disability, and improved exercise compliance. Better ability for the patient to self-actualize. Improved abilities to manage subsequent exacerbations or recurrences.

Harms

Negligible

Frequency/Dose/Duration

Intervention is provided at the time a fear avoidance belief (FAB) is voiced or uncovered; this includes whether voiced during a medical examination or therapy visit. Should particularly address a de-emphasis on anatomical abnormalities, encouraging active management by the patient and education. When a FAB is identified, subsequent vigilance on the part of the clinician may help to reinforce proper beliefs and then would usually consist of 2 to 3 appointments and could range up to a total of approximately 6 appointments. Patients with particularly strong FABs may require up to 12 appointments.

Rationale

Fear avoidant beliefs and kinesiophobia have been associated with worse clinical outcomes and addressing these factors have been used for treatment of patients with pain (see evidence table). FABT has been evaluated in patients with acute, subacute, and chronic pain, most of whom had spine pain (George SZ, 2003, Klaber Moffett JA, 2004, Pfingsten M, 2001, Slater MA, 2009, Sorensen et al., 2010, Moffett et al., 2006)(George et al., 2003, Klaber Moffett JA, 2004, Pfingsten M, 2001, Slater MA, 2009, Sorensen et al., 2010). One study of acute LBP that included FABT found those with elevated FABs benefitted (Klaber Moffett JA, 2004). The other studies also suggest that those with elevated fear avoidance beliefs (FABs) benefited from interventions to address those beliefs/kinesiophobia (Storheim et al., 2003, Klaber Moffett JA, 2004, Pfingsten M, 2001, Storheim K, 2005, Fritz et al., 2002, Yamada et al., 2023, Murillo et al., 2023, Galan-Martin, 2020, Miller et al., 2020, James et al., 2021, Jørgensen et al., 2011, Moraes et al., 2021, Mansell et al., 2017, Khosrokiani et al., 2022, Monticone et al., 2018, Ryum et al., 2021, Javdaneh et al., 2020)(Storheim et al., 2003, Klaber Moffett JA, 2004, Pfingsten M, 2001, Storheim K, 2005, Fritz et al., 2002) with only one exception (Magnussen et al., 2007). Those with elevated FAB are particularly successfully treated with these interventions, while those without may not benefit. FABT is not invasive and has no adverse effects. FABT is low to moderate cost as a sole intervention, but low/no cost for educational information in addition to other clinician visits. Thus, FABT is recommended for acute, subacute, or chronic pain patients with elevated FABs at baseline.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Fear avoidance, Kinesiophobia, Tampa Scale of Kinesiophobia; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 173 articles in PubMed, 110 in CINAHL, 92 in Cochrane Library, 8770 in Google Scholar, and 37 from other sources. We considered for inclusion 28 from PubMed, 7 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 38 articles considered for inclusion, 20 randomized trials and 11 systematic studies met the inclusion criteria.

BIOFEEDBACK

BIOFEEDBACK FOR CHRONIC PAIN

Sometimes Recommended

Biofeedback is recommended for select treatment of chronic pain.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Indications

Patients with chronic pain who have been treated and are compliant with aerobic and strengthening exercises, CBT approaches, NSAIDs, etc., with ongoing significant impairment needing multidisciplinary rehabilitation. Biofeedback also is a reasonable as an intervention for patients who also have significant stress-related issues combined with chronic pain. Biofeedback requires motivated and compliant patients and is often performed in conjunction with other self-regulation strategies (e.g., relaxation training, mindfulness meditation, self-hypnosis). Biofeedback may be of greater benefit for those thought to have muscle tension syndrome, stress and/or anxiety.

Benefits

Improvement in stress management, anxiety, and functional recovery, including exercise compliance. Better ability for the patient to self-actualize. Improved abilities to manage subsequent exacerbation or recurrence.

Harms

Negligible.

Frequency/Dose/Duration

Requires a series of appointments to teach techniques and verify appropriate use, generally starting with 5 to 6 appointments. Appointments also needed to reinforce home use. Should generally be used to subsequently enhance functional gains, e.g., increasing activity or exercise levels. May require up to 12 appointments.

Indications for discontinuation

No significant improvement after up to 5 to 6 appointments.

Rationale

Biofeedback has been used for treatment of chronic pain (Tsiringakis et al., 2020, Campo et al., 2021). While many trials are low quality, there are several moderate-quality studies evaluating biofeedback for pain treatments (see evidence table), most of which assessed

treatment of chronic low back pain, neck pain, and fibromyalgia. The highest quality trial found biofeedback to be of no additive benefit to cognitive functional therapy (Kent et al., 2019). Others of the highest quality studies suggest modest efficacy for treatment of back pain (Kent et al., 2015) and fibromyalgia (Babu et al., 2007), although the remainder of the moderate quality studies conflict regarding efficacy (van Santen et al., 2002, Altmaier et al., 1992, Frih et al., 2009). One metanalysis conclude there was a small to moderate effect on neck pain but no effect on pain or work ability (Campo et al., 2021). Another metanalysis concluded there was evidence that motor control training of deep neck flexors and pressure biofeedback was more effective than strength-endurance training of cervical muscles for improving pain and disability in patients with neck pain (Tsiringakis et al., 2020). There are numerous low-quality RCTs.

Biofeedback is not invasive, has negligible adverse effects, is moderate cost, has conflicting evidence on efficacy with most trials suggesting some efficacy. Thus, biofeedback is recommended for treatment of select patients.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: biofeedback; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 114 articles in PubMed, 66 in CINAHL, 21 in Cochrane, 17,800 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 0 from CINAHL, 0 from Cochrane, 7 from Google Scholar, and 0 from other sources. Of the 10 articles considered for inclusion, 5 randomized controlled trials and 2 systematic reviews met the inclusion criteria.

Biofeedback is a behavioral medicine method to treat conditions by teaching self-awareness of specific sensory sensations and functions, and through this to be able to gain control over bodily processes that are typically thought of as being involuntary [(671-679)]. Biofeedback has been used for numerous conditions, including hypertension, stress management, temporomandibular joint pain and incontinence.

Biofeedback is theorized to be efficacious by providing means for the patient to gain control over these functions, especially muscle tenseness regarding LBP or other skeletal pain may be reduced and the patient may gain a feeling that pain is a manageable symptom. Biofeedback obtained its name since the patient receives specific feedback of body functions typically through visual or auditory stimuli. For example, the warmth of the finger is measured with a surface temperature probe. A graphic representation may be fed to a computer monitor, and the patient can learn to warm the digits, indicating a decrease in autonomic nervous system arousal. Other examples of physiological processes that can be trained with biofeedback include brain waves (e.g. neurofeedback), skin conductance (e.g. hand perspiration), respiratory rate, and heart rate variability (to modify baroreflex activity and parasympathetic “braking”). For purposes of LBP, the most typical biofeedback modality

is surface electromyogram (SEMG), in which muscle activity is measured and fed back to the patient and therapist through a visual display or audible signal, although respiratory biofeedback has also been used. Through this feedback, the patient can gain increased awareness of excess muscle tension, muscle inhibition during movements and exercises, and postural imbalances, which may be contributing to decreased function and increased pain. Through training and practice, patients can learn to modify dysfunctional muscle habits and to control the degree to which the muscles are contracted or relaxed. Relaxation has been reported to be associated with functional restoration program outcomes [680,681,682]. Adherents further believe that the training may alter work habits to reduce involvement of injured structures and avoid further injury [178].

ACCEPTANCE AND COMMITMENT THERAPY

ACCEPTANCE AND COMMITMENT THERAPY FOR CHRONIC PAIN

Recommended

Acceptance and commitment therapy (ACT) is recommended for treatment of chronic pain.

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Acceptance and commitment therapy is indicated for all patients with subacute and chronic pain conditions. Additional indications that further increase the need and potential benefits for the use of ACT in chronic pain conditions include one or more of the following:

1. Inadequate results from traditional physical (or occupational) therapy and exercise program
2. Reduced function at home, work, and in the community
3. Clinically significant problems of noncompliance or nonadherence to prescribed medical or physical regimens
4. Mood disorders that complicate the management of the pain condition
5. Planned vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work)
6. Resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions
7. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification
8. Sleep disturbance due to pain

Benefits

Increase in psychological flexibility by using mindfulness and changing behavior to improve chronic pain's effects by reducing struggles against pain that reduce function and increase

disability. ACT results in accepting thoughts and feelings; improves recognition that thoughts are not facts; improves living in the current moment; improves self actuation including that the pain being experienced and the disorder causing the pain is not the person; improving the patient's focus on the person's priorities in life; and commit to acting on those values and priorities to create a fulfilling life. These result in improvements in management of pain, pain perception, pain intensity, pain interference, mood, depression, anxiety, insomnia, and functioning in home, work, and community settings (see evidence table).

Harms

Negligible

Frequency/Dose/Duration

ACT protocols varied widely in quality studies and included the following:

- Eight 2.5-hour sessions (Luciano et al., 2014)
- Eight weekly sessions (Taheri et al., 2020)
- Two 1-hour sessions and one phone follow-up (Godfrey et al., 2020)
- Four 4-hour sessions (three sessions in one week and one session the following week, McCracken et al., 2013)
- Eight weekly self-administered modules with follow-up e-coaching (Lin et al., 2017)
- Nine internet-based self-administered modules to be completed over 9-12 weeks (Trompetter et al., 2015)

Two reports also suggest that ACT may be successfully delivered via the internet (Rickardsson et al., 2021, Lin et al., 2017).

There are no comparative trials to suggest either an optimal dose of sessions or superiority of live vs. distance-based administration.

Indications for discontinuation

Noncompliance, failure to obtain functional or behavioral improvement, cognitive impairment or low literacy prevents the patient from benefiting from ACT, or resolution of problems.

Rationale

Many moderate quality studies consistently document modest efficacy of ACT for treatment of chronic pain. Benefits shown in individual studies include improved function (Luciano et al., 2014), reduced disability (Godfrey et al., 2020, McCracken et al., 2013), reduced pain interference (Wetherell, 2011, Rickardsson et al., 2021), pain acceptance (Lin et al., 2017, McCracken et al., 2013), improved mood (Wetherell, 2011), reduced pain perception (Taheri et al., 2020), reduced pain/intensity (Rickardsson et al., 2021, Trompetter et al., 2015), reduced depression (Rickardsson et al., 2021, McCracken et al., 2013, Lin et al., 2017), reduced anxiety (Rickardsson et al., 2021), and improvements in insomnia (Rickardsson et al., 2021). However, evidence of efficacy in Cochrane metanalyses is sparse, viewed as

mostly low quality, and suggests reduction in disability (Williams ACC, 2020). Evidence of persistence of effects after treatment have been reported (Luciano et al., 2014, Rickardsson et al., 2021, McCracken et al., 2013, Lin et al., 2017).

There also is evidence ACT may be successfully self-administered by internet (Rickardsson et al., 2021, Lin et al., 2017).

ACT has consistent evidence of efficacy, is not invasive, has no adverse effects, and is low to moderate cost depending on numbers of visits. Thus, ACT is recommended for treatment of subacute and chronic pain. It is particularly recommended when there is reduction in function, pain interference, poor pain acceptance, and/or accompanying depression, anxiety, reduced mood, and/or insomnia.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Acceptance and Commitment therapy, ACT; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 85 articles in PubMed, 11 in CINAHL, 0 in Cochrane, 19,500 in Google Scholar, and 0 from other sources. We considered for inclusion 13 from PubMed, 0 from CINAHL, 0 from Cochrane, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 10 randomized controlled trials and 3 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

EMOTIONAL AWARENESS AND EXPRESSION TRAINING

EMOTIONAL AWARENESS AND EXPRESSION TRAINING FOR CHRONIC PAIN

Recommended

Emotional awareness and expression training (EAET) is recommended for treatment of chronic pain.

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Emotional awareness and expression training is indicated for all patients with subacute and chronic pain conditions. Additional indications that further increase the need and potential benefits for the use of EAET in chronic pain conditions include one or more of the following:

1. Inadequate results from traditional physical (or occupational) therapy and exercise program
2. Reduced function at home, work, and in the community
3. Clinically significant problems of noncompliance or nonadherence to prescribed medical or physical regimens
4. Mood disorders that complicate the management of the pain condition
5. Planned vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work)
6. Resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions
7. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification
8. Sleep disturbance due to pain

Benefits

Reductions in pain severity, pain interference, overall symptoms, widespread pain, physical functioning, cognitive dysfunction, anxiety, depression, positive affect, sleep problems, life satisfaction (Lumley et al., 2017, Bellomo et al., 2020, Yarns et al., 2024, Yarns et al., 2020, Ziadni et al., 2018)

Harms

Negligible

Frequency/Dose/Duration

EAET protocols varied widely in quality studies. These include:

- Eight 90-minute sessions (Lumley et al., 2017, Bellomo et al., 2020)
- One 90-minute individual session, then eight 90-minute sessions (Yarns et al., 2024, Yarns et al., 2020)
- One 90-minute interview (Ziadni et al., 2018)

There are no comparative trials to suggest an optimal dose of sessions.

Indications for discontinuation

Noncompliance, failure to obtain functional or behavioral improvement, cognitive impairment or low literacy prevents the patient from benefiting from the EAET protocol, or resolution of problems.

Rationale

Multiple trials suggest efficacy of EAET (Lumley et al., 2017, Bellomo et al., 2020, Yarns et al., 2024, Ziadni et al., 2018). One trial suggested lack of superiority to relaxation training for headaches (Slavin-Spenny et al., 2013). Two trials suggested superiority of EAET to CBT (Yarns et al., 2024, Bellomo et al., 2020, Yarns et al., 2020), while in another trial, most measures suggested equivalent effects between EAET and CBT (Lumley et al., 2017).

Quality studies document efficacy of EAET for treatment of chronic pain with benefits shown in individual studies including improvements in pain severity (Yarns et al., 2024, Ziadni et al., 2018, Bellomo et al., 2020), pain reduction (Yarns et al., 2024, Yarns et al., 2020), pain interference (Ziadni et al., 2018), overall symptoms (Lumley et al., 2017), widespread pain (Lumley et al., 2017), physical functioning (Lumley et al., 2017), cognitive dysfunction (Lumley et al., 2017), anxiety (Lumley et al., 2017, Yarns et al., 2024, Yarns et al., 2020), depression (Lumley et al., 2017, Yarns et al., 2024), PTSD symptoms (Yarns et al., 2024), positive affect (Lumley et al., 2017), sleep problems (Ziadni et al., 2018), and life satisfaction (Lumley et al., 2017, Yarns et al., 2024).

EAET has consistent evidence of efficacy across the few published trials, is not invasive, has no adverse effects, and is low to moderate cost depending on numbers of visits and thus is recommended for treatment of subacute and chronic pain. It is particularly recommended when there is any reduction in function, pain interference, poor pain acceptance, and/or accompanying depression, anxiety, reduced mood, and/or insomnia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Emotional awareness and expression training; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 18,754 articles in PubMed, 15 in CINAHL, 12 in Cochrane Library, 17,800 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MINDFULNESS AND MEDITATION

MINDFULNESS-BASED STRESS REDUCTION AND MINDFULNESS MEDITATION FOR CHRONIC PAIN

Recommended

Mindfulness-based stress reduction and mindfulness meditation are recommended for treatment of subacute and chronic pain.

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Low

Indications

Mindfulness-based stress reduction (MBSR) and mindfulness meditation (MM) are indicated for all patients with subacute and chronic pain conditions. Additional indications that further increase the need and potential benefits for the use of ACT in chronic pain conditions include one or more of the following:

1. Inadequate results from traditional physical (or occupational) therapy and exercise program
2. Reduced function at home, work, and in the community
3. Clinically significant problems of noncompliance or non-adherence to prescribed medical or physical regimens
4. Mood disorders that complicate the management of the pain condition
5. Planned vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work)
6. Resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions
7. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification
8. Sleep disturbance due to pain

Benefits

The highest quality studies suggest improvements associated with MBSR in pain (Cherkin et al., 2016, Burns et al., 2022), pain interference (Burns et al., 2022), physical function (Burns et al., 2022), catastrophizing (Turner et al., 2016), PTSD (Kearney et al., 2016), mindfulness (Turner et al., 2016), self-efficacy (Turner et al., 2016), acceptance (Turner et al., 2016), depression (Burns et al., 2022), and sleep disturbance (Burns et al., 2022, also see the evidence table). Mindfulness meditation has been associated with improvements in pain severity (Williams et al., 2022), pain interference (Williams et al., 2022), depression (Williams et al., 2022). Mindfulness-based cognitive therapy has been associated with durable improvements in pain interference, physical function, and depression (Day et al., 2019). Mindful self-compassion (MSC) has been associated with improvements in self-

compassion, pain acceptance, pain interference, catastrophizing, and anxiety (Torrijos-Zarcero et al., 2021).

Harms

Negligible

Frequency/Dose/Duration

MBSR/MM protocols varied widely in quality studies. The highest quality studies include:

- Eight 2.5-hour weekly MBSR group sessions plus two 7-hour sessions on two Saturdays (Kearney et al., 2016)
- Eight 2.5-hour weekly MBSR group sessions (Cherkin et al., 2016)
- Eight 2-hour weekly MBSR group sessions (Turner et al., 2016)
- Eight 150-minute weekly group sessions for MSC (Torrijos-Zarcero et al., 2021)
- Eight 90-minute weekly group sessions over 8-10 weeks (MM, Williams et al., 2022)
- Eight 1-hour weekly group sessions (MBCT, Day et al., 2019)
- Eight 90-minute weekly individual sessions (Burns et al., 2022)
- Eight 3-hour meetings plus one 4.5-hour meeting (la Cour et al., 2015)

There are no comparative trials to suggest an optimal dose of sessions.

Indications for discontinuation

Noncompliance, failure to obtain functional or behavioral improvement, cognitive impairment or low literacy prevents the patient from benefiting from MBSR/MM or resolution of problems.

Rationale

There are a number of mindfulness-based interventions, with MBSR being the most utilized in the quality published studies. MBSR has been reportedly effective for treatment of back pain, chronic pain, and failed back surgery syndrome (Turner et al., 2016, Cherkin et al., 2016, Burns et al., 2022, la Cour et al., 2015, Esmer et al., 2010). Equivalency with CBT has been reported (Cherkin et al., 2016). Another study suggested modestly superior but clinically questionable differences between MBSR and CBT (Turner et al., 2016). The highest quality studies suggest improvements associated with MBSR in pain (Cherkin et al., 2016, Burns et al., 2022), pain interference (Burns et al., 2022), physical function (Burns et al., 2022), catastrophizing (Turner et al., 2016), PTSD (Kearney et al., 2016), mindfulness (Turner et al., 2016), self-efficacy (Turner et al., 2016), acceptance (Turner et al., 2016), depression (Burns et al., 2022), and sleep disturbance (Burns et al., 2022),. Efficacy of MBSR for treatment of PTSD symptoms was shown (Kearney et al., 2016). One trial of MBSR for breast cancer survivors with neuropathic pain found lack of efficacy (Shergill et al., 2022). A systematic review and metanalysis found efficacy of MBSR for reducing the RMDQ scores at 8-weeks and 6-month follow-up of CLBP patients (Soundararajan et al., 2022).

Mindfulness meditation has been associated with improvements in pain severity, pain interference, and depression (Williams et al., 2022). Mindfulness-based cognitive therapy

has been associated with durable improvements in pain interference, physical function, depression, and fibromyalgia impact (Day et al., 2019, Parra-Delgado et al., 2013). Mindful self-compassion (MSC) has been associated with improvements in self-compassion, pain acceptance, pain interference, catastrophizing and anxiety (Torrijos-Zarcero et al., 2021). One trial suggested superiority of mindfulness-based cognitive therapy to MM at followup as per measures of pain interference, physical function and depression (Day et al., 2019). A systematic review and metanalysis of mindfulness-based cognitive therapy found evidence of efficacy for depressive symptoms and mindfulness, but not for pain interference and pain acceptance (Pei et al., 2021).

Other trials of mindfulness suggest efficacy (Pal et al., 2023, Howarth et al., 2019, Garland et al., 2013). One trial combining integrative meditation with exercise therapy found efficacy (Polaski et al., 2021). Mindful self-compassion (MSC) has been associated with improvements in self-compassion, pain acceptance, pain interference, catastrophizing and anxiety (Torrijos-Zarcero et al., 2021). A trial of mindful walking found lack of efficacy (Rotter et al., 2022).

Persisting benefits beyond the treatment period of 3 to 12 months were shown by multiple studies (Turner et al., 2016, Cherkin et al., 2016, Williams et al., 2022). Improvements in PTSD symptoms did not persist at 6 months (Kearney et al., 2016).

MBSR/MM has reasonably consistent evidence of efficacy, is not invasive, has no adverse effects, and is low to moderate cost depending on numbers of visits and thus is recommended for treatment of subacute and chronic pain. It is particularly recommended when there is any of: reduction in function, pain interference, poor pain acceptance, and/or accompanying depression, anxiety, reduced mood, and/or insomnia.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar with date limits of 2015 to the present using the following terms: Mindfulness, mindfulness-based stress reduction, mindfulness meditation; chronic pain, neuralgia, neuropathic pain, nerve pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly, systematic, systematic review, retrospective, prospective studies. We found and reviewed 18,895 articles in PubMed, 136 in CINAHL, 3 in Cochrane Library, 20,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 29 from CINAHL, 1 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 35 articles considered for inclusion, 26 randomized trials and 8 systematic reviews met the inclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of

100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

MONITORING / AUDITING CRITERIA

The clinician is recommended to assure:

1. Patients with unimproving upper or lower extremity pain, tingling, and numbness of >6 weeks duration are evaluated with EMG/nerve conduction studies. Target 60%
2. Patients with chronic persistent pain are treated with aerobic exercises. Target >90%
3. Patients with chronic persistent pain requiring analgesia are treated with NSAIDs including aspirin. Target >75%
4. Patients with chronic pain without depression are not treated with SSRI antidepressants (other than fibromyalgia). Target 0%
5. Neuropathic pain patients are treated with Duloxetine. Target >60%
6. Patients with chronic persistent pain are referred for behavioral health evaluation and potentially for treatment. Target >75%

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REFERENCES

1. Melhorn, J.,et al. AMA Guides® to the Evaluation of Disease and Injury Causation, second edition.*American Medical Association*; 2014.

2. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008.*MMWR*; 2011.

3. Center for the Evaluative Clinical Sciences. Spine surgery. A Report by the Dartmouth Atlas of Health Care.*CMS-FDA Collaborative*; 2006.

4. Centers for Disease Control and Prevention (CDC). Vital signs: risk of overdose from methadone used for pain relief-United States, 1999-2010.*MMWR*; 2012.

5. Institute of Medicine. Standards for Developing Trustworthy Clinical Practice Guidelines. *https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/inline-files/Clinical%20Practice%20Guidelines%202011%20Insert_0.pdf*; 2011.

6. The, AGREE Research Trust. Appraisal of Guidelines for Research & Evaluation II (AGREE II) Instrument.2009.

7. Danielsen, J. M., Johnsen, R., Kibsgaard, S. K., Hellevik, E. Early aggressive exercise for postoperative rehabilitation after discectomy.*Spine*; Apr 15 2000.

8. Cohen, I., Rainville, J. Aggressive exercise as treatment for chronic low back pain.*Sports Med*; 2002.

9. Mannion, A. F., Muntener, M., Taimela, S., Dvorak, J. Comparison of three active therapies for chronic low back pain: results of a randomized clinical trial with one-year follow-up.*Rheumatology (Oxford)*; Jul 2001.

10. Lynch NT, et al. Advocagenic Illness in an Occupational Medicine Clinic (Grady L, Ed.).*Cath Acad Sci*; 2010.

11. Lynch NT, et al. Advocagenic Illness: A new name for an old phenomenon.*Legal Medicine Perspectives*; 1998.

12. ACOEM, American College of Occupational and Environmental Medicine. Methodology for the Update of the Occupational Medicine Practice Guidelines. *www.acoem.org/uploadedFiles/Knowledge_Centers/ Practice_Guidelines/ACOEM%20Practice%20Guidelines%20Methodology.pdf*; 2006.

13. Harris, J.S.,et al. Methodology to update the practice recommendations in the American College of Occupational and Environmental Medicine's Occupational Medicine Practice Guidelines.*JOEM*; 2008.

14. Engel, G. L. The need for a new medical model: a challenge for biomedicine.*Science*; Apr 08 1977.

15. Bruns, D. The psychological assessment of patients with chronic pain.*Treatment of pain by integrative approaches : the American Academy of Pain Medicine textbook on patient management*; 2015.

16. Bruns, D., Disorbio, J. M. The Psychological Evaluation of Patients with Chronic Pain: a Review of BHI 2 Clinical and Forensic Interpretive Considerations.*Psychol Inj Law*; 2014.

17. Watkins, E. A., Wollan, P. C., Melton, L. J.,3rd, Yawn, B. P. A population in pain: report from the Olmsted County health study.*Pain Med*; Mar 2008.

18. Physiopedia. The Flag System.*https://www.physio-pedia.com/The_Flag_System*; n.d.

19. Gross, D. P., Battie, M. C., Asante, A. Development and validation of a short-form functional capacity evaluation for use in claimants with low back disorders.*J Occup Rehabil*; Mar 2006.

20. Mayer, T. G., Gatchel, R. J., Kishino, N., Keeley, J., Capra, P., Mayer, H., Barnett, J., Mooney, V. Objective assessment of spine function following industrial injury. A prospective study with comparison group and one-year follow-up.*Spine*; Jul-Aug 1985.

21. Mayer, T. G., Gatchel, R.J. Functional Restoration for Spinal Disorders: The Sport Medicine Approach.1988.

22. Mayer, T. G., Gatchel, R. J., Kishino, N., Keeley, J., Mayer, H., Capra, P., Mooney, V. A prospective short-term study of chronic low back pain patients utilizing novel objective functional measurement.*Pain*; Apr 1986.

23. Mayer, T. G., Gatchel, R. J., Mayer, H., Kishino, N. D., Keeley, J., Mooney, V. A prospective two-year study of functional restoration in industrial low back injury. An objective assessment procedure.*Jama*; Oct 2 1987.

24. Rainville, J., Kim, R. S., Katz, J. N. A review of 1985 Volvo Award winner in clinical science: objective assessment of spine function following industrial injury: a prospective study with comparison group and 1-year follow-up.*Spine*; Aug 15 2007.

25. Jousset, N., Fanello, S., Bontoux, L., Dubus, V., Billabert, C., Vielle, B., Roquelaure, Y., Penneau-Fontbonne, D., Richard, I. Effects of functional restoration versus 3 hours per week physical therapy: a randomized controlled study.*Spine*; Mar 1 2004.

26. Hildebrandt, J., Pfingsten, M., Saur, P., Jansen, J. Prediction of success from a multidisciplinary treatment program for chronic low back pain.*Spine*; May 1 1997.

27. Aronoff, G. M., Mandel, S., Genovese, E., Maitz, E. A., Dorto, A. J., Klimek, E. H., Staats, T. E. Evaluating malingering in contested injury or illness.*Pain Pract*; Jun 2007.

28. Borsook, D., Becerra, L. Functional imaging of pain and analgesia--a valid diagnostic tool?.*Pain*; Oct 2005.

29. IASP, International Association for the Study of Pain. IASP Announces Revised Definition of Pain. *https://www.iasp-pain.org/publications/iasp-news/iasp-announces-revised-definition-of-pain/*; 2020.

30. CDC, . Prevalence and most common causes of disability among adults--United States, 2005.*MMWR: Morbidity and Mortality weekly report*; 2009.

31. Yong, R Jason, Mullins, Peter M, Bhattacharyya, Neil. Prevalence of chronic pain among adults in the United States.*Pain*; 2022.

32. The American Academy of Pain Medicine. AAPM Facts and Figures on Pain.

33. Dieleman, J. L., Baral, R., Birger, M., Bui, A. L., Bulchis, A., Chapin, A., Hamavid, H., Horst, C., Johnson, E. K., Joseph, J., Lavado, R., Lomsadze, L., Reynolds, A., Squires, E., Campbell, M., DeCenso, B., Dicker, D., Flaxman, A. D., Gabert, R., Highfill, T., Naghavi, M., Nightingale, N., Templin, T., Tobias, M. I., Vos, T., Murray, C. J. US Spending on Personal Health Care and Public Health, 1996-2013.*Jama*; Dec 27 2016.

34. Dubois, M. Y., Follett, K. A. Pain medicine: The case for an independent medical specialty and training programs.*Acad Med*; Jun 2014.

35. Gaskin, D. J., Richard, P. The economic costs of pain in the United States.*J Pain*; Aug 2012.

36. Salvagioni, D. A. J., Melanda, F. N., Mesas, A. E., González, A. D., Gabani, F. L., Andrade, S. M. Physical, psychological and occupational consequences of job burnout: A systematic review of prospective studies.*PLoS One*; 2017.

37. Grimani, A., Aboagye, E., Kwak, L. The effectiveness of workplace nutrition and physical activity interventions in improving productivity, work performance and workability: a systematic review.*BMC Public Health*; Dec 12 2019.

38. Ospina, M. B., Dennett, L., Waye, A., Jacobs, P., Thompson, A. H. A systematic review of measurement properties of instruments assessing presenteeism.*Am J Manag Care*; Feb 1 2015.

39. Kigozi, J., Jowett, S., Lewis, M., Barton, P., Coast, J. The Estimation and Inclusion of Presenteeism Costs in Applied Economic Evaluation: A Systematic Review.*Value Health*; Mar 2017.

40. Schultz, A. B., Edington, D. W. Employee health and presenteeism: a systematic review.*J Occup Rehabil*; Sep 2007.

41. Ricci, J. A., Stewart, W. F., Chee, E., Leotta, C., Foley, K., Hochberg, M. C. Back pain exacerbations and lost productive time costs in United States workers.*Spine*; Dec 15 2006.

42. Goetzel, R. Z., Long, S. R., Ozminkowski, R. J., Hawkins, K., Wang, S., Lynch, W. Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers.*J Occup Environ Med*; Apr 2004.

43. Boles, M., Pelletier, B., Lynch, W. The relationship between health risks and work productivity.*J Occup Environ Med*; Jul 2004.

44. Burton, W. N., Chen, C. Y., Conti, D. J., Schultz, A. B., Edington, D. W. The association between health risk change and presenteeism change.*J Occup Environ Med*; Mar 2006.

45. Burton, W. N., Chen, C. Y., Conti, D. J., Schultz, A. B., Pransky, G., Edington, D. W. The association of health risks with on-the-job productivity.*J Occup Environ Med*; Aug 2005.

46. Allen, H., Hubbard, D., Sullivan, S. The burden of pain on employee health and productivity at a major provider of business services.*J Occup Environ Med*; Jul 2005.

47. Chen, J. J. Outpatient pain rehabilitation programs.*Iowa Orthop J*; 2006.

48. Burton, W. N., Pransky, G., Conti, D. J., Chen, C. Y., Edington, D. W. The association of medical conditions and presenteeism.*J Occup Environ Med*; Jun 2004.

49. The Center for Workforce Health and Performance, . Musculoskeletal Disorders, Workforce Health and Productivity in the United States.2015.

50. Schrepf A, Phan V,Clemens JQ,et al. ICD-10 Codes for the Study of Chronic Overlapping Pain Conditions in Administrative Databases.*J Pain*; 2020.

51. Maixner W, Fillingim RB,Williams DA,et al. Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification.*J Pain*; 2016.

52. Yunus, MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes.*Semin Arthritis Rheum*; 2007.

53. Grandhi R, Tavakoli S,Ortega C,Simmonds MJ. A Review of Chronic Pain and Cognitive, Mood, and Motor Dysfunction Following Mild Traumatic Brain Injury: Complex, Comorbid, and/or Overlapping Conditions?.*Brain Sci*; 2017.

54. Fishbain DA, Bruns D,Disorbio JM,et al. Exploration of the illness uncertainty concept in acute and chronic pain patients vs community patients.*Pain Med*; 2010.

55. Fishbain DA, Cole B,Lewis JE,Gao J. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review.*Pain Med*; 2014.

56. Krebs EE, Lorenz KA,Bair MJ,et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference.*J Gen Intern Med*; 2009.

57. Bruns, D., Disorbio, J. M. Assessment of biopsychosocial risk factors for medical treatment: a collaborative approach.*J Clin Psychol Med Settings*; Jun 2009.

58. Waddell, G., McCulloch, J. A., Kummel, E., Venner, R. M. Nonorganic physical signs in low-back pain.*Spine*; Mar-Apr 1980.

59. Gaines, W. G.,Jr., Hegmann, K. T. Effectiveness of Waddell's nonorganic signs in predicting a delayed return to regular work in patients experiencing acute occupational low back pain.*Spine*; Feb 15 1999.

60. Cohen SP, Doshi TL,Kurihara C,et al. Waddell (Nonorganic) Signs and Their Association With Interventional Treatment Outcomes for Low Back Pain.*Anesth Analg*; 2021.

61. Henningsen, P., Zipfel, S., Herzog, W. Management of functional somatic syndromes.*Lancet*; Mar 17 2007.

62. Siddall, P. J., Cousins, M. J. Persistent pain as a disease entity: implications for clinical management.*Anesth Analg*; Aug 2004.

63. Gallagher, RM., Verma, S. Mood and anxiety disorders in chronic pain.*Pyschosocial Aspects of Pain: A Handbook for Health Care Providers.*; 2004.

64. European Federation of ISAP Chapters, . EFIC's declaration on pain as a major problem, a disease in its own right.2008.

65. Niv, D., Devor, M. Chronic pain as a disease in its own right.*Pain Pract*; Sep 2004.

66. Basbaum, A. I., Julius, D. Toward better pain control.*Sci Am*; Jun 2006.

67. Ballantyne, J. C. Opioids for chronic nonterminal pain.*South Med J*; Nov 2006.

68. Ballantyne, Jane C., Sullivan, Mark D. Is Chronic Pain a Disease?.*The Journal of Pain*; 2022/10/01/.

69. Quinter, J.,Cohen,M. Is chronic pain really a disease?.2023.

70. Raja SN, Carr DB,Cohen M,et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises.*Pain*; 2020.

71. Vaegter HB, Kinnunen M Verbrugghe J et al. Physical activity should be the primary intervention for individuals living with chronic pain A position paper from the European Pain Federation (EFIC) On the Move Task Force.*Eur J Pain*; 2024.

72. Mescouto, K., Olson, R. E., Hodges, P. W., Setchell, J. A critical review of the biopsychosocial model of low back pain care: time for a new approach?.*Disabil Rehabil*; Jun 2022.

73. Nicholas, M. K. The biopsychosocial model of pain 40 years on: time for a reappraisal?.*Pain*; Nov 1 2022.

74. Suls, J., Rothman, A. Evolution of the biopsychosocial model: prospects and challenges for health psychology.*Health Psychol*; Mar 2004.

75. Gatchel, R. J. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective.*Am Psychol*; Nov 2004.

76. Urban, M. O., Gebhart, G. F. Supraspinal contributions to hyperalgesia.*Proc Natl Acad Sci U S A*; Jul 6 1999.

77. Yang, S., Chang, M. C. Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States.*Int J Mol Sci*; Jun 26 2019.

78. van Wilgen, C. P., Keizer, D. The sensitization model to explain how chronic pain exists without tissue damage.*Pain Manag Nurs*; Mar 2012.

79. Nackley, A. G., Tan, K. S., Fecho, K., Flood, P., Diatchenko, L., Maixner, W. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors.*Pain*; Apr 2007.

80. Lotsch, J., Geisslinger, G. Current evidence for a modulation of nociception by human genetic polymorphisms.*Pain*; Nov 2007.

81. McIntosh, A. M., Hall, L. S., Zeng, Y., Adams, M. J., Gibson, J., Wigmore, E., Hagenaars, S. P., Davies, G., Fernandez-Pujals, A. M., Campbell, A. I., Clarke, T. K., Hayward, C., Haley, C. S., Porteous, D. J., Deary, I. J., Smith, D. J., Nicholl, B. I., Hinds, D. A., Jones, A. V., Scollen, S., Meng, W., Smith, B. H., Hocking, L. J. Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis.*PLoS Med*; Aug 2016.

82. Johnston, K. J. A., Adams, M. J., Nicholl, B. I., Ward, J., Strawbridge, R. J., Ferguson, A., McIntosh, A. M., Bailey, M. E. S., Smith, D. J. Genome-wide association study of multisite chronic pain in UK Biobank.*PLoS Genet*; Jun 2019.

83. Hocking, L. J., Morris, A. D., Dominiczak, A. F., Porteous, D. J., Smith, B. H. Heritability of chronic pain in 2195 extended families.*Eur J Pain*; Aug 2012.

84. Weiner, B. K. Spine update: the biopsychosocial model and spine care.*Spine*; Jan 15 2008.

85. Gentili, C., Rickardsson, J., Zetterqvist, V., Simons, L. E., Lekander, M., Wicksell, R. K. Psychological Flexibility as a Resilience Factor in Individuals With Chronic Pain.*Front Psychol*; 2019.

86. Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., Lillis, J. Acceptance and commitment therapy: model, processes and outcomes.*Behav Res Ther*; Jan 2006.

87. Coulter, A., Ellins, J. Effectiveness of strategies for informing, educating, and involving patients.*Bmj*; Jul 7 2007.

88. Joypaul, S., Kelly, F., McMillan, S. S., King, M. A. Multi-disciplinary interventions for chronic pain involving education: A systematic review.*PLoS One*; 2019.

89. Nijs, Jo, Paul van Wilgen, C., Van Oosterwijck, Jessica, van Ittersum, Miriam, Meeus, Mira. How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: Practice guidelines.*Manual Therapy*; 2011/10/01/.

90. Linton, S. J., McCracken, L. M., Vlaeyen, J. W. Reassurance: help or hinder in the treatment of pain.*Pain*; Jan 2008.

91. Robinson, Victoria, King, Richard, Ryan, Cormac G., Martin, Denis J. A qualitative exploration of people's experiences of pain neurophysiological education for chronic pain: The importance of relevance for the individual.*Manual Therapy*; 2016/04/01/.

92. Pincus T, Holt N,Vogel S,et al. Cognitive and affective reassurance and patient outcomes in primary care: a systematic review.*Pain*; 2013.

93. Kim, Hyunjoong, Lee, Seungwon. Effects of pain neuroscience education on kinesiophobia in patients with chronic pain: a systematic review and meta-analysis.*Physical Therapy Rehabilitation Science*; 2020.

94. Egerton, T., Bennell, K. L., McManus, F., Lamb, K. E., Hinman, R. S. Comparative effect of two educational videos on self-efficacy and kinesiophobia in people with knee osteoarthritis: an online randomised controlled trial.*Osteoarthritis and Cartilage*; 2022/10/01/.

95. John, J. N., Ugwu, E. C., Okezue, O. C., Ekechukwu, E. N. D., Mgbeojedo, U. G., John, D. O., Ezeukwu, A. O. Kinesiophobia and associated factors among patients with chronic non-specific low back pain.*Disabil Rehabil*; Aug 2023.

96. Aily, J. B., de Almeida, A. C., Ramírez, P. C., da Silva Alexandre, T., Mattiello, S. M. Lower education is an associated factor with the combination of pain catastrophizing and kinesiophobia in patients with knee osteoarthritis?.*Clin Rheumatol*; Jun 2021.

97. Lawton, M. P., Brody, E. M. Assessment of older people: self-maintaining and instrumental activities of daily living.*Gerontologist*; Autumn 1969.

98. Elsawy, B., Higgins, K. E. The geriatric assessment.*Am Fam Physician*; Jan 1 2011.

99. Nazarov, S., Manuwald, U., Leonardi, M., Silvaggi, F., Foucaud, J., Lamore, K., Guastafierro, E., Scaratti, C., Lindström, J., Rothe, U. Chronic Diseases and Employment: Which Interventions Support the Maintenance of Work and Return to Work among Workers with Chronic Illnesses? A Systematic Review.*Int J Environ Res Public Health*; May 27 2019.

100. Tagliaferri, S. D., Miller, C. T., Owen, P. J., Mitchell, U. H., Brisby, H., Fitzgibbon, B., Masse-Alarie, H., Van Oosterwijck, J., Belavy, D. L. Domains of Chronic Low Back Pain and Assessing Treatment Effectiveness: A Clinical Perspective.*Pain Pract*; Feb 2020.

101. Driscoll, M. A., Edwards, R. R., Becker, W. C., Kaptchuk, T. J., Kerns, R. D. Psychological Interventions for the Treatment of Chronic Pain in Adults.*Psychol Sci Public Interest*; Sep 2021.

102. Abegglen S, Hoffmann-Richter U,Schade V,Znoj HJ. Work and Health Questionnaire (WHQ): A Screening Tool for Identifying Injured Workers at Risk for a Complicated Rehabilitation.*J Occup Rehabil*; 2017.

103. Corbière M, Negrini A,Durand MJ,et al. Development of the Return-to-Work Obstacles and Self-Efficacy Scale (ROSES) and Validation with Workers Suffering from a Common Mental Disorder or Musculoskeletal Disorder.*J Occup Rehabil*; 2017.

104. Marhold C, Linton SJ,Melin L. Identification of obstacles for chronic pain patients to return to work: evaluation of a questionnaire.*J Occup Rehabil*; 2002.

105. Park J, Roberts MR,Esmail S,et al. Validation of the Readiness for Return-To-Work Scale in Outpatient Occupational Rehabilitation in Canada.*J Occup Rehabil*; 2018.

106. Truchon M, Schmouth MÈ,Côté D,et al. Absenteeism screening questionnaire (ASQ): a new tool for predicting long-term absenteeism among workers with low back pain.*J Occup Rehabil*; 2012.

107. Thiveos L, Kent P,Pocovi NC,et al. Cognitive Functional Therapy for Chronic Low Back Pain: A Systematic Review and Meta-Analysis.*Phys Ther*; 2024.

108. Conrad, R., Schilling, G., Bausch, C., Nadstawek, J., Wartenberg, H. C., Wegener, I., Geiser, F., Imbierowicz, K., Liedtke, R. Temperament and character personality profiles and personality disorders in chronic pain patients.*Pain*; Dec 15 2007.

109. Pincus, T., Burton, A. K., Vogel, S., Field, A. P. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain.*Spine (Phila Pa 1976)*; Mar 1 2002.

110. Engel, C. C., von Korff, M., Katon, W. J. Back pain in primary care: predictors of high health-care costs.*Pain*; May-Jun 1996.

111. Croft, P. R., Dunn, K. M., Raspe, H. Course and prognosis of back pain in primary care: the epidemiological perspective.*Pain*; May 2006.

112. Epping-Jordan, J. E., Wahlgren, D. R., Williams, R. A., Pruitt, S. D., Slater, M. A., Patterson, T. L., Grant, I., Webster, J. S., Atkinson, J. H. Transition to chronic pain in men with low back pain: predictive relationships among pain intensity, disability, and depressive symptoms.*Health Psychol*; Sep 1998.

113. Davis, D. A., Luecken, L. J., Zautra, A. J. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature.*Clin J Pain*; Sep-Oct 2005.

114. Linton, S. J. Occupational psychological factors increase the risk for back pain: a systematic review.*J Occup Rehabil*; Mar 2001.

115. Gatchel, R. J., Polatin, P. B., Kinney, R. K. Predicting outcome of chronic back pain using clinical predictors of psychopathology: a prospective analysis.*Health Psychol*; Sep 1995.

116. Bildt, C., Alfredsson, L., Michelsen, J., al., et. Occupational and nonoccupational risk indicators for incident and chronic low back pain in a sample of the Swedish general population during a 4-year period: an influence of depression?.*Intl J Bavioral Med.*; 2000.

117. Macfarlane, GJ. Who will develop chronic pain and why? The epidemilogical evidence.*In: Flor, H. Kalso, E., Dostrovsky, JO. eds. Proceedings of the 11th World Congress on Pain*; 2006.

118. Mannion, A. F., Muntener, M., Taimela, S., Dvorak, J. A randomized clinical trial of three active therapies for chronic low back pain.*Spine*; Dec 1 1999.

119. Dersh, J., Gatchel, R. J., Mayer, T., Polatin, P., Temple, O. R. Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders.*Spine*; May 1 2006.

120. Carragee, E. J., Alamin, T. F., Miller, J. L., Carragee, J. M. Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain.*Spine J*; Jan-Feb 2005.

121. Enthoven, P., Skargren, E., Carstensen, J., Oberg, B. Predictive factors for 1-year and 5-year outcome for disability in a working population of patients with low back pain treated in primary care.*Pain*; May 2006.

122. Pincus, T., Burton, A. K., Vogel, S., Field, A. P. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain.*Spine*; Mar 1 2002.

123. Pincus, T., Vlaeyen, J. W., Kendall, N. A., Von Korff, M. R., Kalauokalani, D. A., Reis, S. Cognitive-behavioral therapy and psychosocial factors in low back pain: directions for the future.*Spine*; Mar 1 2002.

124. Schultz, I. Z., Crook, J. M., Berkowitz, J., Meloche, G. R., Milner, R., Zuberbier, O. A., Meloche, W. Biopsychosocial multivariate predictive model of occupational low back disability.*Spine*; Dec 1 2002.

125. Linton, S. J. A review of psychological risk factors in back and neck pain.*Spine*; May 1 2000.

126. Gatchel, R. J., Okifuji, A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain.*J Pain*; Nov 2006.

127. Linton, SJ., Hellsing, AL., Bryngelsson, IL. Psychosocial and functional risk factors in the early stages of back pain: effects on moderate pain.*Intl J Behavioral Med.*; 2000.

128. Linton, S. J. Do psychological factors increase the risk for back pain in the general population in both a cross-sectional and prospective analysis?.*Eur J Pain*; Aug 2005.

129. Keefe, F. J., Rumble, M. E., Scipio, C. D., Giordano, L. A., Perri, L. M. Psychological aspects of persistent pain: current state of the science.*J Pain*; May 2004.

130. Johnston, V., Jimmieson, N. L., Souvlis, T., Jull, G. Interaction of psychosocial risk factors explain increased neck problems among female office workers.*Pain*; Jun 2007.

131. Hazard, R. G., Haugh, L. D., Reid, S., Preble, J. B., MacDonald, L. Early prediction of chronic disability after occupational low back injury.*Spine*; Apr 15 1996.

132. Wong, C. K., Mak, R. Y., Kwok, T. S., Tsang, J. S., Leung, M. Y., Funabashi, M., Macedo, L. G., Dennett, L., Wong, A. Y. Prevalence, Incidence, and Factors Associated With Non-Specific Chronic Low Back Pain in Community-Dwelling Older Adults Aged 60 Years and Older: A Systematic Review and Meta-Analysis.*J Pain*; Apr 2022.

133. Kapellusch, J. M., Garg, A., Boda, S., Hegmann, K. T., Moore, J. S., Thiese, M. S., Merryweather, A., Tomich, S., Foster, J. C., Bloswick, D., Malloy, E. J. Association between lifting and use of medication for low back pain: results from the Backworks Prospective Cohort Study.*J Occup Environ Med*; Aug 2014.

134. Parreira, P., Maher, C. G., Steffens, D., Hancock, M. J., Ferreira, M. L. Risk factors for low back pain and sciatica: an umbrella review.*Spine J*; Sep 2018.

135. Waddell, G., Newton, M., Henderson, I., Somerville, D., Main, C. J. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability.*Pain*; Feb 1993.

136. Fritz, J. M., George, S. Z. Identifying psychosocial variables in patients with acute work-related low back pain: the importance of fear-avoidance beliefs.*Phys Ther*; Oct 2002.

137. Dobscha SK, Corson K,Perrin NA,et al. Collaborative care for chronic pain in primary care: a cluster randomized trial.*JAMA*; 2009.

138. Lalonde L, Choinière M,Martin E,et al. Priority interventions to improve the management of chronic non-cancer pain in primary care: a participatory research of the ACCORD program.*J Pain Res*; 2015.

139. Sullivan MJ, Adams H,Horan S,et al. The role of perceived injustice in the experience of chronic pain and disability: scale development and validation.*J Occup Rehabil*; 2008.

140. Tait, R. C., Chibnall, J. T. Work injury management of refractory low back pain: relations with ethnicity, legal representation and diagnosis.*Pain*; Mar 2001.

141. Dworkin, R. H., Handlin, D. S., Richlin, D. M., Brand, L., Vannucci, C. Unraveling the effects of compensation, litigation, and employment on treatment response in chronic pain.*Pain*; Sep 1985.

142. Suter, P. B. Employment and litigation: improved by work, assisted by verdict.*Pain*; Dec 2002.

143. Vaccaro, A. R., Ring, D., Scuderi, G., Cohen, D. S., Garfin, S. R. Predictors of outcome in patients with chronic back pain and low-grade spondylolisthesis.*Spine*; Sep 1 1997.

144. Kasdan, M. L., Vender, M. I., Lewis, K., Stallings, S. P., Melhorn, J. M. Carpal tunnel syndrome. Effects of litigation on utilization of health care and physician workload.*J Ky Med Assoc*; Jul 1996.

145. Reynolds, S., Paniak, C., Toller-Lobe, G., Nagy, J. A longitudinal study of compensation-seeking and return to work in a treated mild traumatic brain injury sample.*J Head Trauma Rehabil*; Mar-Apr 2003.

146. LaCaille, R. A., DeBerard, M. S., LaCaille, L. J., Masters, K. S., Colledge, A. L. Obesity and litigation predict workers' compensation costs associated with interbody cage lumbar fusion.*Spine J*; May-Jun 2007.

147. Gun, R. T., Osti, O. L., O'Riordan, A., Mpelasoka, F., Eckerwall, C. G., Smyth, J. F. Risk factors for prolonged disability after whiplash injury: a prospective study.*Spine*; Feb 15 2005.

148. Bernacki, E. J., Yuspeh, L., Tao, X. Determinants of escalating costs in low risk workers' compensation claims.*J Occup Environ Med*; Jul 2007.

149. Bellamy, R. Compensation neurosis: financial reward for illness as nocebo.*Clin Orthop Relat Res*; Mar 1997.

150. Wheeler, A. J., Smith, A. L., Gundy, J. M., Sautter, T., DeBerard, M. S. Predicting back pain treatment outcomes among workers' compensation patients: important information for clinical neuropsychologists.*Clin Neuropsychol*; 2013.

151. Gruson, K. I., Huang, K., Wanich, T., Depalma, A. A. Workers' compensation and outcomes of upper extremity surgery.*J Am Acad Orthop Surg*; Feb 2013.

152. Mandalia, K., Ames, A., Parzick, J. C., Ives, K., Ross, G., Shah, S. Social determinants of health influence clinical outcomes of patients undergoing rotator cuff repair: a systematic review.*J Shoulder Elbow Surg*; Feb 2023.

153. Barrett, G. R., Rook, R. T., Nash, C. R., Coggin, M. R. The effect of Workers' Compensation on clinical outcomes of arthroscopic-assisted autogenous patellar tendon anterior cruciate ligament reconstruction in an acute population.*Arthroscopy*; Feb 2001.

154. Koerner, J. D., Glaser, J., Radcliff, K. Which Variables Are Associated With Patient-reported Outcomes After Discectomy? Review of SPORT Disc Herniation Studies.*Clin Orthop Relat Res*; Jun 2015.

155. Kim, K. C., Lee, W. Y., Shin, H. D., Han, S. C., Yeon, K. W. Do patients receiving workers' compensation who undergo arthroscopic rotator cuff repair have worse outcomes than non-recipients? Retrospective case-control study.*J Orthop Surg (Hong Kong)*; May-Aug 2018.

156. Horner, N., Chapman, R. S., Larson, J., Hevesi, M., Nho, S. J. Workers' Compensation Patients Undergoing Hip Arthroscopy for Femoroacetabular Impingement Syndrome Experience Worse Mid-term Outcomes but Similar Return-to-Work: A Propensity-Matched Analysis at 5-Year Follow-Up.*Arthroscopy*; Apr 24 2023.

157. Lu, Y., Agarwalla, A., Patel, B. H., Nolte, M. T., Cancienne, J., Verma, N., Cole, B. J., Forsythe, B. Influence of workers' compensation status on postoperative outcomes in patients following biceps tenodesis: a matched-pair cohort analysis.*J Shoulder Elbow Surg*; Dec 2020.

158. Anderson, J. T., Haas, A. R., Percy, R., Woods, S. T., Ahn, U. M., Ahn, N. U. Single-level lumbar fusion for degenerative disc disease is associated with worse outcomes compared with fusion for spondylolisthesis in a workers' compensation setting.*Spine (Phila Pa 1976)*; Mar 1 2015.

159. Wagner, E. R., Woodmass, J. M., Chang, M. J., Welp, K. M., Higgins, L. D., Warner, J. J. P. The impact of workers' compensation on recovery after biceps tenodesis.*J Shoulder Elbow Surg*; Sep 2020.

160. van der Horst, A. S., Stephens, A. R., Wei, G., Presson, A. P., Tashjian, R. Z., Kazmers, N. H. Prognostic Factors Affecting Long-Term Outcomes After Elbow Dislocation: A Longitudinal Cohort Study.*J Hand Surg Glob Online*; Sep 2021.

161. Anderson, J. T., Haas, A. R., Percy, R., Woods, S. T., Ahn, U. M., Ahn, N. U. Return to Work After Diskogenic Fusion in Workers' Compensation Subjects.*Orthopedics*; Dec 2015.

162. Giummarra, M. J., Murgatroyd, D., Tran, Y., Adie, S., Mittal, R., Ponsford, J., Cameron, P., Gabbe, B., Harris, I. A., Cameron, I. D. Health and return to work in the first two years following road traffic injury: a comparison of outcomes between compensation claimants in Victoria and New South Wales, Australia.*Injury*; Oct 2020.

163. Anderson, J. T., Haas, A. R., Percy, R., Woods, S. T., Ahn, U. M., Ahn, N. U. Workers' Compensation, Return to Work, and Lumbar Fusion for Spondylolisthesis.*Orthopedics*; Jan-Feb 2016.

164. Frangiamore, S., Dornan, G. J., Horan, M. P., Mannava, S., Fritz, E. M., Hussain, Z. B., Moatshe, G., Godin, J. A., Pogorzelski, J., Millett, P. J. Predictive Modeling to Determine Functional Outcomes After Arthroscopic Rotator Cuff Repair.*Am J Sports Med*; Jun 2020.

165. Slosar, P. J., Reynolds, J. B., Schofferman, J., Goldthwaite, N., White, A. H., Keaney, D. Patient satisfaction after circumferential lumbar fusion.*Spine (Phila Pa 1976)*; Mar 15 2000.

166. Crombez, G., Vlaeyen, J. W., Heuts, P. H., Lysens, R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability.*Pain*; Mar 1999.

167. Buer, N., Linton, S. J. Fear-avoidance beliefs and catastrophizing: occurrence and risk factor in back pain and ADL in the general population.*Pain*; Oct 2002.

168. Al-Obaidi, S. M., Nelson, R. M., Al-Awadhi, S., Al-Shuwaie, N. The role of anticipation and fear of pain in the persistence of avoidance behavior in patients with chronic low back pain.*Spine*; May 1 2000.

169. Woby, S. R., Watson, P. J., Roach, N. K., Urmston, M. Adjustment to chronic low back pain--the relative influence of fear-avoidance beliefs, catastrophizing, and appraisals of control.*Behav Res Ther*; Jul 2004.

170. Brox, J. I., Storheim, K., Holm, I., Friis, A., Reikeras, O. Disability, pain, psychological factors and physical performance in healthy controls, patients with sub-acute and chronic low back pain: a case-control study.*J Rehabil Med*; Mar 2005.

171. Vangronsveld, K., Peters, M., Goossens, M., Linton, S., Vlaeyen, J. Applying the fear-avoidance model to the chronic whiplash syndrome.*Pain*; Oct 2007.

172. Vlaeyen, J. W., de Jong, J., Geilen, M., Heuts, P. H., van Breukelen, G. The treatment of fear of movement/(re)injury in chronic low back pain: further evidence on the effectiveness of exposure in vivo.*Clin J Pain*; Jul-Aug 2002.

173. Flor, H., Braun, C., Elbert, T., Birbaumer, N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients.*Neurosci Lett*; Mar 7 1997.

174. Loeser, JD. Managing the Chronic Pain Patient.1989.

175. Loeser, J. D. Low back pain.*Res Publ Assoc Res Nerv Ment Dis*; 1980.

176. IASP Task Force on Pain in the Workplace, . Back Pain: Management of Disability in Nonspecific Conditions.1995.

177. Keefe, F. J., Dunsmore, J., Burnett, R. Behavioral and cognitive-behavioral approaches to chronic pain: recent advances and future directions.*J Consult Clin Psychol*; Aug 1992.

178. Keefe, F. J., Lefebrre, J. Pain behavior concepts: controversies, current status, and future directions.*In: Gebhart GF, eds. Progress in Pain Research and Management.*; 1994.

179. Fordyce, W.E. Environmental factors in the genesis of low back pain.*In: Bonica JJ, ed. Advances in Pain Research and Therapy*; 1979.

180. Fordyce, W. E. Pain and suffering. A reappraisal.*Am Psychol*; Apr 1988.

181. Merskey, H., Bogduk, N., Eds., . Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.*Task Force on Taxonomy of the International Association for the Study of Pain*; 1994.

182. Sullivan, M. Exaggerated pain behavior: by what standard?.*Clin J Pain*; Nov-Dec 2004.

183. Holzl, R., Kleinbohl, D., Huse, E. Implicit operant learning of pain sensitization.*Pain*; May 2005.

184. Flor, H., Knost, B., Birbaumer, N. The role of operant conditioning in chronic pain: an experimental investigation.*Pain*; Jan 2002.

185. Schneider, C., Palomba, D., Flor, H. Pavlovian conditioning of muscular responses in chronic pain patients: central and peripheral correlates.*Pain*; Dec 2004.

186. Hrobjartsson, A. The uncontrollable placebo effect.*Eur J Clin Pharmacol*; 1996.

187. Hunter, P. A question of faith. Exploiting the placebo effect depends on both the susceptibility of the patient to suggestion and the ability of the doctor to instill trust.*EMBO Rep.*; 2007.

188. Kaptchuk, T. J. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance?.*Ann Intern Med*; Jun 4 2002.

189. Linde, K., Witt, C. M., Streng, A., Weidenhammer, W., Wagenpfeil, S., Brinkhaus, B., Willich, S. N., Melchart, D. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain.*Pain*; Apr 2007.

190. McCrae RR, Costa PT Jr. A contemplated revision of the NEO Five-Factor Inventory.*Pers Indiv Differ*; 2004.

191. Turner, J. A., Deyo, R. A., Loeser, J. D., Von Korff, M., Fordyce, W. E. The importance of placebo effects in pain treatment and research.*Jama*; May 25 1994.

192. Linton, S. J., Vlaeyen, J., Ostelo, R. The back pain beliefs of health care providers: are we fear-avoidant?.*J Occup Rehabil*; Dec 2002.

193. Aaron, L. A., Arguelles, L. M., Ashton, S., Belcourt, M., Herrell, R., Goldberg, J., Smith, W. R., Buchwald, D. Health and functional status of twins with chronic regional and widespread pain.*J Rheumatol*; Nov 2002.

194. Aaron, L. A., Buchwald, D. A review of the evidence for overlap among unexplained clinical conditions.*Ann Intern Med*; May 1 2001.

195. Goldenberg, D. L., Simms, R. W., Geiger, A., Komaroff, A. L. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice.*Arthritis Rheum*; Mar 1990.

196. Wolfe, F., Aarflot, T., Bruusgaard, D., Henriksson, K. G., Littlejohn, G., Moldofsky, H., Raspe, H., Vaeroy, H. Fibromyalgia and disability. Report of the Moss International Working Group on medico-legal aspects of chronic widespread musculoskeletal pain complaints and fibromyalgia.*Scand J Rheumatol*; 1995.

197. Yunus, M., Masi, A. T., Calabro, J. J., Miller, K. A., Feigenbaum, S. L. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls.*Semin Arthritis Rheum*; Aug 1981.

198. Popkirov, Stoyan, Enax-Krumova, Elena K., Mainka, Tina, Hoheisel, Matthias, Hausteiner-Wiehle, Constanze. Functional pain disorders – more than nociplastic pain.*NeuroRehabilitation*; 2020.

199. Fitzcharles, M. A., Ste-Marie, P. A., Gamsa, A., Ware, M. A., Shir, Y. Opioid Use, Misuse, and Abuse in Patients Labeled as Fibromyalgia.*American Journal of Medicine*; Oct 2011.

200. Zamani, Mohammad, Alizadeh-Tabari, Shaghayegh, Zamani, Vahid. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome.*Alimentary pharmacology & therapeutics*; 2019.

201. Boersma, K., Linton, S. J. Screening to identify patients at risk: profiles of psychological risk factors for early intervention.*Clin J Pain*; Jan-Feb 2005.

202. Sullivan, MJ. Risk-factor targeted psychological interventions for pain-related disability.*In: Flor H.Proceedings of the 11th World Congress on Pain*; 2006.

203. Kendall, NAS., Linton, SJ., Main, C. Assessing Yellow Flags in Acute Low Back Pain: Risk Factors for Long Term Disablitiy and Work Loss.2004.

204. Ohkubo Y, Kishikawa H,Araki E,et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.*Diabetes Res Clin Pract*; 1995.

205. Diabetes Control and Complications Trial Research Group, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.*N Engl J Med*; 1993.

206. American Chronic Pain Associaton, . Ten Steps From Patient to Person.2008.

207. Harden, RN. Complex Regional Pain Syndrome: Treatment Guidelines.2006.

208. Skelly, Andrea Clare, Chou, Roger, Dettori, Joseph R, Turner, Judith A, Friedly, Janna L, Rundell, Sean D, Fu, Rongwei, Brodt, Erika D, Wasson, Ngoc, Kantner, Shelby. Noninvasive nonpharmacological treatment for chronic pain: a systematic review update.2020.

209. Talmage, J. B., Melhorn, J. M., eds., . A Physcian's Guide to Return to Work.2007.

210. Talmage, James B, Melhorn, J Mark, Hyman, Mark H, Association, American,Medical. AMA guides to the evaluation of work ability and return to work.2011.

211. Jetha A, LaMontagne AD,Lilley R,et al. Workplace Social System and Sustained Return-to-Work: A Study of Supervisor and Co-worker Supportiveness and Injury Reaction.*J Occup Rehabil*; 2018.

212. Galer, B. S., Bruehl, S., Harden, R. N. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. International Association for the Study of Pain.*Clin J Pain*; Mar 1998.

213. Harden, R. N., Bruehl, S., Perez, R. S., Birklein, F., Marinus, J., Maihofner, C., Lubenow, T., Buvanendran, A., Mackey, S., Graciosa, J., Mogilevski, M., Ramsden, C., Chont, M., Vatine, J. J. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome.*Pain*; Aug 2010.

214. Harden, R. N., McCabe, C. S., Goebel, A., Massey, M., Suvar, T., Grieve, S., Bruehl, S. Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines, 5th Edition.*Pain Med*; Jun 10 2022.

215. Eisenberg E, Melamed E. Can complex regional pain syndrome be painless?.*Pain*; 2003.

216. Ferraro MC, O'Connell NE,Sommer C,et al. Complex regional pain syndrome: advances in epidemiology, pathophysiology, diagnosis, and treatment.*Lancet Neurol*; 2024.

217. Geha, P. Y., Baliki, M. N., Harden, R. N., Bauer, W. R., Parrish, T. B., Apkarian, A. V. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions.*Neuron*; Nov 26 2008.

218. Mansour, A. R., Farmer, M. A., Baliki, M. N., Apkarian, A. V. Chronic pain: the role of learning and brain plasticity.*Restor Neurol Neurosci*; 2014.

219. Simons LE, Erpelding N,Hernandez JM,et al. Fear and Reward Circuit Alterations in Pediatric CRPS.*Front Hum Neurosci*; 2016.

220. Hotta J, Saari J,Koskinen M,et al. Abnormal brain responses to action observation in complex regional pain syndrome.*J Pain*; 2017.

221. Mutso AA, Radzicki D,Baliki MN,et al. Abnormalities in hippocampal functioning with persistent pain.*J Neurosci*; 2012.

222. Barad, M. J., Ueno, T., Younger, J., Chatterjee, N., Mackey, S. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain.*J Pain*; Feb 2014.

223. Liu HY, Lee PL,Chou KH,et al. Brain morphometry changes with fatigue severity in fibromyalgia.*Clin Exp Rheumatol*; 2023.

224. Apkarian, A Vania, Sosa, Yamaya, Krauss, Beth R, Thomas, P Sebastian, Fredrickson, Bruce E, Levy, Robert E, Harden, R Norman, Chialvo, Dante R. Chronic pain patients are impaired on an emotional decision-making task.*Pain*; 2004.

225. Baliki MN, Mansour AR,Baria AT,et al. Functional reorganization of the default mode network across chronic pain conditions.*PLoS One*; 2014.

226. de Mos, M., de Bruijn, A. G., Huygen, F. J., Dieleman, J. P., Stricker, B. H., Sturkenboom, M. C. The incidence of complex regional pain syndrome: a population-based study.*Pain*; May 2007.

227. Sandroni, Paola, Benrud-Larson, Lisa M., McClelland, Robyn L., Low, Phillip A. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study.*PAIN®*; 2003/05/01/.

228. Sandroni, P., Benrud-Larson, L. M., McClelland, R. L., Low, P. A. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study.*Pain*; May 2003.

229. Dijkstra, P. U., Groothoff, J. W., ten Duis, H. J., Geertzen, J. H. Incidence of complex regional pain syndrome type I after fractures of the distal radius.*Eur J Pain*; 2003.

230. Bruehl, S., Maihofner, C., Stanton-Hicks, M., Perez, R. S., Vatine, J. J., Brunner, F., Birklein, F., Schlereth, T., Mackey, S., Mailis-Gagnon, A., Livshitz, A., Harden, R. N. Complex regional pain syndrome: evidence for warm and cold subtypes in a large prospective clinical sample.*Pain*; Aug 2016.

231. Bruehl S, Harden RN,Galer BS,et al. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome?.*Pain*; 2002.

232. Sebastin, SJ. Complex regional pain syndrome.*Indian J Plast Surg*; 2011.

233. van de Beek, W. J., Schwartzman, R. J., van Nes, S. I., Delhaas, E. M., van Hilten, J. J. Diagnostic criteria used in studies of reflex sympathetic dystrophy.*Neurology*; Feb 26 2002.

234. Mitchell, S.W., Morehouse, G. R., Keen, W. W. Gunshot Wounds and Other Injuries of the Nerves.1864.

235. Christensen, K., Jensen, E. M., Noer, I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids.*Acta Chir Scand*; 1982.

236. Oerlemans, H. M., Oostendorp, R. A., de Boo, T., van der Laan, L., Severens, J. L., Goris, J. A. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I.*Arch Phys Med Rehabil*; Jan 2000.

237. Taylor, Samantha-Su, Noor, Nazir, Urits, Ivan, Paladini, Antonella, Sadhu, Monica Sri, Gibb, Clay, Carlson, Tyler, Myrcik, Dariusz, Varrassi, Giustino, Viswanath, Omar. Complex regional pain syndrome: a comprehensive review.*Pain and Therapy*; 2021.

238. Treister, A. K., Hatch, M. N., Cramer, S. C., Chang, E. Y. Demystifying Poststroke Pain: From Etiology to Treatment.*PM R*; Jun 16 2016.

239. Berry, H. Chronic whiplash syndrome as a functional disorder.*Arch Neurol*; Apr 2000.

240. Lohnberg, J. A., Altmaier, E. M. A review of psychosocial factors in complex regional pain syndrome.*J Clin Psychol Med Settings*; Jun 2013.

241. Bean DJ, Johnson MH,Kydd RR. Relationships between psychological factors, pain, and disability in complex regional pain syndrome and low back pain.*Clin J Pain*; 2014.

242. Rondinelli, Robert D., Genovese, Elizabeth, Katz, Richard T., Mayer, Tom G., Mueller, Kathryn L., Ranavaya, Mohammed I., Brigham, Christopher R. AMA Guides to the Evaluation of Permanent Impairment, 6th Edition, 2021.2021.

243. Breivik, H. Chronic pain and the sympathetic nervous system.*Acta Anaesthesiol Scand Suppl*; 1997.

244. Iolascon G, de Sire A,Moretti A,Gimigliano F. Complex regional pain syndrome (CRPS) type I: historical perspective and critical issues.*Clin Cases Miner Bone Metab*; 2015.

245. Harden, N. R., Bruehl, S., Perez, Rsgm, Birklein, F., Marinus, J., Maihofner, C., Lubenow, T., Buvanendran, A., Mackey, S., Graciosa, J., Mogilevski, M., Ramsden, C., Chont, M., Vatine, J. J. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome.*Pain*; Aug 2010.

246. Harden, R Norman, Bruehl, Stephen, Galer, Bradley S, Saltz, Samuel, Bertram, Martin, Backonja, Miroslav, Gayles, Richard, Rudin, Nathan, Bhugra, Maninder K, Stanton-Hicks, Michael. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive?.*Pain*; 1999.

247. Bruehl, S., Harden, R. N., Galer, B. S., Saltz, S., Bertram, M., Backonja, M., Gayles, R., Rudin, N., Bhugra, M. K., Stanton-Hicks, M. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain.*Pain*; May 1999.

248. Terkelsen, A. J., Gierthmuhlen, J., Finnerup, N. B., Hojlund, A. P., Jensen, T. S. Bilateral hypersensitivity to capsaicin, thermal, and mechanical stimuli in unilateral complex regional pain syndrome.*Anesthesiology*; May 2014.

249. Harden, R Norman, McCabe, Candida S, Goebel, Andreas, Massey, Michael, Suvar, Tolga, Grieve, Sharon, Bruehl, Stephen. Complex regional pain syndrome: practical diagnostic and treatment guidelines.*Pain Medicine*; 2022.

250. Gradl, G., Schürmann, M. Sympathetic dysfunction as a temporary phenomenon in acute posttraumatic CRPS I.*Clin Auton Res*; Feb 2005.

251. Zych-Litwin, C., Litwin, J. A. Complex regional pain syndrome: diagnosis and treatment at the very onset as the key to success? A case report with implications for first contact doctors.*Reumatologia*; 2019.

252. Park, G. Y., Rak Kwon, D., Gil Kwon, D. Complex regional pain syndrome type II after cervical transforaminal epidural injection: A case report.*Medicine (Baltimore)*; May 2018.

253. Sutbeyaz, S. T., Koseoglu, B. F., Yeşiltepe, E. Simultaneous upper and lower extremity complex regional pain syndrome type I in tetraplegia.*Spinal Cord*; Sep 2005.

254. Pons, T., Shipton, E. A., Williman, J., Mulder, R. T. Potential risk factors for the onset of complex regional pain syndrome type 1: a systematic literature review.*Anesthesiol Res Pract*; 2015.

255. Moseley, G Lorimer, Herbert, Robert D, Parsons, Timothy, Lucas, Samantha, Van Hilten, Jacobus J, Marinus, Johan. Intense pain soon after wrist fracture strongly predicts who will develop complex regional pain syndrome: prospective cohort study.*The Journal of Pain*; 2014.

256. Rho RH, Brewer RP,Lamer TJ,Wilson PR. Complex regional pain syndrome.*Mayo Clin Proc*; 2002.

257. Speck V, Schlereth T,Birklein F,Maihöfner C. Increased prevalence of posttraumatic stress disorder in CRPS.*Eur J Pain*; 2017.

258. Harden, R. N., Bruehl, S., Stanton-Hicks, M., Wilson, P. R. Proposed new diagnostic criteria for complex regional pain syndrome.*Pain Med*; May-Jun 2007.

259. Kuttikat, A., Noreika, V., Shenker, N., Chennu, S., Bekinschtein, T., Brown, C. A. Neurocognitive and Neuroplastic Mechanisms of Novel Clinical Signs in CRPS.*Front Hum Neurosci*; 2016.

260. Backonja, M., Beydoun, A., Edwards, K. R., Schwartz, S. L., Fonseca, V., Hes, M., LaMoreaux, L., Garofalo, E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial.*Jama*; Dec 2 1998.

261. Stanton-Hicks, M., Janig, W., Hassenbusch, S., Haddox, J. D., Boas, R., Wilson, P. Reflex sympathetic dystrophy: changing concepts and taxonomy.*Pain*; Oct 1995.

262. Dotson, R. M. Causalgia--reflex sympathetic dystrophy--sympathetically maintained pain: myth and reality.*Muscle Nerve*; Oct 1993.

263. Rowbotham, M. C. Complex regional pain syndrome type I (reflex sympathetic dystrophy) - More than a myth.*Neurology*; Jul 1998.

264. Wasner, G., Backonja, M. M., Baron, R. Traumatic neuralgias: complex regional pain syndromes (reflex sympathetic dystrophy and causalgia): clinical characteristics, pathophysiological mechanisms and therapy.*Neurol Clin*; Nov 1998.

265. Goebel A, Birklein F,Brunner F,et al. The Valencia consensus-based adaptation of the IASP complex regional pain syndrome diagnostic criteria.*Pain*; 2021.

266. Ochoa, J. L. Reflex sympathetic dystrophy: a disease of medical understanding.*Clin J Pain*; Dec 1992.

267. Ochoa, J. L., Verdugo, R. J. Reflex sympathetic dystrophy. A common clinical avenue for somatoform expression.*Neurol Clin*; May 1995.

268. Perez, R. S., Burm, P. E., Zuurmond, W. W., Bezemer, P. D., Brink, H. E., de Lange, J. J. Physicians' assessments versus measured symptoms of complex regional pain syndrome type 1: presence and severity.*Clin J Pain*; May-Jun 2005.

269. Forouzanfar, T., Kemler, M., Kessels, A. G., Koke, A. J., van Kleef, M., Weber, W. E. Comparison of multiple against single pain intensity measurements in complex regional pain syndrome type I: analysis of 54 patients.*Clin J Pain*; Jul-Aug 2002.

270. Harden, R. N. Pharmacotherapy of complex regional pain syndrome.*Am J Phys Med Rehabil*; Mar 2005.

271. Freeman, R., Wallace, M. S., Sweeney, M., Backonja, M. M. Relationships Among Pain Quality, Pain Impact, and Overall Improvement in Patients with Postherpetic Neuralgia Treated with Gastroretentive Gabapentin.*Pain Med*; Oct 2015.

272. Harden, R. N., Bruehl, S., Galer, B. S., Saltz, S., Bertram, M., Backonja, M., Gayles, R., Rudin, N., Bhugra, M. K., Stanton-Hicks, M. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive?.*Pain*; Nov 1999.

273. Brunner, F., Lienhardt, S. B., Kissling, R. O., Bachmann, L. M., Weber, U. Diagnostic criteria and follow-up parameters in complex regional pain syndrome type I--a Delphi survey.*Eur J Pain*; Jan 2008.

274. Geertzen, J. H., Dijkstra, P. U., Stewart, R. E., Groothoff, J. W., Ten Duis, H. J., Eisma, W. H. Variation in measurements of range of motion: a study in reflex sympathetic dystrophy patients.*Clin Rehabil*; Jun 1998.

275. Louis MH, Meyer C,Legrain V,Berquin A. Biological and psychological early prognostic factors in complex regional pain syndrome: A systematic review.*Eur J Pain*; 2023.

276. Elsamadicy AA, Yang S,Sergesketter AR,et al. Prevalence and Cost Analysis of Complex Regional Pain Syndrome (CRPS): A Role for Neuromodulation.*Neuromodulation*; 2018.

277. National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIAMS. What is fibromyalgia.*https://www.niams.nih.gov/health-topics/fibromyalgia*; 2021.

278. Goldenberg, DL. Fibromyalgia syndrome. An emerging but controversial condition.*JAMA*; 1987.

279. Clauw, DJ. Fibromyalgia: a clinical review.*JAMA*; 2014.

280. Sarzi-Puttini P, Atzeni F,Mease PJ. Chronic widespread pain: from peripheral to central evolution.*Best Pract Res Clin Rheumatol*; 2011.

281. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy.*Nat Rev Rheumatol*; 2011.

282. Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., Russell, A. S., Russell, I. J., Winfield, J. B., Yunus, M. B. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.*Arthritis Care Res (Hoboken)*; May 2010.

283. Bazzichi, L., Giacomelli, C., Consensi, A., Atzeni, F., Batticciotto, A., Di Franco, M., Casale, R., Sarzi-Puttini, P. One year in review 2016: fibromyalgia.*Clin Exp Rheumatol*; Mar-Apr 2016.

284. Vallejo, Miguel A, Rivera, Javier, Esteve-Vives, Joaquim. Development of a self-reporting tool to obtain a Combined Index of Severity of Fibromyalgia (ICAF*).*Health and Quality of Life Outcomes*; 2010.

285. Adams, G., Sim, J. A survey of UK manual therapists' practice of and attitudes towards manipulation and its complications.*Physiother Res Int*; 1998.

286. Pomares FB, Funck T,Feier NA,et al. Histological Underpinnings of Grey Matter Changes in Fibromyalgia Investigated Using Multimodal Brain Imaging.*J Neurosci*; 2017.

287. Staud, R. Abnormal pain modulation in patients with spatially distributed chronic pain: fibromyalgia.*Rheum Dis Clin North Am*; 2009.

288. Dadabhoy D, Crofford LJ,Spaeth M,et al. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome.*Arthritis Res Ther*; 2008.

289. Desmeules JA, Cedraschi C,Rapiti E,et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia.*Arthritis Rheum*; 2003.

290. Petersel, D. L., Dror, V., Cheung, R. Central amplification and fibromyalgia: disorder of pain processing.*J Neurosci Res*; Jan 2011.

291. Uceyler, N., Zeller, J., Kewenig, S., Kittel-Schneider, S., Fallgatter, A. J., Sommer, C. Increased cortical activation upon painful stimulation in fibromyalgia syndrome.*BMC Neurol*; Oct 20 2015.

292. Clauw, D. J. Fibromyalgia and related conditions.*Mayo Clin Proc*; May 2015.

293. Clauw, D. J. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s).*Best Pract Res Clin Rheumatol*; Feb 2015.

294. Clauw, Daniel J. Fibromyalgia: an overview.*The American journal of medicine*; 2009.

295. Cassisi, G., Sarzi-Puttini, P., Casale, R., Cazzola, M., Boccassini, L., Atzeni, F., Stisi, S. Pain in fibromyalgia and related conditions.*Reumatismo*; Jun 06 2014.

296. Affaitati, G., Costantini, R., Fabrizio, A., Lapenna, D., Tafuri, E., Giamberardino, M. A. Effects of treatment of peripheral pain generators in fibromyalgia patients.*Eur J Pain*; Jan 2011.

297. Kosek, E., Ekholm, J., Hansson, P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls.*Pain*; Mar 1996.

298. Desmeules, J., Chabert, J., Rebsamen, M., Rapiti, E., Piguet, V., Besson, M., Dayer, P., Cedraschi, C. Central pain sensitization, COMT Val158Met polymorphism, and emotional factors in fibromyalgia.*J Pain*; Feb 2014.

299. Moshiree, B., Price, D. D., Robinson, M. E., Gaible, R., Verne, G. N. Thermal and visceral hypersensitivity in irritable bowel syndrome patients with and without fibromyalgia.*Clin J Pain*; May 2007.

300. Brown, C. A., El-Deredy, W., Jones, A. K. P. When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis.*European Journal of Neuroscience*; Feb 2014.

301. Kamping, S., Bomba, I. C., Kanske, P., Diesch, E., Flor, H. Deficient modulation of pain by a positive emotional context in fibromyalgia patients.*Pain*; Sep 2013.

302. Lee, S. J., Song, H. J., Decety, J., Seo, J., Kim, S. H., Kim, S. H., Nam, E. J., Kim, S. K., Han, S. W., Lee, H. J., Do, Y., Chang, Y. Do patients with fibromyalgia show abnormal neural responses to the observation of pain in others?.*Neuroscience Research*; Apr 2013.

303. Prist, V., De Wilde, V. A., Masquelier, E. Dystonic pattern in a fibromyalgia patient: relevance of a biopsychosocial rehabilitation approach.*Ann Phys Rehabil Med*; Apr 2012.

304. Sorensen, J., Bengtsson, A., Ahlner, J., Henriksson, K. G., Ekselius, L., Bengtsson, M. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs.*J Rheumatol*; Aug 1997.

305. Staud, R., Nagel, S., Robinson, M. E., Price, D. D. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study.*Pain*; Sep 2009.

306. Staud, R., Weyl, E. E., Bartley, E., Price, D. D., Robinson, M. E. Analgesic and anti-hyperalgesic effects of muscle injections with lidocaine or saline in patients with fibromyalgia syndrome.*Eur J Pain*; Jul 2014.

307. Bradley, L. A. Pathophysiology of fibromyalgia.*Am J Med*; Dec 2009.

308. Ablin, J., Neumann, L., Buskila, D. Pathogenesis of fibromyalgia - a review.*Joint Bone Spine*; May 2008.

309. Mease, P. J., Clauw, D. J., Christensen, R., Crofford, L. J., Gendreau, R. M., Martin, S. A., Simon, L. S., Strand, V., Williams, D. A., Arnold, L. M. Toward development of a fibromyalgia responder index and disease activity score: OMERACT module update.*J Rheumatol*; Jul 2011.

310. Jr, Vierck,CJ. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia).*Pain*; 2006.

311. Nicholas M, Vlaeyen JWS,Rief W,et al. The IASP classification of chronic pain for ICD-11: chronic primary pain.*Pain*; 2019.

312. Scholz J, Finnerup NB,Attal N,et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain.*Pain*; 2019.

313. Perrot S, Cohen M,Barke A,et al. IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain.*Pain*; 2019.

314. Treede RD, Rief W,Barke A,et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11).*Pain*; 2019.

315. Garcia-Hernandez A, de la Coba P,Reyes Del Paso GA. Central sensitisation pain and autonomic deficiencies in fibromyalgia.*Clin Exp Rheumatol*; 2022.

316. Dumolard A, Lefaucheur JP,Hodaj E,et al. Central Sensitization and Small-fiber Neuropathy Are Associated in Patients With Fibromyalgia.*Clin J Pain*; 2023.

317. Falco P, Galosi E,Di Stefano G,et al. Autonomic Small-Fiber Pathology in Patients With Fibromyalgia.*J Pain*; 2024.

318. Marshall A, Rapteas L,Burgess J,et al. Small fibre pathology, small fibre symptoms and pain in fibromyalgia syndrome.*Sci Rep*; 2024.

319. Izuno S, Yoshihara K,Hosoi M,et al. Psychological characteristics associated with the brain volume of patients with fibromyalgia.*Biopsychosoc Med*; 2023.

320. Mosch B, Hagena V,Herpertz S,et al. Neural correlates of control over pain in fibromyalgia patients.*Neuroimage Clin*; 2023.

321. Schreiber KL, Loggia ML,Kim J,et al. Painful After-Sensations in Fibromyalgia are Linked to Catastrophizing and Differences in Brain Response in the Medial Temporal Lobe.*J Pain*; 2017.

322. Kong J, Huang Y,Liu J,et al. Altered functional connectivity between hypothalamus and limbic system in fibromyalgia.*Mol Brain*; 2021.

323. Balducci T, Garza-Villarreal EA,Valencia A,et al. Abnormal functional neurocircuitry underpinning emotional processing in fibromyalgia.*Eur Arch Psychiatry Clin Neurosci*; 2024.

324. Uçar M, Sarp Ü,Karaaslan Ö,et al. Health anxiety and depression in patients with fibromyalgia syndrome.*J Int Med Res*; 2015.

325. Hadlandsmyth K, Dailey DL,Rakel BA,et al. Somatic symptom presentations in women with fibromyalgia are differentially associated with elevated depression and anxiety.*J Health Psychol*; 2020.

326. Dailey, D. L., Rakel, B. A., Vance, C. G., Liebano, R. E., Amrit, A. S., Bush, H. M., Lee, K. S., Lee, J. E., Sluka, K. A. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia.*Pain*; Nov 2013.

327. Cetingok S, Seker O,Cetingok H. The relationship between fibromyalgia and depression, anxiety, anxiety sensitivity, fear avoidance beliefs, and quality of life in female patients.*Medicine (Baltimore)*; 2022.

328. Montoro CI, Galvez-Sánchez CM. The mediating role of depression and pain catastrophizing in the relationship between functional capacity and pain intensity in patients with fibromyalgia.*Behav Neurol*; 2022.

329. Ghiggia A, Romeo A,Tesio V,et al. Alexithymia and depression in patients with fibromyalgia: When the whole is greater than the sum of its parts.*Psychiatry Res*; 2017.

330. Topal İ, Tuman TC. The impact of type D personality traits on quality of life, sleep, anxiety, and depression in fibromyalgia patients: A comparative study with healthy controls.*Med Sci Monit*; 2024.

331. Thompson L, Van Dyne A,Sadler M,et al. The indirect effects of recalled trauma severity on pain ratings among people with fibromyalgia: a moderated mediation model.*Behav Med*; 2023.

332. Shirsat N, Finney N,Strutner S,et al. Characterizing Chronic Pain and Adverse Childhood Experiences in the Lesbian, Gay, Bisexual, Transgender, or Queer Community.*Anesth Analg*; 2024.

333. Puşuroğlu M, Topaloğlu MS,Hocaoğlu Ç,Yıldırım M. Expressing emotions, rejection sensitivity, and attachment in patients with fibromyalgia.*Turk J Phys Med Rehabil*; 2023.

334. Løge-Hagen JS, Sæle A,Juhl C,et al. Prevalence of depressive disorder among patients with fibromyalgia: Systematic review and meta-analysis.*J Affect Disord*; 2019.

335. Singh G, Kaul S. Anxiety and Depression are Common in Fibromyalgia Patients and Correlate with Symptom Severity Score.*Ind J Rheumatol*; 2018.

336. Kassam A, Patten SB. Major depression, fibromyalgia and labour force participation: a population-based cross-sectional study.*BMC Musculoskelet Disord*; 2006.

337. Kleykamp BA, Ferguson MC,McNicol E,et al. The Prevalence of Psychiatric and Chronic Pain Comorbidities in Fibromyalgia: an ACTTION systematic review.*Semin Arthritis Rheum*; 2021.

338. Weir, P. T., Harlan, G. A., Nkoy, F. L., Jones, S. S., Hegmann, K. T., Gren, L. H., Lyon, J. L. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes.*J Clin Rheumatol*; Jun 2006.

339. Forseth, K. O., Forre, O., Gran, J. T. A 5.5 year prospective study of self-reported musculoskeletal pain and of fibromyalgia in a female population: significance and natural history.*Clin Rheumatol*; 1999.

340. Hudson, J. I., Goldenberg, D. L., Pope, H. G.,Jr., Keck, P. E.,Jr., Schlesinger, L. Comorbidity of fibromyalgia with medical and psychiatric disorders.*Am J Med*; Apr 1992.

341. Cole, J. A., Rothman, K. J., Cabral, H. J., Zhang, Y., Farraye, F. A. Migraine, fibromyalgia, and depression among people with IBS: a prevalence study.*BMC Gastroenterol*; 2006.

342. M Adams, Leah, C Turk, Dennis. Psychosocial factors and central sensitivity syndromes.*Current rheumatology reviews*; 2015.

343. Whitehead, W. E., Palsson, O., Jones, K. R. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications?.*Gastroenterology*; Apr 2002.

344. North, C. S., Hong, B. A., Alpers, D. H. Relationship of functional gastrointestinal disorders and psychiatric disorders: implications for treatment.*World J Gastroenterol*; Apr 14 2007.

345. Walitt, B., Nahin, R. L., Katz, R. S., Bergman, M. J., Wolfe, F. The Prevalence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey.*PLoS One*; 2015.

346. Schwartz, A. G., Cote, M. L. Epidemiology of Lung Cancer.*Adv Exp Med Biol*; 2016.

347. Wolfe, Frederick, Anderson, Janice, Harkness, Deborah, Bennett, Robert M, Caro, Xavier J, Goldenberg, Don L, Russell, I Jon, Yunus, Muhammad B. Health status and disease severity in fibromyalgia. Results of a six-center longitudinal study.*Arthritis & Rheumatism*; 1997.

348. Ciccone, Donald S, Chandler, Helena K, Natelson, Benjamin H. Illness trajectories in the chronic fatigue syndrome: a longitudinal study of improvers versus non-improvers.*The Journal of nervous and mental disease*; 2010.

349. Sullivan, Patrick F, Smith, W, Buchwald, D. Latent class analysis of symptoms associated with chronic fatigue syndrome and fibromyalgia.*Psychological medicine*; 2002.

350. Balasubramaniam, R., de Leeuw, R., Zhu, H., Nickerson, R. B., Okeson, J. P., Carlson, C. R. Prevalence of temporomandibular disorders in fibromyalgia and failed back syndrome patients: a blinded prospective comparison study.*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*; Aug 2007.

351. Bell, I. R., Baldwin, C. M., Schwartz, G. E. Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia.*Am J Med*; Sep 28 1998.

352. Tsai, P. S., Fan, Y. C., Huang, C. J. Fibromyalgia is associated with coronary heart disease: a population-based cohort study.*Reg Anesth Pain Med*; Jan-Feb 2015.

353. Su, C. H., Chen, J. H., Lan, J. L., Wang, Y. C., Tseng, C. H., Hsu, C. Y., Huang, L. Increased Risk of Coronary Heart Disease in Patients with Primary Fibromyalgia and Those with Concomitant Comorbidity-A Taiwanese Population-Based Cohort Study.*PLoS One*; 2015.

354. Redelmeier, D. A., Zung, J. D., Thiruchelvam, D., Tibshirani, R. J. Fibromyalgia and the Risk of a Subsequent Motor Vehicle Crash.*J Rheumatol*; Aug 2015.

355. Centers for Disease Control and Prevention, CDC. Fibromyalgia.*https://www.cdc.gov/arthritis/types/fibromyalgia.htm*; 2022.

356. Vlaeyen, J. W., Linton, S. J. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art.*Pain*; Apr 2000.

357. van Eijk-Hustings, Y., Kroese, M., Boonen, A., Bessems-Beks, M., Landewe, R. Predictors for health improvement in patients with fibromyalgia: a 2-year follow-up study.*Clin Rheumatol*; Jan 2015.

358. Mohabbat AB, Wight EC,Mohabbat NML,et al. The correlation between occupation type and fibromyalgia severity.*Occupational Medicine*; 2023.

359. Wolfe F, Clauw DJ,Fitzcharles MA,et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria.*Semin Arthritis Rheum*; 2016.

360. Arnold LM, Bennett RM,Crofford LJ,et al. AAPT Diagnostic Criteria for Fibromyalgia.*J Pain*; 2019.

361. Kurland, J. E., Coyle, W. J., Winkler, A., Zable, E. Prevalence of irritable bowel syndrome and depression in fibromyalgia.*Dig Dis Sci*; Mar 2006.

362. APS Clinical Practice Guidelines, . Guidelines for the management of fibromyalgia syndrome pain in adults and children.2005.

363. Sims, R. Is there muscle pathology in fibromyalgia syndrome?.*Pain Med*; 1996.

364. Goldenberg, D. L. Diagnosis and differential diagnosis of fibromyalgia.*Am J Med*; Dec 2009.

365. Harden, R. N., Revivo, G., Song, S., Nampiaparampil, D., Golden, G., Kirincic, M., Houle, T. T. A critical analysis of the tender points in fibromyalgia.*Pain Med*; Mar 2007.

366. Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., Tugwell, P., Campbell, S. M., Abeles, M., Clark, P., et al., . The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.*Arthritis Rheum*; Feb 1990.

367. Metyas, S., Rezk, T., Arkfeld, D., Leptich, T. The Inflammatory Fibromyalgia.*Curr Rheumatol Rev*; Sep 19 2016.

368. Kadetoff, D., Lampa, J., Westman, M., Andersson, M., Kosek, E. Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels.*J Neuroimmunol*; Jan 18 2012.

369. Rodriguez-Pinto, I., Agmon-Levin, N., Howard, A., Shoenfeld, Y. Fibromyalgia and cytokines.*Immunol Lett*; Oct 2014.

370. Ranzolin, A., Duarte, A. L., Bredemeier, M., da Costa Neto, C. A., Ascoli, B. M., Wollenhaupt-Aguiar, B., Kapczinski, F., Xavier, R. M. Evaluation of cytokines, oxidative stress markers and brain-derived neurotrophic factor in patients with fibromyalgia - A controlled cross-sectional study.*Cytokine*; Aug 2016.

371. Geiss, A., Rohleder, N., Anton, F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia.*Psychoneuroendocrinology*; May 2012.

372. Sanada, K., Diez, M. A., Valero, M. S., Perez-Yus, M. C., Demarzo, M. M., Garcia-Toro, M., Garcia-Campayo, J. Effects of non-pharmacological interventions on inflammatory biomarker expression in patients with fibromyalgia: a systematic review.*Arthritis Res Ther*; 2015.

373. Wolfe, F., Brahler, E., Hinz, A., Hauser, W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population.*Arthritis Care Res (Hoboken)*; May 2013.

374. Jones GT, Atzeni F,Beasley M,et al. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria.*Arthritis Rheumatol*; 2015.

375. Vincent, A., Lahr, B. D., Wolfe, F., Clauw, D. J., Whipple, M. O., Oh, T. H., Barton, D. L., St Sauver, J. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project.*Arthritis Care Res (Hoboken)*; May 2013.

376. Kindler, L. L., Jones, K. D., Perrin, N., Bennett, R. M. Risk factors predicting the development of widespread pain from chronic back or neck pain.*J Pain*; Dec 2010.

377. Wright, L. J., Schur, E., Noonan, C., Ahumada, S., Buchwald, D., Afari, N. Chronic pain, overweight, and obesity: findings from a community-based twin registry.*J Pain*; Jul 2010.

378. McCabe, P. S., Pye, S. R., Mc Beth, J., Lee, D. M., Tajar, A., Bartfai, G., Boonen, S., Bouillon, R., Casanueva, F., Finn, J. D., Forti, G., Giwercman, A., Huhtaniemi, I. T., Kula, K., Pendleton, N., Punab, M., Vanderschueren, D., Wu, F. C., O'Neill, T. W., Group, Emas,Study. Low vitamin D and the risk of developing chronic widespread pain: results from the European male ageing study.*BMC Musculoskelet Disord*; Jan 16 2016.

379. Mork, P. J., Vasseljen, O., Nilsen, T. I. L. Association Between Physical Exercise, Body Mass Index, and Risk of Fibromyalgia: Longitudinal Data From the Norwegian Nord-Trondelag Health Study.*Arthritis Care & Research*; May 2010.

380. Pellegrino, MJ, Waylonis, GW, Sommer, A. Familial occurrence of primary fibromyalgia.*Archives of physical medicine and rehabilitation*; 1989.

381. Roizenblatt, S., Tufik, S., Goldenberg, J., Pinto, L. R., Hilario, M. O., Feldman, D. Juvenile fibromyalgia: clinical and polysomnographic aspects.*J Rheumatol*; Mar 1997.

382. Buskila, D., Neumann, L. Fibromyalgia syndrome (FM) and nonarticular tenderness in relatives of patients with FM.*J Rheumatol*; May 1997.

383. Arnold, Lesley M, Hudson, James I, Hess, Evelyn V, Ware, Avis E, Fritz, Deborah A, Auchenbach, Megan B, Starck, Linsey O, Keck, Paul E. Family study of fibromyalgia.*Arthritis & Rheumatism*; 2004.

384. Buskila D, Sarzi-Puttini P. Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome.*Arthritis Res Ther*; 2006.

385. Vargas-Alarcón G, Fragoso JM,Cruz-Robles D,et al. Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains.*Arthritis Rheum*; 2009.

386. Smith SB, Maixner DW,Fillingim RB. Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia.*Arthritis Rheum*; 2012.

387. Arnold LM, Hudson JI,Hess EV,et al. Family study of fibromyalgia.*Arthritis Rheum*; 2004.

388. Hellou R, Häuser W,Brenner I,et al. Self-Reported Childhood Maltreatment and Traumatic Events among Israeli Patients Suffering from Fibromyalgia and Rheumatoid Arthritis.*Pain Res Manag*; 2017.

389. Robinson, J. N., Sandom, J., Chapman, P. T. Efficacy of pamidronate in complex regional pain syndrome type I.*Pain Med*; Sep 2004.

390. Wolfe, F., Hauser, W., Hassett, A. L., Katz, R. S., Walitt, B. T. The development of fibromyalgia--I: examination of rates and predictors in patients with rheumatoid arthritis (RA).*Pain*; Feb 2011.

391. Petri, M., Naqibuddin, M., Carson, K. A., Wallace, D. J., Weisman, M. H., Holliday, S. L., Sampedro, M., Padilla, P. A., Brey, R. L. Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus.*J Rheumatol*; Oct 2010.

392. Benjamin, S., Morris, S., McBeth, J., Macfarlane, G. J., Silman, A. J. The association between chronic widespread pain and mental disorder: a population-based study.*Arthritis & Rheumatism*; 2000.

393. Ciccone, D. S., Busichio, K., Vickroy, M., Natelson, B. H. Psychiatric morbidity in the chronic fatigue syndrome: are patients with personality disorder more physically impaired?.*J Psychosom Res*; May 2003.

394. Hellstrom, O., Bullington, J., Karlsson, G., Lindqvist, P., Mattsson, B. A phenomenological study of fibromyalgia. Patient perspectives.*Scand J Prim Health Care*; Mar 1999.

395. Katon, W., Rutter, C., Ludman, E. J., Von Korff, M., Lin, E., Simon, G., Bush, T., Walker, E., Unutzer, J. A randomized trial of relapse prevention of depression in primary care.*Arch Gen Psychiatry*; Mar 2001.

396. Offenbaecher, M., Glatzeder, K., Ackenheil, M. Self-reported depression, familial history of depression and fibromyalgia (FM), and psychological distress in patients with FM.*Z Rheumatol*; 1998.

397. Wolfe, F. What use are fibromyalgia control points?.*J Rheumatol*; Mar 1998.

398. Riera, R. Selective serotonin reuptake inhibitors for fibromyalgia syndrome.*Sao Paulo Med J*; Sep-Oct 2015.

399. Chang, M. H., Hsu, J. W., Huang, K. L., Su, T. P., Bai, Y. M., Li, C. T., Yang, A. C., Chang, W. H., Chen, T. J., Tsai, S. J., Chen, M. H. Bidirectional Association Between Depression and Fibromyalgia Syndrome: A Nationwide Longitudinal Study.*J Pain*; Sep 2015.

400. Ivanova, J. I., Birnbaum, H. G., Kidolezi, Y., Subramanian, G., Khan, S. A., Stensland, M. D. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder.*Curr Med Res Opin*; Oct 2010.

401. Fietta, Pierluigi, Manganelli, P. Fibromyalgia and psychiatric disorders.*Acta Bio Medica Atenei Parmensis*; 2007.

402. Yunus, M. B., Celiker, R., Aldag, J. C. Fibromyalgia in men: comparison of psychological features with women.*J Rheumatol*; Dec 2004.

403. White, Kevin P, Nielson, Warren R, Harth, Manfred, Ostbye, Truls, Speechley, Mark. Chronic widespread musculoskeletal pain with or without fibromyalgia: psychological distress in a representative community adult sample.*The Journal of rheumatology*; 2002.

404. Goldenberg, DL. An overview of psychologic studies in fibromyalgia.*The Journal of rheumatology. Supplement*; 1989.

405. Lukkahatai, N., Walitt, B., Espina, A., Gelio, A., Saligan, L. N. Understanding the Association of Fatigue With Other Symptoms of Fibromyalgia: Development of a Cluster Model.*Arthritis Care Res (Hoboken)*; Jan 2016.

406. Montoro, Casandra I, del Paso, Gustavo A Reyes. Personality and fibromyalgia: Relationships with clinical, emotional, and functional variables.*Personality and Individual Differences*; 2015.

407. Yunus, M. B., Young, C. S., Saeed, S. A., Mountz, J. M., Aldag, J. C. Positron emission tomography in patients with fibromyalgia syndrome and healthy controls.*Arthritis Rheum*; Aug 15 2004.

408. Frølund Pedersen, Heidi, Frostholm, Lisbeth, Søndergaard Jensen, Jens, Ørnbøl, Eva, Schröder, Andreas. Neuroticism and maladaptive coping in patients with functional somatic syndromes.*British Journal of Health Psychology*; 2016.

409. Seto A, Han X,Price LL,et al. The role of personality in patients with fibromyalgia.*Clin Rheumatol*; 2019.

410. Camerini, L., Schulz, P. J. Effects of functional interactivity on patients' knowledge, empowerment, and health outcomes: an experimental model-driven evaluation of a web-based intervention.*J Med Internet Res*; 2012.

411. Oliver, K., Cronan, T. A., Walen, H. R., Tomita, M. Effects of social support and education on health care costs for patients with fibromyalgia.*J Rheumatol*; Dec 2001.

412. Campbell, C. M., McCauley, L., Bounds, S. C., Mathur, V. A., Conn, L., Simango, M., Edwards, R. R., Fontaine, K. R. Changes in pain catastrophizing predict later changes in fibromyalgia clinical and experimental pain report: cross-lagged panel analyses of dispositional and situational catastrophizing.*Arthritis Res Ther*; 2012.

413. Angst F, Lehmann S,Sandor PS,Benz T. Catastrophizing as a prognostic factor for pain and physical function in the multidisciplinary rehabilitation of fibromyalgia and low back pain.*Eur J Pain*; 2022.

414. Wilke, William S, Gota, Carmen E, Muzina, David J. Fibromyalgia and bipolar disorder: a potential problem?.*Bipolar disorders*; 2010.

415. Keel, P. J., Bodoky, C., Gerhard, U., Muller, W. Comparison of integrated group therapy and group relaxation training for fibromyalgia.*Clin J Pain*; Sep 1998.

416. Lotti, M., Bergamo, L., Murer, B. Occupational toxicology of asbestos-related malignancies.*Clin Toxicol (Phila)*; Jul 2010.

417. Martinez, V., Uceyler, N., Ben Ammar, S., Alvarez, J. C., Gaudot, F., Sommer, C., Bouhassira, D., Fletcher, D. Clinical, histological, and biochemical predictors of postsurgical neuropathic pain.*Pain*; Nov 2015.

418. Aggarwal, V. R., McBeth, J., Zakrzewska, J. M., Lunt, M., Macfarlane, G. J. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors?.*Int J Epidemiol*; Apr 2006.

419. Kirmayer, L. J., Robbins, J. M., Kapusta, M. A. Somatization and depression in fibromyalgia syndrome.*Am J Psychiatry*; Aug 1988.

420. McBeth, J., Macfarlane, G. J., Benjamin, S., Silman, A. J. Features of somatization predict the onset of chronic widespread pain: results of a large population-based study.*Arthritis Rheum*; Apr 2001.

421. McBeth, J., Macfarlane, G. J., Hunt, I. M., Silman, A. J. Risk factors for persistent chronic widespread pain: a community-based study.*Rheumatology (Oxford)*; Jan 2001.

422. Sverdrup, B. Use less cosmetics--suffer less from fibromyalgia?.*J Womens Health (Larchmt)*; Mar 2004.

423. Castro, I., Barrantes, F., Tuna, M., Cabrera, G., Garcia, C., Recinos, M., Espinoza, L. R., Garcia-Kutzbach, A. Prevalence of abuse in fibromyalgia and other rheumatic disorders at a specialized clinic in rheumatic diseases in Guatemala City.*J Clin Rheumatol*; Jun 2005.

424. Ciccone, D. S., Elliott, D. K., Chandler, H. K., Nayak, S., Raphael, K. G. Sexual and physical abuse in women with fibromyalgia syndrome: a test of the trauma hypothesis.*Clin J Pain*; Sep-Oct 2005.

425. Howard, Krista J, Mayer, Tom G, Neblett, Randy, Perez, Yoheli, Cohen, Howard, Gatchel, Robert J. Fibromyalgia syndrome in chronic disabling occupational musculoskeletal disorders: prevalence, risk factors, and posttreatment outcomes.*Journal of Occupational and Environmental Medicine*; 2010.

426. Mayer, J., Mooney, V., Dagenais, S. Evidence-informed management of chronic low back pain with lumbar extensor strengthening exercises.*Spine J*; Jan-Feb 2008.

427. Moss, P., Knight, E., Wright, A. Subjects with Knee Osteoarthritis Exhibit Widespread Hyperalgesia to Pressure and Cold.*PLoS One*; 2016.

428. Kapoor, S. R., Hider, S. L., Brownfield, A., Mattey, D. L., Packham, J. C. Fibromyalgia in patients with rheumatoid arthritis: driven by depression or joint damage?.*Clin Exp Rheumatol*; Nov-Dec 2011.

429. Andersson, M. L., Svensson, B., Bergman, S. Chronic widespread pain in patients with rheumatoid arthritis and the relation between pain and disease activity measures over the first 5 years.*J Rheumatol*; Dec 2013.

430. Priori, R., Iannuccelli, C., Alessandri, C., Modesti, M., Antonazzo, B., Di Lollo, A. C., Valesini, G., Di Franco, M. Fatigue in Sjogren's syndrome: relationship with fibromyalgia, clinical and biologic features.*Clin Exp Rheumatol*; Nov-Dec 2010.

431. Baker, K., Pope, J., Fortin, P., Silverman, E., Peschken, C., Faces of Lupus, Investigators, CaNios, . Work disability in systemic lupus erythematosus is prevalent and associated with socio-demographic and disease related factors.*Lupus*; Dec 2009.

432. Ang, D. C., Chakr, R., France, C. R., Mazzuca, S. A., Stump, T. E., Hilligoss, J., Lengerich, A. Association of nociceptive responsivity with clinical pain and the moderating effect of depression.*J Pain*; Mar 2011.

433. Russell, I. J., Vipraio, G. A., Michalek, J. E., Craig, F. E., Kang, Y. K., Richards, A. B. Lymphocyte markers and natural killer cell activity in fibromyalgia syndrome: effects of low-dose, sublingual use of human interferon-alpha.*J Interferon Cytokine Res*; Aug 1999.

434. Russell, I. J., Michalek, J. E., Kang, Y. K., Richards, A. B. Reduction of morning stiffness and improvement in physical function in fibromyalgia syndrome patients treated sublingually with low doses of human interferon-alpha.*J Interferon Cytokine Res*; Aug 1999.

435. Zachrisson, O., Colque-Navarro, P., Gottfries, C. G., Regland, B., Mollby, R. Immune modulation with a staphylococcal preparation in fibromyalgia/chronic fatigue syndrome: relation between antibody levels and clinical improvement.*Eur J Clin Microbiol Infect Dis*; Feb 2004.

436. Tietjen, Gretchen E, Brandes, Jan L, Peterlin, B Lee, Eloff, Arnolda, Dafer, Rima M, Stein, Michael R, Drexler, Ellen, Martin, Vincent T, Hutchinson, Susan, Aurora, Sheena K. Childhood maltreatment and migraine (part III). Association with comorbid pain conditions.*Headache: The Journal of Head and Face Pain*; 2010.

437. Paras, Molly L, Murad, Mohammad Hassan, Chen, Laura P, Goranson, Erin N, Sattler, Amelia L, Colbenson, Kristina M, Elamin, Mohamed B, Seime, Richard J, Prokop, Larry J, Zirakzadeh, Ali. Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis.*Jama*; 2009.

438. Bohn, Daniela, Bernardy, Kathrin, Wolfe, Frederick, Häuser, Winfried. The association among childhood maltreatment, somatic symptom intensity, depression, and somatoform dissociative symptoms in patients with fibromyalgia syndrome: a single-center cohort study.*Journal of Trauma & Dissociation*; 2013.

439. McBeth, John, Lacey, Rosie J, Wilkie, Ross. Predictors of New-Onset Widespread Pain in Older Adults: Results From a Population-Based Prospective Cohort Study in the UK.*Arthritis & Rheumatology*; 2014.

440. Mork, Paul J, Nilsen, Tom IL. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway.*Arthritis & Rheumatism*; 2012.

441. Belt, NK, Kronholm, E, Kauppi, MJ. Sleep problems in fibromyalgia and rheumatoid arthritis compared with the general population.*Clinical & Experimental Rheumatology*; 2009.

442. Gupta, D., Mishra, S., Bhatnagar, S. Somatization disorder, a cause of difficult pain: a case report.*Am J Hosp Palliat Care*; Jun-Jul 2007.

443. Jason, L. A., Taylor, R. R., Kennedy, C. L. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms.*Psychosom Med*; Sep-Oct 2000.

444. McBeth, J., Macfarlane, G. J., Benjamin, S., Morris, S., Silman, A. J. The association between tender points, psychological distress, and adverse childhood experiences: a community-based study.*Arthritis Rheum*; Jul 1999.

445. McBeth, J., Silman, A. J. The role of psychiatric disorders in fibromyalgia.*Curr Rheumatol Rep*; Apr 2001.

446. McBeth, J., Chiu, Y. H., Silman, A. J., Ray, D., Morriss, R., Dickens, C., Gupta, A., Macfarlane, G. J. Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents.*Arthritis Res Ther*; 2005.

447. Light, K. C., Bragdon, E. E., Grewen, K. M., Brownley, K. A., Girdler, S. S., Maixner, W. Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder.*J Pain*; May 2009.

448. Mohammad, Ausaf, Carey, John J, Storan, Eoin, Scarry, Margaret, Coughlan, Robert J, Lee, John M. High prevalence of fibromyalgia in patients with HFE-related hereditary hemochromatosis.*Journal of clinical gastroenterology*; 2013.

449. Mohammad, Ausaf, Carey, John J, Storan, Eoin, Scarry, Margaret, Coughlan, Robert J, Lee, John M. Prevalence of fibromyalgia among patients with chronic hepatitis C infection: relationship to viral characteristics and quality of life.*Journal of clinical gastroenterology*; 2012.

450. Poynard, T, Cacoub, P, Ratziu, V, Myers, RP, Dezailles, MH, Mercadier, A, Ghillani, P, Charlotte, F, Piette, JC, Moussalli, J. Fatigue in patients with chronic hepatitis C.*Journal of viral hepatitis*; 2002.

451. Rogal, Shari S, Bielefeldt, Klaus, Wasan, Ajay D, Szigethy, Eva, Lotrich, Francis, DiMartini, Andrea F. Fibromyalgia symptoms and cirrhosis.*Digestive diseases and sciences*; 2015.

452. Buskila, Dan, Atzeni, Fabiola, Sarzi-Puttini, Piercarlo. Etiology of fibromyalgia: the possible role of infection and vaccination.*Autoimmunity reviews*; 2008.

453. Cruz, Boris A, Catalan-Soares, Bernadete, Proietti, Fernando. Higher prevalence of fibromyalgia in patients infected with human T cell lymphotropic virus type I.*The Journal of rheumatology*; 2006.

454. Bazzichi, Laura, Rossi, Alessandra, Giuliano, Tiziana, De Feo, Francesca, Giacomelli, Camillo, Consensi, Arianna, Ciapparelli, Antonio, Consoli, Giorgio, Dell'Osso, Liliana, Bombardieri, Stefano. Association between thyroid autoimmunity and fibromyalgic disease severity.*Clinical rheumatology*; 2007.

455. Heidari, Behzad, Shirvani, Javad Shokri, Firouzjahi, Alireza, Heidari, Parnaz, HAJIAN-TILAKI, Karim O. Association between nonspecific skeletal pain and vitamin D deficiency.*International journal of rheumatic diseases*; 2010.

456. Nees, F., Ruddel, H., Mussgay, L., Kuehl, L. K., Romer, S., Schachinger, H. Alteration of delay and trace eyeblink conditioning in fibromyalgia patients.*Psychosom Med*; May 2010.

457. Ottman, Ruth, Lipton, Richard B, Ettinger, Alan B, Cramer, Joyce A, Reed, Michael L, Morrison, Alan, Wan, George J. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey.*Epilepsia*; 2011.

458. Duhn PH, Locht H,Wæhrens EE,et al. Prognostic factors for work disability in patients with chronic widespread pain and fibromyalgia: protocol for a cohort study.*BMJ Open*; 2021.

459. Helfenstein M Jr, Goldenfum MA,Siena CA. Fibromyalgia: clinical and occupational aspects.*Rev Assoc Med Bras*; 2012.

460. Fitzcharles, M. A., Ste-Marie, P. A., Rampakakis, E., Sampalis, J. S., Shir, Y. Disability in Fibromyalgia Associates with Symptom Severity and Occupation Characteristics.*J Rheumatol*; May 2016.

461. Makela, M., Heliovaara, M. Prevalence of primary fibromyalgia in the Finnish population.*BMJ*; Jul 27 1991.

462. McLean, S. A., Ulirsch, J. C., Slade, G. D., Soward, A. C., Swor, R. A., Peak, D. A., Jones, J. S., Rathlev, N. K., Lee, D. C., Domeier, R. M., Hendry, P. L., Bortsov, A. V., Bair, E. Incidence and predictors of neck and widespread pain after motor vehicle collision among US litigants and nonlitigants.*Pain*; Feb 2014.

463. Gauffin J, Hankama T,Kautiainen H,et al. Neuropathic pain and use of PainDETECT in patients with fibromyalgia: a cohort study.*BMC Neurol*; 2013.

464. Fayaz, A., Croft, P., Langford, R. M., Donaldson, L. J., Jones, G. T. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies.*BMJ Open*; 2016.

465. van Hecke O, Austin SK,Khan RA,et al. Neuropathic pain in the general population: a systematic review of epidemiological studies.*Pain*; 2014.

466. Rogan WJ, Gladen B. Estimating prevalence from the results of a screening test.*Am J Epidemiol*; 1978.

467. Sun J, Wang Y,Zhang X,et al. Prevalence of peripheral neuropathy in patients with diabetes.*Prim Care Diabetes*; 2020.

468. Paolucci, S., Martinuzzi, A., Scivoletto, G., Smania, N., Solaro, C., Aprile, I., Armando, M., Bergamaschi, R., Berra, E., Berto, G., Carraro, E., Cella, M., Gandolfi, M., Masciullo, M., Molinari, M., Pagliano, E., Pecchioli, C., Roncari, L., Torre, M., Trabucco, E., Vallies, G., Zerbinati, P., Tamburin, S., Italian Consensus Conference on Pain in, Neurorehabilitation. Assessing and treating pain associated with stroke, multiple sclerosis, cerebral palsy, spinal cord injury and spasticity. Evidence and recommendations from the Italian Consensus conference on Pain in Neurorehabilitation.*Eur J Phys Rehabil Med*; Aug 31 2016.

469. Liampas A, Velidakis N,Georgiou T,et al. Prevalence and Management Challenges in Central Post-Stroke Neuropathic Pain: A Systematic Review and Meta-analysis.*Adv Ther*; 2020.

470. Ouyang H, Li X,Xu H,et al. Risk factors of neuropathic pain in multiple sclerosis: a retrospective case-cohort study.*Front Immunol*; 2024.

471. Dworkin, R. H., O'Connor, A. B., Kent, J., Mackey, S. C., Raja, S. N., Stacey, B. R., Levy, R. M., Backonja, M., Baron, R., Harke, H., Loeser, J. D., Treede, R. D., Turk, D. C., Wells, C. D. Interventional management of neuropathic pain: NeuPSIG recommendations.*Pain*; Nov 2013.

472. Lin CS, Lin YC,Lao HC,Chen CC. Interventional Treatments for Postherpetic Neuralgia: A Systematic Review.*Pain Physician*; 2019.

473. Paolucci, S., Iosa, M., Toni, D., Barbanti, P., Bovi, P., Cavallini, A., Candeloro, E., Mancini, A., Mancuso, M., Monaco, S., Pieroni, A., Recchia, S., Sessa, M., Strambo, D., Tinazzi, M., Cruccu, G., Truini, A., Neuropathic pain special interest group of the Italian Neurological, Society. Prevalence and Time Course of Post-Stroke Pain: A Multicenter Prospective Hospital-Based Study.*Pain Med*; May 2016.

474. Oh, H., Seo, W. A Comprehensive Review of Central Post-Stroke Pain.*Pain Manag Nurs*; Oct 2015.

475. Klit, H., Hansen, A. P., Marcussen, N. S., Finnerup, N. B., Jensen, T. S. Early evoked pain or dysesthesia is a predictor of central poststroke pain.*Pain*; Dec 2014.

476. Klit, H., Finnerup, N. B., Jensen, T. S. Central post-stroke pain: clinical characteristics, pathophysiology, and management.*Lancet Neurol*; Sep 2009.

477. Kim, J. S. Pharmacological management of central post-stroke pain: a practical guide.*CNS Drugs*; Sep 2014.

478. van Kollenburg, E. G., Lavrijsen, J. C., Verhagen, S. C., Zuidema, S. U., Schalkwijk, A., Vissers, K. C. Prevalence, causes, and treatment of neuropathic pain in Dutch nursing home residents: a retrospective chart review.*J Am Geriatr Soc*; Aug 2012.

479. Oosterling, A., te Boveldt, N., Verhagen, C., van der Graaf, W. T., Van Ham, M., Van der Drift, M., Vissers, K., Engels, Y. Neuropathic Pain Components in Patients with Cancer: Prevalence, Treatment, and Interference with Daily Activities.*Pain Pract*; Apr 2016.

480. Nicholson, D., Chiu, W. Neuroleptic malignant syndrome.*Geriatrics*; Aug 2004.

481. MacDonald, B. K., Cockerell, O. C., Sander, J. W., Shorvon, S. D. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK.*Brain*; Apr 2000.

482. Hong, J. H., Choi, B. Y., Chang, C. H., Kim, S. H., Jung, Y. J., Lee, D. G., Kwon, Y. H., Jang, S. H. The prevalence of central poststroke pain according to the integrity of the spino-thalamo-cortical pathway.*Eur Neurol*; 2012.

483. Bugnicourt, J. M., Garcia, P. Y., Canaple, S., Lamy, C., Godefroy, O. Central neuropathic pain after cerebral venous thrombosis is not so uncommon: an observational study.*J Neurol*; Jun 2011.

484. Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lanteri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., Vicaut, E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4).*Pain*; Mar 2005.

485. Andersen, G., Vestergaard, K., Ingeman-Nielsen, M., Jensen, T. S. Incidence of central post-stroke pain.*Pain*; May 1995.

486. Fontes, F., Pereira, S., Castro-Lopes, J. M., Lunet, N. A prospective study on the neurological complications of breast cancer and its treatment: Updated analysis three years after cancer diagnosis.*Breast*; Oct 2016.

487. Roberto, A., Deandrea, S., Greco, M. T., Corli, O., Negri, E., Pizzuto, M., Ruggeri, F. Prevalence of Neuropathic Pain in Cancer Patients: Pooled Estimates From a Systematic Review of Published Literature and Results From a Survey Conducted in 50 Italian Palliative Care Centers.*J Pain Symptom Manage*; Jun 2016.

488. Hughes, R. E., Holland, L. R., Zanino, D., Link, E., Michael, N., Thompson, K. E. Prevalence and Intensity of Pain and Other Physical and Psychological Symptoms in Adolescents and Young Adults Diagnosed with Cancer on Referral to a Palliative Care Service.*J Adolesc Young Adult Oncol*; Jun 2015.

489. Burke, D., Fullen, B. M., Stokes, D., Lennon, O. Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis.*Eur J Pain*; Jun 24 2016.

490. Andresen, S. R., Biering-Sorensen, F., Hagen, E. M., Nielsen, J. F., Bach, F. W., Finnerup, N. B. Pain, spasticity and quality of life in individuals with traumatic spinal cord injury in Denmark.*Spinal Cord*; Apr 12 2016.

491. Mahnig, S., Landmann, G., Stockinger, L., Opsommer, E. Pain assessment according to the International Spinal Cord Injury Pain classification in patients with spinal cord injury referred to a multidisciplinary pain center.*Spinal Cord*; Oct 2016.

492. Gupta, M., Sahi, M. S., Bhargava, A. K., Talwar, V. The Prevalence and Characteristics of Pain in Critically Ill Cancer Patients: A Prospective Nonrandomized Observational Study.*Indian J Palliat Care*; Sep-Dec 2015.

493. Truini, A., Barbanti, P., Pozzilli, C., Cruccu, G. A mechanism-based classification of pain in multiple sclerosis.*J Neurol*; Feb 2013.

494. Heitmann, H., Biberacher, V., Tiemann, L., Buck, D., Loleit, V., Selter, R. C., Knier, B., Tolle, T. R., Muhlau, M., Berthele, A., Hemmer, B., Ploner, M. Prevalence of neuropathic pain in early multiple sclerosis.*Mult Scler*; Aug 2016.

495. Foley, P. L., Vesterinen, H. M., Laird, B. J., Sena, E. S., Colvin, L. A., Chandran, S., MacLeod, M. R., Fallon, M. T. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis.*Pain*; May 2013.

496. Bible, E. Pain: Comorbidity of neuropathic pain and migraine in patients with multiple sclerosis.*Nat Rev Neurol*; Oct 2013.

497. Nordin, M.,et al. Back schools in prevention of chronicity.*Baillieres Clin Rheumatol*; 1992.

498. Grau-Lopez, L., Sierra, S., Martinez-Caceres, E., Ramo-Tello, C. Analysis of the pain in multiple sclerosis patients.*Neurologia*; May 2011.

499. Nurmikko, T. J., Gupta, S., Maclver, K. Multiple sclerosis-related central pain disorders.*Curr Pain Headache Rep*; Jun 2010.

500. Osterberg, A., Boivie, J., Thuomas, K. A. Central pain in multiple sclerosis--prevalence and clinical characteristics.*Eur J Pain*; Oct 2005.

501. Solaro, C., Brichetto, G., Amato, M. P., Cocco, E., Colombo, B., D'Aleo, G., Gasperini, C., Ghezzi, A., Martinelli, V., Milanese, C., Patti, F., Trojano, M., Verdun, E., Mancardi, G. L., Pa, I.

M. S. Study Group. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study.*Neurology*; Sep 14 2004.

502. Beiske, A. G., Pedersen, E. D., Czujko, B., Myhr, K. M. Pain and sensory complaints in multiple sclerosis.*Eur J Neurol*; Jul 2004.

503. Stenager, E., Knudsen, L., Jensen, K. Acute and chronic pain syndromes in multiple sclerosis. A 5-year follow-up study.*Ital J Neurol Sci*; Dec 1995.

504. Glennie, R. A., Ailon, T., Yang, K., Batke, J., Fisher, C. G., Dvorak, M. F., Vaccaro, A. R., Fehlings, M. G., Arnold, P., Harrop, J. S., Street, J. T. Incidence, impact, and risk factors of adverse events in thoracic and lumbar spine fractures: an ambispective cohort analysis of 390 patients.*Spine J*; Apr 1 2015.

505. Saulino, M. Spinal cord injury pain.*Phys Med Rehabil Clin N Am*; May 2014.

506. Sjolund, B. H. Pain and rehabilitation after spinal cord injury: the case of sensory spasticity?.*Brain Res Brain Res Rev*; Oct 2002.

507. Paolucci T, Zangrando F,Iosa M,et al. Improved interoceptive awareness in chronic low back pain: a comparison of Back school versus Feldenkrais method.*Disabil Rehabil*; 2017.

508. Repp, K., Lorbeer, R., Ittermann, T., Glaser, S., John, U., Hoffmann, W., Volzke, H. Occupational exposure to asbestos is associated with increased mortality in men recruited for a population-based study in Germany.*Int J Occup Med Environ Health*; 2015.

509. Ferreccio, C., Yuan, Y., Calle, J., Benitez, H., Parra, R. L., Acevedo, J., Smith, A. H., Liaw, J., Steinmaus, C. Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer.*Epidemiology*; Nov 2013.

510. Rushton, L., Bagga, S., Bevan, R., Brown, T. P., Cherrie, J. W., Holmes, P., Fortunato, L., Slack, R., Van Tongeren, M., Young, C., Hutchings, S. J. Occupation and cancer in Britain.*Br J Cancer*; Apr 27 2010.

511. Lash, T. L., Crouch, E. A., Green, L. C. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer.*Occup Environ Med*; Apr 1997.

512. Takkouche, B., Gestal-Otero, J. J. The epidemiology of lung cancer: review of risk factors and Spanish data.*Eur J Epidemiol*; Aug 1996.

513. Jarvholm, B., Larsson, S., Hagberg, S., Olling, S., Ryd, W., Toren, K. Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: a case-referent study.*Eur Respir J*; Oct 1993.

514. Vineis, P., Simonato, L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach.*Arch Environ Health*; Jan-Feb 1991.

515. Talcott, J. A., Thurber, W. A., Kantor, A. F., Gaensler, E. A., Danahy, J. F., Antman, K. H., Li, F. P. Asbestos-associated diseases in a cohort of cigarette-filter workers.*N Engl J Med*; Nov 2 1989.

516. Steenland, K., Thun, M. Interaction between tobacco smoking and occupational exposures in the causation of lung cancer.*J Occup Med*; Feb 1986.

517. Hillerdal, G., Karlen, E., Aberg, T. Tobacco consumption and asbestos exposure in patients with lung cancer: a three year prospective study.*Br J Ind Med*; Nov 1983.

518. Meurman, L. O., Kiviluoto, R., Hakama, M. Combined effect of asbestos exposure and tobacco smoking on Finnish anthophyllite miners and millers.*Ann N Y Acad Sci*; 1979.

519. Bleecker, M. L. Toxic peripheral neuropathy. In Rom WN, ed. Environmental and Occupational Medicine. 4th ed.

520. Sullivan, J. B., Krieger, G. R., eds., . Clinical Environmental Health and Toxic Exposures. 2nd ed.2001.

521. Ligon, C. O., Moloney, R. D., Greenwood-Van Meerveld, B. Targeting Epigenetic Mechanisms for Chronic Pain: A Valid Approach for the Development of Novel Therapeutics.*J Pharmacol Exp Ther*; Apr 2016.

522. Momi, S. K., Fabiane, S. M., Lachance, G., Livshits, G., Williams, F. M. Neuropathic pain as part of chronic widespread pain: environmental and genetic influences.*Pain*; Oct 2015.

523. Latremoliere, A., Latini, A., Andrews, N., Cronin, S. J., Fujita, M., Gorska, K., Hovius, R., Romero, C., Chuaiphichai, S., Painter, M., Miracca, G., Babaniyi, O., Remor, A. P., Duong, K., Riva, P., Barrett, L. B., Ferreiros, N., Naylor, A., Penninger, J. M., Tegeder, I., Zhong, J., Blagg, J., Channon, K. M., Johnsson, K., Costigan, M., Woolf, C. J. Reduction of Neuropathic and Inflammatory Pain through Inhibition of the Tetrahydrobiopterin Pathway.*Neuron*; Jun 17 2015.

524. Oliveira-e-Silva, T., Campos Pinheiro, L., Rocha Mendes, J., Barroso, E., Monteiro Pereira, N. Peripheral polyneuropathy and female sexual dysfunction--familial amyloidotic polyneuropathy as an example besides diabetes mellitus.*J Sex Med*; Feb 2013.

525. Belfer, I., Segall, S. COMT genetic variants and pain.*Drugs Today (Barc)*; Jun 2011.

526. Auer-Grumbach, M. Hereditary sensory neuropathy type I.*Orphanet J Rare Dis*; 2008.

527. Hanewinckel, R., van Oijen, M., Ikram, M. A., van Doorn, P. A. The epidemiology and risk factors of chronic polyneuropathy.*Eur J Epidemiol*; Jan 2016.

528. Callaghan, B. C., Price, R. S., Feldman, E. L. Distal Symmetric Polyneuropathy: A Review.*JAMA*; Nov 24 2015.

529. Kazamel, M., Dyck, P. J. Sensory manifestations of diabetic neuropathies: anatomical and clinical correlations.*Prosthet Orthot Int*; Feb 2015.

530. Ziegler, D., Papanas, N., Vinik, A. I., Shaw, J. E. Epidemiology of polyneuropathy in diabetes and prediabetes.*Handb Clin Neurol*; 2014.

531. Lazo Mde, L., Bernabe-Ortiz, A., Pinto, M. E., Ticse, R., Malaga, G., Sacksteder, K., Miranda, J. J., Gilman, R. H. Diabetic peripheral neuropathy in ambulatory patients with type 2 diabetes in a general hospital in a middle income country: a cross-sectional study.*PLoS One*; 2014.

532. Boulton, A. J. Diabetic neuropathy and foot complications.*Handb Clin Neurol*; 2014.

533. Russell, J. W., Zilliox, L. A. Diabetic neuropathies.*Continuum (Minneap Minn)*; Oct 2014.

534. Ziegler, D. Current concepts in the management of diabetic polyneuropathy.*Curr Diabetes Rev*; May 2011.

535. Ziegler, D. Treatment of diabetic polyneuropathy: Update 2006.*Ann N Y Acad Sci*; Nov 2006.

536. Ferrari, L. F., Levine, J. D. Alcohol consumption enhances antiretroviral painful peripheral neuropathy by mitochondrial mechanisms.*Eur J Neurosci*; Sep 2010.

537. Koop, S. M., ten Klooster, P. M., Vonkeman, H. E., Steunebrink, L. M., van de Laar, M. A. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis.*Arthritis Res Ther*; 2015.

538. Xianbin, W., Mingyu, W., Dong, X., Huiying, L., Yan, X., Fengchun, Z., Xiaofeng, Z. Peripheral neuropathies due to systemic lupus erythematosus in China.*Medicine (Baltimore)*; Mar 2015.

539. Honczarenko, K., Budzianowska, A., Ostanek, L. Neurological syndromes in systemic lupus erythematosus and their association with antiphospholipid syndrome.*Neurol Neurochir Pol*; Nov-Dec 2008.

540. Forbes, H. J., Bhaskaran, K., Thomas, S. L., Smeeth, L., Clayton, T., Mansfield, K., Minassian, C., Langan, S. M. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study.*Neurology*; Jul 5 2016.

541. Takao, Y., Miyazaki, Y., Okeda, M., Onishi, F., Yano, S., Gomi, Y., Ishikawa, T., Okuno, Y., Mori, Y., Asada, H., Yamanishi, K., Iso, H. Incidences of Herpes Zoster and Postherpetic Neuralgia in Japanese Adults Aged 50 Years and Older From a Community-based Prospective Cohort Study: The SHEZ Study.*J Epidemiol*; 2015.

542. Bricout, H., Haugh, M., Olatunde, O., Prieto, R. G. Herpes zoster-associated mortality in Europe: a systematic review.*BMC Public Health*; 2015.

543. Reid, J. S., Ah Wong, B. Herpes zoster (shingles) at a large New Zealand general practice: incidence over 5 years.*N Z Med J*; Dec 19 2014.

544. Pica, F., Gatti, A., Divizia, M., Lazzari, M., Ciotti, M., Sabato, A. F., Volpi, A. One-year follow-up of patients with long-lasting post-herpetic neuralgia.*BMC Infect Dis*; 2014.

545. Weitzman, D., Shavit, O., Stein, M., Cohen, R., Chodick, G., Shalev, V. A population based study of the epidemiology of Herpes Zoster and its complications.*J Infect*; Nov 2013.

546. Kamerman, P. R., Wadley, A. L., Cherry, C. L. HIV-associated sensory neuropathy: risk factors and genetics.*Curr Pain Headache Rep*; Jun 2012.

547. Ellis, R. J., Rosario, D., Clifford, D. B., McArthur, J. C., Simpson, D., Alexander, T., Gelman, B. B., Vaida, F., Collier, A., Marra, C. M., Ances, B., Atkinson, J. H., Dworkin, R. H., Morgello, S., Grant, I., Group, Charter,Study. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study.*Arch Neurol*; May 2010.

548. Werner, R. N., Nikkels, A. F., Marinovic, B., Schafer, M., Czarnecka-Operacz, M., Agius, A. M., Bata-Csorgo, Z., Breuer, J., Girolomoni, G., Gross, G. E., Langan, S., Lapid-Gortzak, R., Lesser, T. H., Pleyer, U., Sellner, J., Verjans, G. M., Wutzler, P., Dressler, C., Erdmann, R., Rosumeck, S., Nast, A. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment.*J Eur Acad Dermatol Venereol*; Aug 31 2016.

549. Raicher, I., Stump, P. R., Baccarelli, R., Marciano, L. H., Ura, S., Virmond, M. C., Teixeira, M. J., Ciampi de Andrade, D. Neuropathic pain in leprosy.*Clin Dermatol*; Jan-Feb 2016.

550. Yelland, M. J., Poulos, C. J., Pillans, P. I., Bashford, G. M., Nikles, C. J., Sturtevant, J. M., Vine, N., Del Mar, C. B., Schluter, P. J., Tan, M., Chan, J., Mackenzie, F., Brown, R. N-of-1 randomized trials to assess the efficacy of gabapentin for chronic neuropathic pain.*Pain Med*; May-Jun 2009.

551. Majithia, N., Temkin, S. M., Ruddy, K. J., Beutler, A. S., Hershman, D. L., Loprinzi, C. L. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons.*Support Care Cancer*; Mar 2016.

552. Beijers, A. J., Vreugdenhil, G., Oerlemans, S., Eurelings, M., Minnema, M. C., Eeltink, C. M., van de Poll-Franse, L. V., Mols, F. Chemotherapy-induced neuropathy in multiple myeloma: influence on quality of life and development of a questionnaire to compose common toxicity criteria grading for use in daily clinical practice.*Support Care Cancer*; Jun 2016.

553. Davies, M., Brophy, S., Williams, R., Taylor, A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes.*Diabetes Care*; Jul 2006.

554. Dyck, P. J., Kratz, K. M., Karnes, J. L., Litchy, W. J., Klein, R., Pach, J. M., Wilson, D. M., O'Brien, P. C., Melton, L. J.,3rd, Service, F. J. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study.*Neurology*; Apr 1993.

555. Gordh, T. E., Stubhaug, A., Jensen, T. S., Arner, S., Biber, B., Boivie, J., Mannheimer, C., Kalliomaki, J., Kalso, E. Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study.*Pain*; Aug 31 2008.

556. Neghab, M., Soleimani, E., Khamoushian, K. Electrophysiological studies of shoemakers exposed to sub-TLV levels of n-hexane.*J Occup Health*; 2012.

557. Kutlu, G., Gomceli, Y. B., Sonmez, T., Inan, L. E. Peripheral neuropathy and visual evoked potential changes in workers exposed to n-hexane.*J Clin Neurosci*; Oct 2009.

558. Sendur, O. F., Turan, Y., Bal, S., Gurgan, A. Toxic neuropathy due to N-hexane: report of three cases.*Inhal Toxicol*; Feb 2009.

559. Huang, C. C. Polyneuropathy induced by n-hexane intoxication in Taiwan.*Acta Neurol Taiwan*; Mar 2008.

560. Misirli, H., Domac, F. M., Somay, G., Araal, O., Ozer, B., Adiguzel, T. N-hexane induced polyneuropathy: a clinical and electrophysiological follow up.*Electromyogr Clin Neurophysiol*; Mar 2008.

561. Puri, V., Chaudhry, N., Tatke, M. N-hexane neuropathy in screen printers.*Electromyogr Clin Neurophysiol*; May-Jun 2007.

562. Centers for Disease, Control, Prevention, . n-Hexane-related peripheral neuropathy among automotive technicians--California, 1999-2000.*MMWR Morb Mortal Wkly Rep*; Nov 16 2001.

563. Paulson, G. W., Waylonis, G. W. Polyneuropathy due to n-hexane.*Arch Intern Med*; Aug 1976.

564. Yu, S. F., Wei, X. M., Yan, F. F., Wang, S. E., Zhang, C. L., Yang, X. W. The Role of NF mRNA and Calpain in NF Reduction of Acrylamide Neuropathy.*Biomed Environ Sci*; Jun 2015.

565. Calleman, C. J., Wu, Y., He, F., Tian, G., Bergmark, E., Zhang, S., Deng, H., Wang, Y., Crofton, K. M., Fennell, T., et al., . Relationships between biomarkers of exposure and neurological effects in a group of workers exposed to acrylamide.*Toxicol Appl Pharmacol*; Jun 1994.

566. Bachmann, M., Myers, J. E., Bezuidenhout, B. N. Acrylamide monomer and peripheral neuropathy in chemical workers.*Am J Ind Med*; 1992.

567. Sinczuk-Walczak, H., Janasik, B. M., Trzcinka-Ochocka, M., Stanislawska, M., Szymczak, M., Halatek, T., Walusiak-Skorupa, J. Neurological and neurophysiological examinations of workers exposed to arsenic levels exceeding hygiene standards.*Int J Occup Med Environ Health*; Dec 2014.

568. Sinczuk-Walczak, H., Szymczak, M., Halatek, T. Effects of occupational exposure to arsenic on the nervous system: clinical and neurophysiological studies.*Int J Occup Med Environ Health*; 2010.

569. Barton, A., McLean, B. An unusual case of peripheral neuropathy possibly due to arsenic toxicity secondary to excessive intake of dietary supplements.*Ann Clin Biochem*; Sep 2013.

570. Singh, G. D., Garcia-Motta, A. V., Hang, W. M. Evaluation of the posterior airway space following Biobloc therapy: geometric morphometrics.*Cranio*; Apr 2007.

571. Tseng, H. P., Wang, Y. H., Wu, M. M., The, H. W., Chiou, H. Y., Chen, C. J. Association between chronic exposure to arsenic and slow nerve conduction velocity among adolescents in Taiwan.*J Health Popul Nutr*; Jun 2006.

572. Fujino, Y., Guo, X., Shirane, K., Liu, J., Wu, K., Miyatake, M., Tanabe, K., Kusuda, T., Yoshimura, T., Japan Inner Mongolia Arsenic Pollution Study, Group. Arsenic in drinking water and peripheral nerve conduction velocity among residents of a chronically arsenic-affected area in Inner Mongolia.*J Epidemiol*; Sep 2006.

573. Baker, B. A., Topliff, A. R., Messing, R. B., Durkin, D., Johnson, J. S. Persistent neuropathy and hyperkeratosis from distant arsenic exposure.*J Agromedicine*; 2005.

574. Gerr, F., Letz, R. Epidemiological case definitions of peripheral neuropathy: experience from two neurotoxicity studies.*Neurotoxicology*; Oct 2000.

575. Gerr, F., Letz, R., Ryan, P. B., Green, R. C. Neurological effects of environmental exposure to arsenic in dust and soil among humans.*Neurotoxicology*; Aug 2000.

576. Lagerkvist, B. J., Zetterlund, B. Assessment of exposure to arsenic among smelter workers: a five-year follow-up.*Am J Ind Med*; Apr 1994.

577. Rao, D. B., Jortner, B. S., Sills, R. C. Animal models of peripheral neuropathy due to environmental toxicants.*ILAR J*; 2014.

578. Gelbke, H. P., Goen, T., Maurer, M., Sulsky, S. I. A review of health effects of carbon disulfide in viscose industry and a proposal for an occupational exposure limit.*Crit Rev Toxicol*; Oct 2009.

579. Godderis, L., Braeckman, L., Vanhoorne, M., Viaene, M. Neurobehavioral and clinical effects in workers exposed to CS(2).*Int J Hyg Environ Health*; Mar 2006.

580. Huang, C. C., Chu, C. C., Wu, T. N., Shih, T. S., Chu, N. S. Clinical course in patients with chronic carbon disulfide polyneuropathy.*Clin Neurol Neurosurg*; May 2002.

581. Reinhardt, F., Drexler, H., Bickel, A., Claus, D., Angerer, J., Ulm, K., Lehnert, G., Neundorfer, B. Neurotoxicity of long-term low-level exposure to carbon disulphide: results of questionnaire, clinical neurological examination and neuropsychological testing.*Int Arch Occup Environ Health*; 1997.

582. Reinhardt, F., Drexler, H., Bickel, A., Claus, D., Ulm, K., Angerer, J., Lehnert, G., Neundorfer, B. Electrophysiological investigation of central, peripheral and autonomic nerve function in workers with long-term low-level exposure to carbon disulphide in the viscose industry.*Int Arch Occup Environ Health*; 1997.

583. Chu, C. C., Huang, C. C., Chu, N. S., Wu, T. N. Carbon disulfide induced polyneuropathy: sural nerve pathology, electrophysiology, and clinical correlation.*Acta Neurol Scand*; Oct 1996.

584. Hirata, M., Ogawa, Y., Goto, S. A cross-sectional study on nerve conduction velocities among workers exposed to carbon disulphide.*Med Lav*; Jan-Feb 1996.

585. Ruijten, M. W., Salle, H. J., Verberk, M. M. Verification of effects on the nervous system of low level occupational exposure to CS2.*Br J Ind Med*; Apr 1993.

586. Aaserud, O., Hommeren, O. J., Tvedt, B., Nakstad, P., Mowe, G., Efskind, J., Russell, D., Jorgensen, E. B., Nyberg-Hansen, R., Rootwelt, K., et al., . Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers.*Am J Ind Med*; 1990.

587. Grasso, P. Neurotoxic and neurobehavioral effects of organic solvents on the nervous system.*Occup Med*; Jul-Sep 1988.

588. Gilron, I., Baron, R., Jensen, T. Neuropathic pain: principles of diagnosis and treatment.*Mayo Clin Proc*; Apr 2015.

589. Baker, E. L., Feldman, R. G., White, R. A., Harley, J. P., Niles, C. A., Dinse, G. E., Berkey, C. S. Occupational lead neurotoxicity: a behavioural and electrophysiological evaluation. Study design and year one results.*Br J Ind Med*; Aug 1984.

590. Bordo, B., Massetto, N., Musicco, M., Filippini, G., Boeri, R. Electrophysiologic changes in workers with "low" blood lead levels.*Am J Ind Med*; 1982.

591. Melgaard, B., Clausen, J., Rastogi, S. C. Heavy metal levels and delta-amino-levulinic acid dehydrase levels in peripheral polyneuropathy.*Acta Neurol Scand*; Apr 1976.

592. Seppalainen, A. M., Hernberg, S. Sensitive technique for detecting subclinical lead neuropathy.*Br J Ind Med*; Oct 1972.

593. Seppalainen, A. M. Lead poisoning: neurophysiological aspects.*Acta Neurol Scand Suppl*; 1982.

594. Catton, M. J., Harrison, M. J., Fullerton, P. M., Kazantzis, G. Subclinical neuropathy in lead workers.*Br Med J*; Apr 11 1970.

595. Franzblau, A., d'Arcy, H., Ishak, M. B., Werner, R. A., Gillespie, B. W., Albers, J. W., Hamann, C., Gruninger, S. E., Chou, H. N., Meyer, D. M. Low-level mercury exposure and peripheral nerve function.*Neurotoxicology*; Jun 2012.

596. Kazantzis, G. Mercury exposure and early effects: an overview.*Med Lav*; May-Jun 2002.

597. Letz, R., Gerr, F., Cragle, D., Green, R. C., Watkins, J., Fidler, A. T. Residual neurologic deficits 30 years after occupational exposure to elemental mercury.*Neurotoxicology*; Aug 2000.

598. Beyaz, S. G., Ozocak, H., Ergonenc, T., Palabyk, O., Tuna, A. T., Kaya, B., Erkorkmaz, U., Akdemir, N. Chronic postsurgical pain and neuropathic symptoms after abdominal hysterectomy: A silent epidemic.*Medicine (Baltimore)*; Aug 2016.

599. Razmjou, H., Boljanovic, D., Wright, S., Murnaghan, J., Holtby, R. Association between Neuropathic Pain and Reported Disability after Total Knee Arthroplasty.*Physiother Can*; Fall 2015.

600. Mauck, M., Van de Ven, T., Shaw, A. D. Epigenetics of chronic pain after thoracic surgery.*Curr Opin Anaesthesiol*; Feb 2014.

601. Murphy D, Lester D,Clay S,Balakhanlou,E. Peripheral neuropathic pain.*NeuroRehabilitation*; 2020.

602. Lehmann, Helmar C, Wunderlich, Gilbert, Fink, Gereon R, Sommer, Claudia. Diagnosis of peripheral neuropathy.*Neurological research and practice*; 2020.

603. Finnerup NB, Kuner R,Jensen TS. Neuropathic Pain: From Mechanisms to Treatment.*Physiol Rev*; 2021.

604. Fordham B, Ji C,Hansen Z,Lall R,Lamb SE. Explaining How Cognitive Behavioral Approaches Work for Low Back Pain: Mediation Analysis of the Back Skills Training Trial.*Spine (Phila Pa 1976)*; 2017.

605. Hansen Z, Daykin A,Lamb SE. A cognitive-behavioural programme for the management of low back pain in primary care: a description and justification of the intervention used in the Back Skills Training Trial (BeST; ISRCTN 54717854).*Physiotherapy*; 2010.

606. Lamb SE, Mistry D,Lall R,et al. Group cognitive behavioural interventions for low back pain in primary care: extended follow-up of the Back Skills Training Trial (ISRCTN54717854).*Pain*; 2012.

607. Richmond H, Hall AM Hansen Z et al. Exploring physiotherapists experiences of implementing a cognitive behavioural approach for managing low back pain and identifying barriers to long-term implementation.*Physiotherapy*; 2018.

608. Sugavanam T, Williamson E,Fordham B,et al. Evaluation of the implementation of the Back Skills Training (BeST) programme using online training: a cohort implementation study.*Physiotherapy*; 2020.

609. Lamb SE, Lall R,Hansen Z,et al. A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial.*Health Technol Assess*; 2010.

610. World Health Organisation, WHO. Package of interventions for rehabilitation. Module 2: Musculoskeletal conditions.2023.

611. Main CJ, Sowden G Hill JC et al. Integrating physical and psychological approaches to treatment in low back pain: the development and content of the STarT Back trial high-risk intervention (StarT Back; ISRCTN 37113406).*Physiotherapy*; 2012.

612. Whitehurst DG, Bryan S,Lewis M,et al. Exploring the cost-utility of stratified primary care management for low back pain compared with current best practice within risk-defined subgroups.*Ann Rheum Dis*; 2012.

613. Hay EM, Dunn KM,Hill JC,et al. A randomised clinical trial of subgrouping and targeted treatment for low back pain compared with best current care. The STarT Back Trial Study Protocol.*BMC Musculoskelet Disord*; 2008.

614. O'Keeffe M, O'Sullivan P,Purtill H,et al. Cognitive functional therapy compared with a group-based exercise and education intervention for chronic low back pain: a multicentre randomised controlled trial (RCT).*Br J Sports Med*; 2020.

615. Newton C, Singh G,Nolan D,et al. Cognitive Functional Therapy compared with usual physiotherapy care in people with persistent low back pain: a mixed methods feasibility randomised controlled trial in the United Kingdom National Health Service.*Physiotherapy*; 2024.

616. Castro J, Correia L,Donato BS,et al. Cognitive functional therapy compared with core exercise and manual therapy in patients with chronic low back pain: randomised controlled trial.*Pain*; 2022.

617. O'Sullivan K, Dankaerts W,O'Sullivan L,et al. Cognitive Functional Therapy for Disabling Nonspecific Chronic Low Back Pain: Multiple Case-Cohort Study.*Phys Ther*; 2015.

618. Zhang J, Jiang N,Xu H,et al. Efficacy of cognitive functional therapy in patients with low back pain: A systematic review and meta-analysis.*Int J Nurs Stud*; 2024.

619. Kent P, Haines T,O'Sullivan P,et al. Cognitive functional therapy with or without movement sensor biofeedback versus usual care for chronic, disabling low back pain (RESTORE): a randomised, controlled, three-arm, parallel group, phase 3, clinical trial.*Lancet*; 2023.

620. Ahmad SNS, Letafatkar A,Brewer BW,et al. Comparison of cognitive functional therapy and movement system impairment treatment in chronic low back pain patients: a randomized controlled trial.*BMC Musculoskelet Disord*; 2023.

621. Avila L, da Silva MD,Neves ML,et al. Effectiveness of Cognitive Functional Therapy Versus Core Exercises and Manual Therapy in Patients With Chronic Low Back Pain After Spinal Surgery: Randomized Controlled Trial.*Phys Ther*; 2024.

622. Vibe Fersum, K., Smith, A., Kvåle, A., Skouen, J. S., O'Sullivan, P. Cognitive functional therapy in patients with non-specific chronic low back pain-a randomized controlled trial 3-year follow-up.*Eur J Pain*; Sep 2019.

623. Devonshire JJ, Wewege MA,Hansford HJ,et al. Effectiveness of Cognitive Functional Therapy for Reducing Pain and Disability in Chronic Low Back Pain: A Systematic Review and Meta-analysis.*J Orthop Sports Phys Ther*; 2023.

624. Vibe Fersum, K.,et al. Efficacy of classification-based cognitive functional therapy in patients with non-specific chronic low back pain: A randomized controlled trial.*European journal of pain*; 2013.

625. O'Sullivan PB, Caneiro JP,O'Keeffe M,et al. Cognitive Functional Therapy: An Integrated Behavioral Approach for the Targeted Management of Disabling Low Back Pain.*Phys Ther*; 2018.

626. Avila L, Neves ML,Abreu AR,et al. Cognitive functional therapy (CFT) compared with core training exercise (CTE) in patients with failed back surgery syndrome (FBSS): A study protocol for a randomized controlled trial.*J Bodyw Mov Ther*; 2021.

627. Javdaneh N, Letafatkar A,Shojaedin S,et al. Scapular exercise combined with cognitive functional therapy is more effective at reducing chronic neck pain and kinesiophobia than scapular exercise alone: a randomized controlled trial.*Clin Rehabil*; 2020.

628. Vaegter HB, Ussing K,Johansen JV,et al. Improvements in clinical pain and experimental pain sensitivity after cognitive functional therapy in patients with severe persistent low back pain.*Pain Rep*; 2019.

629. (METRC), Major,Extremity,Trauma,Research,Consortium. Cognitive-Behavioral-Based Physical Therapy for Improving Recovery After a Traumatic Lower-Extremity Injury: The Results of a Randomized Controlled Trial.*J Bone Joint Surg Am*; 2024.

630. Beneciuk JM, George SZ,Greco CM,et al. Targeted interventions to prevent transitioning from acute to chronic low back pain in high-risk patients: development and delivery of a pragmatic training course of psychologically informed physical therapy for the TARGET trial.*Trials*; 2019.

631. Clark H, Bassett S,Siegert R. The effectiveness of web-based patient education and action and coping plans as an adjunct to patient treatment in physiotherapy: A randomized controlled trial.*Physiother Theory Pract*; 2019.

632. GP, Bostick. Effectiveness of psychological interventions delivered by non-psychologists on low back pain and disability: a qualitative systematic review.*Spine J*; 2017.

633. Godfrey, Emma, Wileman, Vari, Galea Holmes, Melissa, McCracken, Lance M., Norton, Sam, Moss-Morris, Rona, Noonan, Sandra, Barcellona, Massimo, Critchley, Duncan. Physical Therapy Informed by Acceptance and Commitment Therapy (PACT) Versus Usual Care Physical Therapy for Adults With Chronic Low Back Pain: A Randomized Controlled Trial.*The Journal of Pain*; 2020.

634. Miller J, MacDermid JC,Walton DM,et al. Chronic Pain Self-Management Support With Pain Science Education and Exercise (COMMENCE) for People With Chronic Pain and Multiple Comorbidities: A Randomized Controlled Trial.*Arch Phys Med Rehabil*; 2020.

635. Petrozzi MJ, Spencer G,Mackey MG. A process evaluation of the Mind Your Back trial examining psychologically informed physical treatments for chronic low back pain.*Chiropr Man Therap*; 2021.

636. Coronado RA, Ehde DM,Pennings JS,et al. Psychosocial Mechanisms of Cognitive-Behavioral-Based Physical Therapy Outcomes After Spine Surgery: Preliminary Findings From Mediation Analyses.*Phys Ther*; 2020.

637. Heymans, M. W., van Tulder, M. W., Esmail, R., Bombardier, C., Koes, B. W. Back schools for nonspecific low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group.*Spine (Phila Pa 1976)*; Oct 1 2005.

638. M, Revel. Rehabilitation of low back pain patients. A review.*Rev Rhum Engl Ed*; 1995.

639. Bendix, A. F., Bendix, T., Vaegter, K., Lund, C., Frolund, L., Holm, L. Multidisciplinary intensive treatment for chronic low back pain: a randomized, prospective study.*Cleve Clin J Med*; Jan-Feb 1996.

640. Linton, S.J. and M. Ryberg. A cognitive-behavioral group intervention as prevention for persistent neck and back pain in a non-patient population: a randomized controlled trial.*Pain*; 2001.

641. Jordan, A., Bendix, T., Nielsen, H., Hansen, F. R., Host, D., Winkel, A. Intensive training, physiotherapy, or manipulation for patients with chronic neck pain. A prospective, single-blinded, randomized clinical trial.*Spine*; Feb 1 1998.

642. American Physical Therapy Association, . Guidelines: Occupational Health Physical Therapy: Work Conditioning and Work Hardening Programs.

643. Chou R, Atlas SJ,Stanos SP,Rosenquist RW. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline.*Spine (Phila Pa 1976)*; 2009.

644. Guzman, J., Esmail, R., Karjalainen, K., Malmivaara, A., Irvin, E., Bombardier, C. Multidisciplinary rehabilitation for chronic low back pain: systematic review.*Bmj*; Jun 23 2001.

645. Guzmán J, Esmail R,Karjalainen K,Malmivaara A,Irvin E,Bombardier C. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain.*Cochrane Database Syst Rev*; 2002.

646. Karjalainen, K., Malmivaara, A., van Tulder, M., Roine, R., Jauhiainen, M., Hurri, H., Koes, B. Multidisciplinary biopsychosocial rehabilitation for subacute low back pain in working-age adults: a systematic review within the framework of the Cochrane Collaboration Back Review Group.*Spine*; Feb 1 2001.

647. Karppinen J, Shen FH,Luk KD,Andersson GB,Cheung KM,Samartzis D. Management of degenerative disk disease and chronic low back pain.*Orthop Clin North Am*; 2011.

648. Norlund A, Ropponen A,Alexanderson K. Multidisciplinary interventions: review of studies of return to work after rehabilitation for low back pain.*J Rehabil Med*; 2009.

649. Ravenek, Michael J, Hughes, Ian D, Ivanovich, Nathan, Tyrer, Kevin, Desrochers, Christopher, Klinger, Lisa, Shaw, Lynn. A systematic review of multidisciplinary outcomes in the management of chronic low back pain.*Work*; 2010.

650. Scascighini L, Toma V,Dober-Spielmann S,Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes.*Rheumatology (Oxford)*; 2008.

651. van Middelkoop M, Rubinstein SM,Kuijpers T,Verhagen AP,Ostelo R,Koes BW,van Tulder MW. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain.*Eur Spine J*; 2011.

652. Williams RM, Westmorland MG,Lin CA,Schmuck G,Creen M. Effectiveness of workplace rehabilitation interventions in the treatment of work-related low back pain: a systematic review.*Disabil Rehabil*; 2007.

653. van Geen JW, Edelaar MJ,Janssen M,van Eijk JT. The long-term effect of multidisciplinary back training: a systematic review.*Spine (Phila Pa 1976)*; 2007.

654. Cutforth G, Peter A,Taenzer P. The Alberta Health Technology Assessment (HTA) Ambassador Program: The Development of a Contextually Relevant, Multidisciplinary Clinical Practice Guideline for Non-specific Low Back Pain: A Review.*Physiother Can*; 2011.

655. Kool, J. P., Oesch, P. R., Bachmann, S., Knuesel, O., Dierkes, J. G., Russo, M., de Bie, R. A., van den Brandt, P. A. Increasing days at work using function-centered rehabilitation in nonacute nonspecific low back pain: a randomized controlled trial.*Arch Phys Med Rehabil*; May 2005.

656. Anema, J.R.,et al. Multidisciplinary rehabilitation for subacute low back pain: graded activity or workplace intervention or both? A randomized controlled trial.*Spine*; 2007.

657. Loisel P, Abenhaim L,Durand P,et al. A population-based, randomized clinical trial on back pain management.*Spine*; 1997.

658. Connell, Natalie B, Prathivadi, Pallavi, Lorenz, Karl A, Zupanc, Sophia N, Singer, Sara J, Krebs, Erin E, Yano, Elizabeth M, Wong, Hong-nei, Giannitrapani, Karleen F. Teaming in interdisciplinary chronic pain management interventions in primary care: a systematic review of randomized controlled trials.*Journal of general internal medicine*; 2022.

659. Lewis, Gwyn N, Bean, Debbie J. What Influences Outcomes From Inpatient Multidisciplinary Pain Management Programs?: A Systematic Review and Meta-analysis.*The Clinical Journal of Pain*; 2021.

660. Roelofs, Jeffrey, Goubert, Liesbet, Peters, Madelon L, Vlaeyen, Johan WS, Crombez, Geert. The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia.*European Journal of Pain*; 2004.

661. Coppieters, I., Meeus, M., Kregel, J., Caeyenberghs, K., De Pauw, R., Goubert, D., Cagnie, B. Relations Between Brain Alterations and Clinical Pain Measures in Chronic Musculoskeletal Pain: A Systematic Review.*J Pain*; Sep 2016.

662. Martucci, K. T., Mackey, S. C. Imaging Pain.*Anesthesiol Clin*; Jun 2016.

663. Schmidt-Wilcke, T. Neuroimaging of chronic pain.*Best Pract Res Clin Rheumatol*; Feb 2015.

664. Kregel, J., Meeus, M., Malfliet, A., Dolphens, M., Danneels, L., Nijs, J., Cagnie, B. Structural and functional brain abnormalities in chronic low back pain: A systematic review.*Semin Arthritis Rheum*; Oct 2015.

665. Crombez G, De Paepe AL,Veirman E,et al. Let's talk about pain catastrophizing measures: an item content analysis.*PeerJ*; 2020.

666. Bordeleau, Martine, Vincenot, Matthieu, Lefevre, Salomé, Duport, Arnaud, Seggio, Lucas, Breton, Tomy, Lelard, Thierry, Serra, Eric, Roussel, Nathalie, Neves, Jeremy Fonseca Das. Treatments for kinesiophobia in people with chronic pain: A scoping review.*Frontiers in behavioral neuroscience*; 2022.

667. Andersson, G. B. Epidemiological features of chronic low-back pain.*Lancet*; Aug 14 1999.

668. Atkinson, J. H., Slater, M. A., Patterson, T. L., Grant, I., Garfin, S. R. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study.*Pain*; May 1991.

669. Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., Borges, G. L., Bromet, E. J., Demytteneare, K., de Girolamo, G., de Graaf, R., Gureje, O., Lepine, J. P., Haro, J. M., Levinson, D., Oakley Browne, M. A., Posada-Villa, J., Seedat, S., Watanabe, M. Common

chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders.*J Pain*; Oct 2008.

670. Currie, S. R., Wang, J. Chronic back pain and major depression in the general Canadian population.*Pain*; Jan 2004.

671. Matheve T1, Brumagne S,Timmermans AA. The Effectiveness of Technology-Supported Exercise Therapy for Low Back Pain: A Systematic Review.*Am J Phys Med Rehabil.*; 2016.

672. Weeks, Douglas L, Whitney, Anthony A, Tindall, Angelique G, Carter, Gregory T. Pilot Randomized Trial Comparing Intersession Scheduling of Biofeedback Results to Individuals with Chronic Pain: Influence on Psychologic Function and Pain Intensity.*American Journal of Physical Medicine & Rehabilitation*; 2015.

673. Buckelew, S. P., Conway, R., Parker, J., Deuser, W. E., Read, J., Witty, T. E., Hewett, J. E., Minor, M., Johnson, J. C., Van Male, L., McIntosh, M. J., Nigh, M., Kay, D. R. Biofeedback/relaxation training and exercise interventions for fibromyalgia: a prospective trial.*Arthritis Care Res*; Jun 1998.

674. Sarnoch, H., Adler, F., Scholz, O. B. Relevance of muscular sensitivity, muscular activity, and cognitive variables for pain reduction associated with EMG biofeedback in fibromyalgia.*Percept Mot Skills*; Jun 1997.

675. Theadom, A., Cropley, M., Smith, H. E., Feigin, V. L., McPherson, K. Mind and body therapy for fibromyalgia.*Cochrane Database Syst Rev*; 2015.

676. Wellington, J. Noninvasive and alternative management of chronic low back pain (efficacy and outcomes).*Neuromodulation*; Oct 2014.

677. Glombiewski JA, Bernardy K,Häuser W. Efficacy of EMG- and EEG-Biofeedback in Fibromyalgia Syndrome: A Meta-Analysis and a Systematic Review of Randomized Controlled Trials.*Evid Based Complement Alternat Med.*; 2013.

678. Sturmberg C, Marquez J,Heneghan N,Snodgrass S,van Vliet P. Attentional focus of feedback and instructions in the treatment of musculoskeletal dysfunction: a systematic review.*Man Ther*; 2013.

679. Collins NJ, Bisset LM,Crossley KM,Vicenzino B. Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials.*Sports Medicine*; 2012.

680. Ozkan, O., Yildiz, M., Arslan, E., Yildiz, S., Bilgin, S., Akkus, S., Koyuncuoglu, H. R., Koklukaya, E. A Study on the Effects of Sympathetic Skin Response Parameters in Diagnosis of Fibromyalgia Using Artificial Neural Networks.*J Med Syst*; Mar 2016.

681. Kapitza, Karl Peter, Passie, Torsten, Bernateck, Michael, Karst, Matthias. First non-contingent respiratory biofeedback placebo versus contingent biofeedback in patients with chronic low back pain: a randomized, controlled, double-blind trial.*Applied psychophysiology and biofeedback*; 2010.

682. Donaldson, S., ROmney, D., DOnaldson, M., Skubick, D. Randomized study of the application of single motor unit biofeedback training to chronic low back pain.*J Occup Rehabil*; 1994.

683. Rondinelli, R. Guides to the Evaluation of Permanent Impairment. 6th ed.2008.

684. Sanders, S. H., Harden, R. N., Vicente, P. J. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients.*Pain Pract*; Dec 2005.

685. Kumar, K., Hunter, G., Demeria, D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience.*Neurosurgery*; Mar 2006.

686. Lee, A. W., Pilitsis, J. G. Spinal cord stimulation: indications and outcomes.*Neurosurg Focus*; 2006.

687. Segal, R., Stacey, B. R., Rudy, T. E., Baser, S., Markham, J. Spinal cord stimulation revisited.*Neurol Res*; Jul 1998.

688. Taylor, A. G., Anderson, J. G., Riedel, S. L., Lewis, J. E., Kinser, P. A., Bourguignon, C. Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia.*Pain Manag Nurs*; Dec 2013.

689. Bruns, D. Clinical and forensic standards for the psychological assessment of patients with chronic pain.*Psychological Injury and Law*; 2014.

690. American Educational Research Association, American Psychological Association,National Council on Measurement in Education,Joint Committee on Standards for Educational and Psychological Testing. Standards for Educational and Psychological Testing.1999.

691. den Boer, JJ., Oostendorp, RA., Beems, T., Munneke, M., Oerlemans, M., Evers, AW. A systematic review of bio-psychosocial risk factors for an unfavorable outcome after lumbar disc surgery.*European Spine Journal*; 2006.

692. Bigos, S. J. et al. A longitudinal, prospective study of industrial back injury reporting.*Clin Orthop*; 1992.

693. Celestin, J.,Edwards,R. R.,and Jamison,R. N. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis.*Pain Medicine*; 2009.

694. Carragee, E. J,et al. Prospective controlled study of the development of lower back pain in previously asymptomatic subjects undergoing experimental discography.*Spine*; 2004.

695. ACOEM, American College of Occupational and Environmental Medicine. Methodology for Updates to the ACOEM Practice Guidelines.*www.acoem.org/guidelines_summary.aspx*; 2006.

696. Rosenberger, Patricia H. PhD, Jokl, Peter MD, Ickovics, Jeannette PhD. Psychosocial Factors and Surgical Outcomes: An Evidence-Based Literature Review.*Journal of the American Academy of Orthopaedic Surgeons*; 2006.

697. Gaudin D, Krafcik BM,Mansour TR,Alnemari A. Considerations in Spinal Fusion Surgery for Chronic Lumbar Pain: Psychosocial Factors, Rating Scales, and Perioperative Patient Education. A Review of the Literature.*World Neurosurg*; 2016.

698. Clancy C, Quinn A,Wilson F. The aetiologies of failed back surgery syndrome: A systematic review.*J Back Musculoskelet Rehabil*; 2016.

699. Nechanicka N, Barsa P,Harsa P. Psychosocial Factors in Patients Indicated for Lumbar Spinal Stenosis Surgery.*J Neurol Surg A Cent Eur Neurosurg.*; 2016.

700. Toth, C., Brady, S., Gagnon, F., Wigglesworth, K. A randomized, single-blind, controlled, parallel assignment study of exercise versus education as adjuvant in the treatment of peripheral neuropathic pain.*Clin J Pain*; Feb 2014.

701. Moore, R. A., Chi, C. C., Wiffen, P. J., Derry, S., Rice, A. S. Oral nonsteroidal anti-inflammatory drugs for neuropathic pain.*Cochrane Database Syst Rev*; 2015.

702. (CDC), Centers,for,Disease,Control,and,Prevention. Arthritis as a potential barrier to physical activity among adults with diabetes--United States, 2005 and 2007.*MMWR Morb Mortal Wkly Rep*; 2008.

703. Backonja, M. Anticonvulsants for the treatment of neuropathic pain syndromes.*Curr Pain Headache Rep*; Feb 2003.

704. Backonja, M. M., Serra, J. Pharmacologic management part 1: better-studied neuropathic pain diseases.*Pain Med*; Mar 2004.

705. Omer, SR., Ozcan, E., Karan, A., Ketenci, A. Musculoskeletal system disorders in computer users: Effectiveness of training and exercise programs.*J Back Musculoskeletal Rehabil*; 2003.

706. Esenyel, M., Aldemir, T., Gursoy, E., Esenyel, C. Z., Demir, S., Durmusoglu, G. Myofascial pain syndrome: efficacy of different therapies.*Journal of Back & Musculoskeletal Rehabilitation*; 2007.

707. Adams, E. H., Breiner, S., Cicero, T. J., Geller, A., Inciardi, J. A., Schnoll, S. H., Senay, E. C., Woody, G. E. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain.*J Pain Symptom Manage*; May 2006.

708. Ward, N., Bokan, J. A., Phillips, M., Benedetti, C., Butler, S., Spengler, D. Antidepressants in concomitant chronic back pain and depression: doxepin and desipramine compared.*J Clin Psychiatry*; Mar 1984.

709. Ward, N. G. Tricyclic antidepressants for chronic low-back pain. Mechanisms of action and predictors of response.*Spine*; Sep 1986.

710. Gobelet, C. [The role of calcitonin in the treatment of algoneurodystrophy].*Schweiz Rundsch Med Prax*; Jan 7 1986.

711. Hamamci, N., Dursun, E., Ural, C., Cakci, A. Calcitonin treatment in reflex sympathetic dystrophy: a preliminary study.*Br J Clin Pract*; Oct-Nov 1996.

712. Hanna, M. H., Peat, S. J. Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial.*Pain*; Aug 1989.

713. Valtonen, E. J. A controlled clinical trial of chlormezanone, orphenadrine, orphenadrine/paracetamol and placebo in the treatment of painful skeletal muscle spasms.*Ann Clin Res*; Apr 1975.

714. Pipino, F, Menarini, C, Lombardi, G, al., et. A direct myotonolytic (pridinol mesilate) for the management of chronic low back pain: a multicentre, comparative clinical evaluation.*Eur J Clin Res*; 1991.

715. Geertzen, J. H., de Bruijn, H., de Bruijn-Kofman, A. T., Arendzen, J. H. Reflex sympathetic dystrophy: early treatment and psychological aspects.*Arch Phys Med Rehabil*; Apr 1994.

716. Wang, K., Svensson, P., Arendt-Nielsen, L. Effect of acupuncture-like electrical stimulation on chronic tension-type headache: a randomized, double-blinded, placebo-controlled trial.*Clin J Pain*; May 2007.

717. DiLorenzo, L., Traballesi, M., Morelli, D., Pompa, A., Brunelli, S., Buzzi, M. G., Formisano, R. Hemiparetic shoulder pain syndrome treated with deep dry needling during early rehabilitation: a prospective, open-label, randomized investigation.*Journal of Musculoskeletal Pain*; 2004.

718. He, D., Hostmark, A. T., Veiersted, K. B., Medbo, J. I. Effect of intensive acupuncture on pain-related social and psychological variables for women with chronic neck and shoulder pain--an RCT with six month and three year follow up.*Acupunct Med*; Jun 2005.

719. Ilbuldu, E., Cakmak, A., Disci, R., Aydin, R. Comparison of laser, dry needling, and placebo laser treatments in myofascial pain syndrome.*Photomed Laser Surg*; Aug 2004.

720. Ceccherelli, F., Rigoni, M. T., Gagliardi, G., Ruzzante, L. Comparison of superficial and deep acupuncture in the treatment of lumbar myofascial pain: a double-blind randomized controlled study.*Clin J Pain*; May-Jun 2002.

721. Berlin, J., Erdman, W., David, E. Psychosomatic correlations in chronic pain patients using electroacupuncture.*The American Journal Of Chinese Medicine*; 1989.

722. Walach, H., Guthlin, C., Konig, M. Efficacy of massage therapy in chronic pain: a pragmatic randomized trial.*J Altern Complement Med*; Dec 2003.

723. Plews-Ogan, M., Owens, J. E., Goodman, M., Wolfe, P., Schorling, J. A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain.*J Gen Intern Med*; Dec 2005.

724. Mannheimer, C., Lund, S., Carlsson, C. A. The effect of transcutaneous electrical nerve stimulation (TNS) on joint pain in patients with rheumatoid arthritis.*Scand J Rheumatol*; 1978.

725. Lundeberg, T. The pain suppressive effect of vibratory stimulation and transcutaneous electrical nerve stimulation (TENS) as compared to aspirin.*Brain Res*; Mar 5 1984.

726. Yokoyama, M., Itano, Y., Kusume, Y., Oe, K., Mizobuchi, S., Morita, K. Total spinal anesthesia provides transient relief of intractable pain.*Can J Anaesth*; Oct 2002.

727. Petersen, P., Kastrup, J., Zeeberg, I., Boysen, G. Chronic pain treatment with intravenous lidocaine.*Neurol Res*; Sep 1986.

728. Bonelli, S., Conoscente, F., Movilia, P. G., Restelli, L., Francucci, B., Grossi, E. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial.*Pain*; Jul 1983.

729. Strong, J. Incorporating cognitive-behavioral therapy with occupational therapy: a comparative study with patients with low back pain.*J Occup Rehabil*; 1998.

730. Turner, J. A., Clancy, S. Comparison of operant behavioral and cognitive-behavioral group treatment for chronic low back pain.*J Consult Clin Psychol*; Apr 1988.

731. Corey, David T., Koepfler, Louise E., Etlin, David, Day, H. I. A limited functional restoration program for injured workers: A randomized trial.*Journal of Occupational Rehabilitation*; 1996.

732. van den Hout, J. H., Vlaeyen, J. W., Heuts, P. H., Zijlema, J. H., Wijnen, J. A. Secondary prevention of work-related disability in nonspecific low back pain: does problem-solving therapy help? A randomized clinical trial.*Clin J Pain*; Mar-Apr 2003.

733. Flor, H., Birbaumer, N. Comparison of the efficacy of electromyographic biofeedback, cognitive-behavioral therapy, and conservative medical interventions in the treatment of chronic musculoskeletal pain.*J Consult Clin Psychol*; Aug 1993.

734. McCauley, J. D., Thelen, M. H., Frank, R. G., Willard, R. R., Callen, K. E. Hypnosis compared to relaxation in the outpatient management of chronic low back pain.*Arch Phys Med Rehabil*; Nov 1983.

735. Basler, H. D., Jakle, C., Kroner-Herwig, B. Incorporation of cognitive-behavioral treatment into the medical care of chronic low back patients: a controlled randomized study in German pain treatment centers.*Patient Educ Couns*; Jun 1997.

736. Turner, J. A. Comparison of group progressive-relaxation training and cognitive-behavioral group therapy for chronic low back pain.*J Consult Clin Psychol*; Oct 1982.

737. Bru, E., Mykletun, R. J., Svebak, S. Assessment of musculoskeletal and other health complaints in female hospital staff.*Appl Ergon*; Apr 1994.

738. Ryan, M., Gevirtz, R. Biofeedback-based psychophysiological treatment in a primary care setting: an initial feasibility study.*Appl Psychophysiol Biofeedback*; Jun 2004.

739. Spence, S. H., Sharpe, L., Newton-John, T., Champion, D. Effect of EMG biofeedback compared to applied relaxation training with chronic, upper extremity cumulative trauma disorders.*Pain*; Nov 1995.

740. Nouwen, A. EMG biofeedback used to reduce standing levels of paraspinal muscle tension in chronic low back pain.*Pain*; Dec 1983.

741. Stuckey, S. J., Jacobs, A., Goldfarb, J. EMG biofeedback training, relaxation training, and placebo for the relief of chronic back pain.*Percept Mot Skills*; Dec 1986.

742. Andrasik, F., Blanchard, E. B., Neff, D. F., Rodichok, L. D. Biofeedback and relaxation training for chronic headache: a controlled comparison of booster treatments and regular contacts for long-term maintenance.*J Consult Clin Psychol*; Aug 1984.

743. Vlaeyen, J. W., Haazen, I. W., Schuerman, J. A., Kole-Snijders, A. M., van Eek, H. Behavioural rehabilitation of chronic low back pain: comparison of an operant treatment, an operant-cognitive treatment and an operant-respondent treatment.*Br J Clin Psychol*; Feb 1995.

744. Newton-John, T. R., Spence, S. H., Schotte, D. Cognitive-behavioural therapy versus EMG biofeedback in the treatment of chronic low back pain.*Behav Res Ther*; Jul 1995.

745. Rokicki, L. A., Holroyd, K. A., France, C. R., Lipchik, G. L., France, J. L., Kvaal, S. A. Change mechanisms associated with combined relaxation/EMG biofeedback training for chronic tension headache.*Appl Psychophysiol Biofeedback*; Mar 1997.

746. Mitchell, R. I., Carmen, G. M. The functional restoration approach to the treatment of chronic pain in patients with soft tissue and back injuries.*Spine*; Mar 15 1994.

747. Strand, L. I., Ljunggren, A. E., Haldorsen, E. M., Espehaug, B. The impact of physical function and pain on work status at 1-year follow-up in patients with back pain.*Spine*; Apr 1 2001.

748. Peters, J., Large, R. G., Elkind, G. Follow-up results from a randomised controlled trial evaluating in- and outpatient pain management programmes.*Pain*; Jul 1992.

749. Harkapaa, K., Mellin, G., Jarvikoski, A., Hurri, H. A controlled study on the outcome of inpatient and outpatient treatment of low back pain. Part III. Long-term follow-up of pain, disability, and compliance.*Scand J Rehabil Med*; 1990.

750. Lønn JH, Glomsrød B,Soukup MG,Bø K,Larsen S. Active back school: prophylactic management for low back pain. A randomized, controlled, 1-year follow-up study.*Spine (Phila Pa 1976)*; 1999.

751. Berwick DM, Budman S,Feldstein M. No clinical effect of back schools in an HMO. A randomized prospective trial.*Spine (Phila Pa 1976)*; 1989.

752. Donchin M, Woolf O,Kaplan L,Floman Y. Secondary prevention of low-back pain. A clinical trial.*Spine (Phila Pa 1976)*; 1990.

753. Julkunen J, Hurri H,Kankainen J. Psychological factors in the treatment of chronic low back pain. Follow-up study of a back school intervention.*Psychother Psychosom*; 1988.

754. Lankhorst GJ, Van de Stadt RJ,Vogelaar TW,Van der Korst JK,Prevo AJ. The effect of the Swedish Back School in chronic idiopathic low back pain. A prospective controlled study.*Scand J Rehabil Med*; 1983.

755. Bergquist-Ullman M, Larsson U. Acute low back pain in industry. A controlled prospective study with special reference to therapy and confounding factors.*Acta Orthop Scand*; 1977.

756. Versloot JM, Rozeman A,van Son AM,van Akkerveeken PF. The cost-effectiveness of a back school program in industry. A longitudinal controlled field study.*Spine (Phila Pa 1976)*; 1992.

757. Roberts L, Little P,Chapman J,Cantrell T,Pickering R,Langridge J. The back home trial: general practitioner-supported leaflets may change back pain behavior.*Spine (Phila Pa 1976)*; 2002.

758. Klaber Moffett JA, Chase SM,Portek I,Ennis JR. A controlled, prospective study to evaluate the effectiveness of a back school in the relief of chronic low back pain.*Spine (Phila Pa 1976)*; 1986.

759. Penttinen J, Nevala-Puranen N,Airaksinen O,Jääskeläinen M,Sintonen H,Takala J. Randomized controlled trial of back school with and without peer support.*J Occup Rehabil*; 2002.

760. Maul I, Läubli T,Oliveri M,Krueger H. Long-term effects of supervised physical training in secondary prevention of low back pain.*Eur Spine J*; 2005.

761. Sirles AT, Brown K,Hilyer JC. Effects of back school education and exercise in back injured municipal workers.*AAOHN J*; 1991.

762. Lindequist S, Lundberg B,Wikmark R,Bergstad B,Lööf G,Ottermark AC. Information and regime at low back pain.*Scand J Rehabil Med*; 1984.

763. Postacchini, F. Efficacy of Various Forms of Conservative Treatment in Low Back Pain: A comparative study.*Neuro-Orthopedics*; 1988.

764. Schenk RJ, Doran RL,Stachura JJ. Learning effects of a back education program.*Spine (Phila Pa 1976)*; 1996.

765. Overmeer T, Boersma K,Denison E,Linton SJ. Does teaching physical therapists to deliver a biopsychosocial treatment program result in better patient outcomes? A randomized controlled trial.*Phys Ther*; 2011.

766. Stapelfeldt CM, Christiansen DH,Jensen OK,Nielsen CV,Petersen KD,Jensen C. Subgroup analyses on return to work in sick-listed employees with low back pain in a randomised trial comparing brief and multidisciplinary intervention.*BMC Musculoskelet Disord*; 2011.

767. Dirckx, M., Groeneweg, G., Wesseldijk, F., Stronks, D. L., Huygen, F. J. Report of a preliminary discontinued double-blind, randomized, placebo-controlled trial of the anti-TNF-alpha chimeric monoclonal antibody infliximab in complex regional pain syndrome.*Pain Pract*; Nov 2013.

768. Rocha Rde, O., Teixeira, M. J., Yeng, L. T., Cantara, M. G., Faria, V. G., Liggieri, V., Loduca, A., Muller, B. M., Souza, A. C., de Andrade, D. C. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study.*Pain*; Nov 2014.

769. Fialka, V., Resch, K. L., Ritter-Dietrich, D., Alacamlioglu, Y., Chen, O., Leitha, T., Kluger, R., Ernst, E. Acupuncture for reflex sympathetic dystrophy.*Arch Intern Med*; Mar 8 1993.

770. Schilder, J. C., Sigtermans, M. J., Schouten, A. C., Putter, H., Dahan, A., Noldus, L. P., Marinus, J., van Hilten, J. J. Pain relief is associated with improvement in motor function in complex regional pain syndrome type 1: secondary analysis of a placebo-controlled study on the effects of ketamine.*J Pain*; Nov 2013.

771. Wallace, M. S., Ridgeway, B. M., Leung, A. Y., Gerayli, A., Yaksh, T. L. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II.*Anesthesiology*; Jan 2000.

772. Kemler, M. A., Reulen, J. P., Barendse, G. A., van Kleef, M., de Vet, H. C., van den Wildenberg, F. A. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial.*Anesthesiology*; Jul 2001.

773. Meier, K., Nikolajsen, L., Sorensen, J. C., Jensen, T. S. Effect of spinal cord stimulation on sensory characteristics: a randomized, blinded crossover study.*Clin J Pain*; May 2015.

774. Eckmann, M. S., Ramamurthy, S., Griffin, J. G. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: a randomized, double-blinded, crossover study.*Clin J Pain*; Mar-Apr 2011.

775. Imamura, M., Targino, R. A., Hsing, W. T., Imamura, S., Azevedo, R. S., Boas, L. S., Tozetto-Mendoza, T. R., Alfieri, F. M., Filippo, T. R., Battistella, L. R. Concentration of cytokines in patients with osteoarthritis of the knee and fibromyalgia.*Clin Interv Aging*; 2014.

776. Gur, A., Karakoc, M., Nas, K., Remzi, , Cevik, , Denli, A., Sarac, J. Cytokines and depression in cases with fibromyalgia.*J Rheumatol*; Feb 2002.

777. Dejaco, Christian, Klotz, Werner, Larcher, Heike, Duftner, Christina, Schirmer, Michael, Herold, Manfred. Diagnostic value of antibodies against a modified citrullinated vimentin in rheumatoid arthritis.*Arthritis research & therapy*; 2006.

778. Ribeiro, L. S., Proietti, F. A. Interrelations between fibromyalgia, thyroid autoantibodies, and depression.*J Rheumatol*; Oct 2004.

779. Elmas, O., Yildiz, S., Bilgin, S., Demirci, S., Comlekci, S., Koyuncuoglu, H. R., Akkus, S., Colak, O. H., Etem, Koklukaya, Arslan, E., Ozkan, O., Bilgin, G. Physiological parameters as a tool in the diagnosis of fibromyalgia syndrome in females: A preliminary study.*Life Sci*; Jan 15 2016.

780. Xiao Y, Haynes WL,Michalek JE,Russell IJ. Elevated serum high-sensitivity C-reactive protein levels in fibromyalgia syndrome patients correlate with body mass index, interleukin-6, interleukin-8, erythrocyte sedimentation rate.*Rheumatol Int*; 2013.

781. Naschitz, J. E., Sabo, E., Dreyfuss, D., Yeshurun, D., Rosner, I. The head-up tilt test in the diagnosis and management of chronic fatigue syndrome.*Isr Med Assoc J*; Nov 2003.

782. Cohen, H., Neumann, L., Shore, M., Amir, M., Cassuto, Y., Buskila, D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability.*Semin Arthritis Rheum*; Feb 2000.

783. Dogru, M. T., Aydin, G., Tosun, A., Keles, I., Guneri, M., Arslan, A., Ebinc, H., Orkun, S. Correlations between autonomic dysfunction and circadian changes and arrhythmia prevalence in women with fibromyalgia syndrome.*Anadolu Kardiyol Derg*; Apr 2009.

784. Ozgocmen, S., Yoldas, T., Yigiter, R., Kaya, A., Ardicoglu, O. R-R interval variation and sympathetic skin response in fibromyalgia.*Arch Med Res*; Jul 2006.

785. Harris, R. E., Sundgren, P. C., Craig, A. D., Kirshenbaum, E., Sen, A., Napadow, V., Clauw, D. J. Elevated insular glutamate in fibromyalgia is associated with experimental pain.*Arthritis Rheum*; Oct 2009.

786. Elert, J., Kendall, S. A., Larsson, B., Mansson, B., Gerdle, B. Chronic pain and difficulty in relaxing postural muscles in patients with fibromyalgia and chronic whiplash associated disorders.*J Rheumatol*; Jun 2001.

787. Westgaard, R. H., Mork, P. J., Loras, H. W., Riva, R., Lundberg, U. Trapezius activity of fibromyalgia patients is enhanced in stressful situations, but is similar to healthy controls in a quiet naturalistic setting: a case-control study.*BMC Musculoskelet Disord*; Mar 18 2013.

788. Nilsen, K. B., Westgaard, R. H., Stovner, L. J., Helde, G., Ro, M., Sand, T. H. Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography.*Eur J Pain*; Oct 2006.

789. Cakir, Tuncay, Evcik, Deniz, Dundar, Umit, Yigit, Ilknur, Kavuncu, Vural. Evaluation of sympathetic skin response and F wave in fibromyalgia syndrome patients.*Turkish Journal of Rheumatology (Turkish League Against Rheumatism//Turkiye Romatizma Arastirma ve Savas Dernegi)*; 2011.

790. Giannotti, E., Koutsikos, K., Pigatto, M., Rampudda, M. E., Doria, A., Masiero, S. Medium-/long-term effects of a specific exercise protocol combined with patient education on spine mobility, chronic fatigue, pain, aerobic fitness and level of disability in fibromyalgia.*Biomed Res Int*; 2014.

791. Genc, Aysun, Tur, Birkan Sonel, Aytur, Yesim Kurtais, Oztuna, Derya, Erdogan, Murat Faik. Does aerobic exercise affect the hypothalamic-pituitary-adrenal hormonal response in patients with fibromyalgia syndrome?.*Journal of physical therapy science*; 2015.

792. Sañudo Corrales, Francisco de Borja, Carrasco Páez, Luis, Hoyo Lora, Moisés del, Figueroa, A, Saxton, JM. Vagal modulation and symptomatology following a 6-month aerobic exercise programme for women with Fibromyalgia.*Clinical and Experimental Rheumatology, 1-5.*; 2015.

793. Garcia-Martinez, A. M., De Paz, J. A., Marquez, S. Effects of an exercise programme on self-esteem, self-concept and quality of life in women with fibromyalgia: a randomized controlled trial.*Rheumatol Int*; Jul 2012.

794. Richards, S. C., Scott, D. L. Prescribed exercise in people with fibromyalgia: parallel group randomised controlled trial.*Bmj*; Jul 27 2002.

795. Gowans, S. E., deHueck, A., Voss, S., Silaj, A., Abbey, S. E., Reynolds, W. J. Effect of a randomized, controlled trial of exercise on mood and physical function in individuals with fibromyalgia.*Arthritis Rheum*; Dec 2001.

796. Martin, L., Nutting, A., MacIntosh, B. R., Edworthy, S. M., Butterwick, D., Cook, J. An exercise program in the treatment of fibromyalgia.*J Rheumatol*; Jun 1996.

797. McBeth, J., Prescott, G., Scotland, G., Lovell, K., Keeley, P., Hannaford, P., McNamee, P., Symmons, D. P., Woby, S., Gkazinou, C., Beasley, M., Macfarlane, G. J. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain.*Arch Intern Med*; Jan 9 2012.

798. Dobkin, P. L., Abrahamowicz, M., Fitzcharles, M. A., Dritsa, M., da Costa, D. Maintenance of exercise in women with fibromyalgia.*Arthritis Rheum*; Oct 15 2005.

799. van Koulil, S., van Lankveld, W., Kraaimaat, F. W., van Helmond, T., Vedder, A., van Hoorn, H., Donders, A. R., Wirken, L., Cats, H., van Riel, P. L., Evers, A. W. Tailored cognitive-behavioural therapy and exercise training improves the physical fitness of patients with fibromyalgia.*Ann Rheum Dis*; Dec 2011.

800. van Koulil, S., van Lankveld, W., Kraaimaat, F. W., van Helmond, T., Vedder, A., van Hoorn, H., Donders, R., de Jong, A. J., Haverman, J. F., Korff, K. J., van Riel, P. L., Cats, H. A., Evers, A. W. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia.*Arthritis Care Res (Hoboken)*; Oct 2010.

801. Gowans, S. E., DeHueck, A., Abbey, S. E. Measuring exercise-induced mood changes in fibromyalgia: a comparison of several measures.*Arthritis Rheum*; Dec 15 2002.

802. Burckhardt, C. S., Mannerkorpi, K., Hedenberg, L., Bjelle, A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia.*J Rheumatol*; Apr 1994.

803. van Santen M, Bolwijn P,Landewé R,et al. High or low intensity aerobic fitness training in fibromyalgia: does it matter?.*J Rheumatol.*; 2002.

804. Newcomb, L. W., Koltyn, K. F., Morgan, W. P., Cook, D. B. Influence of preferred versus prescribed exercise on pain in fibromyalgia.*Med Sci Sports Exerc*; Jun 2011.

805. Padawer, Wendy J, Levine, Fredric M. Exercise-induced analgesia: fact or artifact?.*Pain*; 1992.

806. Mayer, T. G., Gatchel, R. J., Polatin, P. B., Evans, T. H. Outcomes comparison of treatment for chronic disabling work-related upper-extremity disorders and spinal disorders.*J Occup Environ Med*; Sep 1999.

807. Bjersing, J. L., Dehlin, M., Erlandsson, M., Bokarewa, M. I., Mannerkorpi, K. Changes in pain and insulin-like growth factor 1 in fibromyalgia during exercise: the involvement of cerebrospinal inflammatory factors and neuropeptides.*Arthritis Res Ther*; 2012.

808. Hoeger Bement, M. K., Weyer, A. D., Yoon, T., Hunter, S. K. Corticomotor excitability during a noxious stimulus before and after exercise in women with fibromyalgia.*J Clin Neurophysiol*; Feb 2014.

809. Sanudo, B., Carrasco, L., de Hoyo, M., McVeigh, J. G. Effects of exercise training and detraining in patients with fibromyalgia syndrome: a 3-yr longitudinal study.*Am J Phys Med Rehabil*; Jul 2012.

810. Bircan, C., Karasel, S. A., Akgun, B., El, O., Alper, S. Effects of muscle strengthening versus aerobic exercise program in fibromyalgia.*Rheumatol Int*; Apr 2008.

811. Torres, J. R., Martos, I. C., Sanchez, I. T., Rubio, A. O., Pelegrina, A. D., Valenza, M. C. Results of an Active Neurodynamic Mobilization Program in Patients With Fibromyalgia Syndrome: A Randomized Controlled Trial.*Arch Phys Med Rehabil*; Oct 2015.

812. Hammond, A., Freeman, K. Community patient education and exercise for people with fibromyalgia: a parallel group randomized controlled trial.*Clin Rehabil*; Oct 2006.

813. Kaleth, A. S., Saha, C. K., Jensen, M. P., Slaven, J. E., Ang, D. C. Effect of moderate to vigorous physical activity on long-term clinical outcomes and pain severity in fibromyalgia.*Arthritis Care Res (Hoboken)*; Aug 2013.

814. Paolucci T, Baldari C,Di Franco M,Didona D,Reis V,Vetrano M,Iosa M,Trifoglio D,Zangrando F,Spadini E,Saraceni VM,Guidetti L. A New Rehabilitation Tool in Fibromyalgia: The Effects of Perceptive Rehabilitation on Pain and Function in a Clinical Randomized Controlled Trial.*Evid Based Complement Alternat Med*; 2015.

815. van Koulil, S., Kraaimaat, F. W., van Lankveld, W., van Helmond, T., Vedder, A., van Hoorn, H., Donders, A. R., Thieme, K., Cats, H., van Riel, P. L., Evers, A. W. Cognitive-behavioral mechanisms in a pain-avoidance and a pain-persistence treatment for high-risk fibromyalgia patients.*Arthritis Care Res (Hoboken)*; Jun 2011.

816. Fontaine, K. R., Conn, L., Clauw, D. J. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial.*Arthritis Res Ther*; 2010.

817. Latorre Roman, P. A., Santos, E. Campos M. A., Garcia-Pinillos, F. Effects of functional training on pain, leg strength, and balance in women with fibromyalgia.*Mod Rheumatol*; 2015.

818. Hakkinen, A., Hakkinen, K., Hannonen, P., Alen, M. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women.*Ann Rheum Dis*; Jan 2001.

819. Panton, L. B., Figueroa, A., Kingsley, J. D., Hornbuckle, L., Wilson, J., St John, N., Abood, D., Mathis, R., VanTassel, J., McMillan, V. Effects of resistance training and chiropractic treatment in women with fibromyalgia.*J Altern Complement Med*; Mar 2009.

820. Valkeinen, H., Hakkinen, K., Pakarinen, A., Hannonen, P., Hakkinen, A., Airaksinen, O., Niemitukia, L., Kraemer, W. J., Alen, M. Muscle hypertrophy, strength development, and serum hormones during strength training in elderly women with fibromyalgia.*Scand J Rheumatol*; Jul-Aug 2005.

821. Kingsley, J. D., Panton, L. B., McMillan, V., Figueroa, A. Cardiovascular autonomic modulation after acute resistance exercise in women with fibromyalgia.*Arch Phys Med Rehabil*; Sep 2009.

822. Gavi, M. B., Vassalo, D. V., Amaral, F. T., Macedo, D. C., Gava, P. L., Dantas, E. M., Valim, V. Strengthening exercises improve symptoms and quality of life but do not change autonomic modulation in fibromyalgia: a randomized clinical trial.*PLoS One*; 2014.

823. Kingsley, J. D., McMillan, V., Figueroa, A. The effects of 12 weeks of resistance exercise training on disease severity and autonomic modulation at rest and after acute leg resistance exercise in women with fibromyalgia.*Arch Phys Med Rehabil*; Oct 2010.

824. Hoeger Bement, M. K., Weyer, A., Hartley, S., Drewek, B., Harkins, A. L., Hunter, S. K. Pain perception after isometric exercise in women with fibromyalgia.*Arch Phys Med Rehabil*; Jan 2011.

825. Valencia, M., Alonso, B., Alvarez, M. J., Barrientos, M. J., Ayan, C., Martin Sanchez, V. Effects of 2 physiotherapy programs on pain perception, muscular flexibility, and illness impact in women with fibromyalgia: a pilot study.*J Manipulative Physiol Ther*; Jan 2009.

826. Burckhardt, C. S., Bjelle, A. Education programmes for fibromyalgia patients: description and evaluation.*Baillieres Clin Rheumatol*; Nov 1994.

827. da Silva, G. D., Lorenzi-Filho, G., Lage, L. V. Effects of yoga and the addition of Tui Na in patients with fibromyalgia.*J Altern Complement Med*; Dec 2007.

828. Altan, L., Korkmaz, N., Bingol, U., Gunay, B. Effect of pilates training on people with fibromyalgia syndrome: a pilot study.*Arch Phys Med Rehabil*; Dec 2009.

829. Evcik, D., Yigit, I., Pusak, H., Kavuncu, V. Effectiveness of aquatic therapy in the treatment of fibromyalgia syndrome: a randomized controlled open study.*Rheumatol Int*; Jul 2008.

830. Mannerkorpi, K., Nyberg, B., Ahlmen, M., Ekdahl, C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study.*J Rheumatol*; Oct 2000.

831. Ortega, E., Garcia, J. J., Bote, M. E., Martin-Cordero, L., Escalante, Y., Saavedra, J. M., Northoff, H., Giraldo, E. Exercise in fibromyalgia and related inflammatory disorders: known effects and unknown chances.*Exerc Immunol Rev*; 2009.

832. Tomas-Carus, P., Hakkinen, A., Gusi, N., Leal, A., Hakkinen, K., Ortega-Alonso, A. Aquatic training and detraining on fitness and quality of life in fibromyalgia.*Med Sci Sports Exerc*; Jul 2007.

833. Zijlstra, T. R., Braakman-Jansen, L. M., Taal, E., Rasker, J. J., van de Laar, M. A. Cost-effectiveness of Spa treatment for fibromyalgia: general health improvement is not for free.*Rheumatology (Oxford)*; Sep 2007.

834. Donmez, A., Karagulle, M. Z., Tercan, N., Dinler, M., Issever, H., Karagulle, M., Turan, M. SPA therapy in fibromyalgia: a randomised controlled clinic study.*Rheumatol Int*; Dec 2005.

835. Koçyiğit, Burhan Fatih, Gür, Ali, Altındağ, Özlem, Akyol, Ahmet, Gürsoy, Savaş. Comparison of education and balneotherapy efficacy in patients with fibromyalgia syndrome: A randomized, controlled clinical study.*Ağrı: Ağrı (Algoloji) Derneği'nin Yayın organıdır= The journal of the Turkish Society of Algology*; 2016.

836. Neumann, L., Sukenik, S., Bolotin, A., Abu-Shakra, M., Amir, M., Flusser, D., Buskila, D. The effect of balneotherapy at the Dead Sea on the quality of life of patients with fibromyalgia syndrome.*Clin Rheumatol*; 2001.

837. Ozkurt, S., Donmez, A., Zeki Karagulle, M., Uzunoglu, E., Turan, M., Erdogan, N. Balneotherapy in fibromyalgia: a single blind randomized controlled clinical study.*Rheumatol Int*; Jul 2012.

838. Buskila, D. Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome.*Curr Opin Rheumatol*; Mar 2001.

839. Eksioglu, E., Yazar, D., Bal, A., Usan, H. D., Cakci, A. Effects of Stanger bath therapy on fibromyalgia.*Clin Rheumatol*; May 2007.

840. Fioravanti, A., Perpignano, G., Tirri, G., Cardinale, G., Gianniti, C., Lanza, C. E., Loi, A., Tirri, E., Sfriso, P., Cozzi, F. Effects of mud-bath treatment on fibromyalgia patients: a randomized clinical trial.*Rheumatol Int*; Oct 2007.

841. Bazzichi, L., Da Valle, Y., Rossi, A., Giacomelli, C., Sernissi, F., Giannaccini, G., Betti, L., Ciregia, F., Giusti, L., Scarpellini, P., Dell'Osso, L., Marazziti, D., Bombardieri, S., Lucacchini, A. A multidisciplinary approach to study the effects of balneotherapy and mud-bath therapy treatments on fibromyalgia.*Clin Exp Rheumatol*; Nov-Dec 2013.

842. Fioravanti, A., Bellisai, B., Capitani, S., Manica, P., Paolazzi, G., Galeazzi, M. Phytothermotherapy: a possible complementary therapy for fibromyalgia patients.*Clin Exp Rheumatol*; Sep-Oct 2009.

843. Kesiktas, N., Karagulle, Z., Erdogan, N., Yazicioglu, K., Yilmaz, H., Paker, N. The efficacy of balneotherapy and physical modalities on the pulmonary system of patients with fibromyalgia.*J Back Musculoskelet Rehabil*; 2011.

844. Ardic, F., Ozgen, M., Aybek, H., Rota, S., Cubukcu, D., Gokgoz, A. Effects of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients.*Rheumatol Int*; Mar 2007.

845. Evcik, D., Kizilay, B., Gokcen, E. The effects of balneotherapy on fibromyalgia patients.*Rheumatol Int*; Jun 2002.

846. Sanudo, B., de Hoyo, M., Carrasco, L., Rodriguez-Blanco, C., Oliva-Pascual-Vaca, A., McVeigh, J. G. Effect of whole-body vibration exercise on balance in women with fibromyalgia syndrome: a randomized controlled trial.*J Altern Complement Med*; Feb 2012.

847. Sanudo, B., de Hoyo, M., Carrasco, L., McVeigh, J. G., Corral, J., Cabeza, R., Rodriguez, C., Oliva, A. The effect of 6-week exercise programme and whole body vibration on strength and quality of life in women with fibromyalgia: a randomised study.*Clin Exp Rheumatol*; Nov-Dec 2010.

848. Jordan, M., Richardson, E. J. Effects of Virtual Walking Treatment on Spinal Cord Injury-Related Neuropathic Pain: Pilot Results and Trends Related to Location of Pain and at-level Neuronal Hypersensitivity.*Am J Phys Med Rehabil*; May 2016.

849. Dixit, Snehil, Maiya, Arun, Shastry, Barkur. Effect of aerobic exercise on quality of life in population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, randomized controlled trial.*Quality of Life Research*; 2014.

850. Dixit, Snehil, Maiya, Arun G, Shastry, BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial.*Journal of Diabetes and its Complications*; 2014.

851. Max, M. B., Schafer, S. C., Culnane, M., Smoller, B., Dubner, R., Gracely, R. H. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia.*Neurology*; Sep 1988.

852. Kudoh, A., Katagai, H., Takazawa, T. Current perception thresholds of patients with long-term administration of maprotiline.*Pharmacopsychiatry*; Mar-Apr 2003.

853. Kishore-Kumar, R., Max, M. B., Schafer, S. C., Gaughan, A. M., Smoller, B., Gracely, R. H., Dubner, R. Desipramine relieves postherpetic neuralgia.*Clin Pharmacol Ther*; Mar 1990.

854. Irving, G., Tanenberg, R. J., Raskin, J., Risser, R. C., Malcolm, S. Comparative safety and tolerability of duloxetine vs. pregabalin vs. duloxetine plus gabapentin in patients with diabetic peripheral neuropathic pain.*Int J Clin Pract*; Sep 2014.

855. Yucel, A., Ozyalcin, S., Koknel Talu, G., Kiziltan, E., Yucel, B., Andersen, O. K., Arendt-Nielsen, L., Disci, R. The effect of venlafaxine on ongoing and experimentally induced pain in neuropathic pain patients: a double blind, placebo controlled study.*Eur J Pain*; Aug 2005.

856. Wernicke, J. F., Pritchett, Y. L., D'Souza, D. N., Waninger, A., Tran, P., Iyengar, S., Raskin, J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain.*Neurology*; Oct 24 2006.

857. Nathan, P. W. Chlorprothixene (taractan) in post-herpetic neuralgia and other severe chronic pains.*Pain*; Dec 1978.

858. Raskin, P., Donofrio, P. D., Rosenthal, N. R., Hewitt, D. J., Jordan, D. M., Xiang, J., Vinik, A. I. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects.*Neurology*; Sep 14 2004.

859. Jensen, M. P., Hsu, P. H., Vanhove, G. F. Early pain reduction can predict treatment response: results of integrated efficacy analyses of a once-daily gastroretentive formulation of gabapentin in patients with postherpetic neuralgia.*Pain Med*; Aug 2012.

860. Jensen, M. P., Irving, G., Rauck, R., Wallace, M., Sweeney, M., Vanhove, G. F. Long-term safety of gastroretentive gabapentin in postherpetic neuralgia patients.*Clin J Pain*; Sep 2013.

861. Tanenberg, R. J., Irving, G. A., Risser, R. C., Ahl, J., Robinson, M. J., Skljarevski, V., Malcolm, S. K. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison.*Mayo Clin Proc*; Jul 2011.

862. Stacey, B. R., Dworkin, R. H., Murphy, K., Sharma, U., Emir, B., Griesing, T. Pregabalin in the treatment of refractory neuropathic pain: results of a 15-month open-label trial.*Pain Med*; Nov 2008.

863. Jensen, M. P., Gammaitoni, A. R., Bolognese, J. A., Alon, A., Smugar, S. S., Galer, B. S., Hewitt, D. J. The pain quality response profile of pregabalin in the treatment of neuropathic pain.*Clin J Pain*; Oct 2012.

864. Gammaitoni, A. R., Smugar, S. S., Jensen, M. P., Galer, B. S., Bolognese, J. A., Alon, A., Hewitt, D. J. Predicting response to pregabalin from pretreatment pain quality: clinical applications of the pain quality assessment scale.*Pain Med*; Apr 2013.

865. Galbraith, A. W. Prevention of post-herpetic neuralgia by amantadine hydrochloride (Symmetrel).*Br J Clin Pract*; Sep 1983.

866. Mondelli, M., Romano, C., Passero, S., Porta, P. D., Rossi, A. Effects of acyclovir on sensory axonal neuropathy, segmental motor paresis and postherpetic neuralgia in herpes zoster patients.*Eur Neurol*; 1996.

867. Rajanandh, M. G., Kosey, S., Prathiksha, G. Assessment of antioxidant supplementation on the neuropathic pain score and quality of life in diabetic neuropathy patients - a randomized controlled study.*Pharmacol Rep*; Feb 2014.

868. Ursini, T., Tontodonati, M., Manzoli, L., Polilli, E., Rebuzzi, C., Congedo, G., Di Profio, S., Toro, P. M., Consorte, A., Placido, G., Lagana, S., D'Amario, C., Granchelli, C., Parruti, G., Pippa, L. Acupuncture for the treatment of severe acute pain in herpes zoster: results of a nested, open-label, randomized trial in the VZV Pain Study.*BMC Complement Altern Med*; 2011.

869. Pan, C., Tan, G. Forty-two cases of greater occipital neuralgia treated by acupuncture plus acupoint-injection.*J Tradit Chin Med*; Sep 2008.

870. Jalali, M. H., Ansarin, H., Soltani-Arabshahi, R. Broad-band ultraviolet B phototherapy in zoster patients may reduce the incidence and severity of postherpetic neuralgia.*Photodermatol Photoimmunol Photomed*; Oct 2006.

871. Peng MF, Li K,Wang C,Zhu XY,Yang Z,Zhang GH,Wang PH,Wang YH,Tang LJ,Zhang L. Therapeutic effect and mechanism of electroacupuncture at Zusanli on plasticity of interstitial cells of Cajal: a study of rat ileum.*BMC Complement Altern Med*; 2014.

872. Shin, Sanghoon, Kim, Kwang Joon, Chang, H-J, Lee, B-W, Yang, W-I, Cha, B-S, Choi, Donghoon. The effect of oral prostaglandin analogue on painful diabetic neuropathy: a double-blind, randomized, controlled trial.*Diabetes, Obesity and Metabolism*; 2013.

873. Keczkes, K., Basheer, A. M. Do corticosteroids prevent post-herpetic neuralgia?.*Br J Dermatol*; May 1980.

874. Grace RF, Power I,Umedaly H,Zammit A,Mersiades M,Cousins MJ,Mather LE. Preoperative dextromethorphan reduces intraoperative but not postoperative morphine requirements after laparotomy.*Anesth Analg*; 1998.

875. Heiskanen T, Härtel B,Dahl ML,Seppälä T,Kalso E. Analgesic effects of dextromethorphan and morphine in patients with chronic pain.*Pain*; 2002.

876. Nelson, K. A., Park, K. M., Robinovitz, E., Tsigos, C., Max, M. B. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia.*Neurology*; May 1997.

877. Miller, A., Harel, D., Laor, A., Lahat, N. Cimetidine as an immunomodulator in the treatment of herpes zoster.*J Neuroimmunol*; Mar 1989.

878. Fuchs, P. N., Pappagallo, M., Meyer, R. A. Topical EMLA pre-treatment fails to decrease the pain induced by 1% topical capsaicin.*Pain*; Apr 1999.

879. Bareggi, S. R., Pirola, R., De Benedittis, G. Skin and plasma levels of acetylsalicylic acid: a comparison between topical aspirin/diethyl ether mixture and oral aspirin in acute herpes zoster and postherpetic neuralgia.*Eur J Clin Pharmacol*; May 1998.

880. Baron, R., Mayoral, V., Leijon, G., Binder, A., Steigerwald, I., Serpell, M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study.*Curr Med Res Opin*; Jul 2009.

881. Baron, R., Mayoral, V., Leijon, G., Binder, A., Steigerwald, I., Serpell, M. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial.*Clin Drug Investig*; 2009.

882. Stepanovic, A., Kolsek, M., Kersnik, J., Erculj, V. Prevention of post-herpetic neuralgia using transcutaneous electrical nerve stimulation.*Wien Klin Wochenschr*; May 2015.

883. Kumru, H., Soler, D., Vidal, J., Navarro, X., Tormos, J. M., Pascual-Leone, A., Valls-Sole, J. The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: an evoked potentials and quantitative thermal testing study.*Eur J Pain*; Jan 2013.

884. Kumru, H., Soler, D., Vidal, J., Tormos, J. M., Pascual-Leone, A., Valls-Sole, J. Evoked potentials and quantitative thermal testing in spinal cord injury patients with chronic neuropathic pain.*Clin Neurophysiol*; Mar 2012.

885. Marineo, G., Iorno, V., Gandini, C., Moschini, V., Smith, T. J. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial.*J Pain Symptom Manage*; Jan 2012.

886. Xiao, P., Zhu, X., Wu, X. Curative effect research on curing intercostal neuralgia through paravertebral nerve block combined with pregabalin.*Pak J Pharm Sci*; Sep 2014.

887. Amjad, M., Mashhood, A. A. The efficacy of local infiltration of triamcinolone acetonide with lignocaine compared with lignocaine alone in the treatment of postherpetic neuralgia.*J Coll Physicians Surg Pak*; Nov 2005.

888. Talaei, A., Siavash, M., Majidi, H., Chehrei, A. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy.*Int J Food Sci Nutr*; 2009.

889. Belfrage, M., Sollevi, A., Segerdahl, M., Sjolund, K. F., Hansson, P. Systemic adenosine infusion alleviates spontaneous and stimulus evoked pain in patients with peripheral neuropathic pain.*Anesth Analg*; Oct 1995.

890. Lynch, M. E., Clark, A. J., Sawynok, J. Intravenous adenosine alleviates neuropathic pain: a double blind placebo controlled crossover trial using an enriched enrolment design.*Pain*; May 2003.

891. Wahren, L. K., Gordh, T.,Jr., Torebjork, E. Effects of regional intravenous guanethidine in patients with neuralgia in the hand; a follow-up study over a decade.*Pain*; Sep 1995.

892. Pasqualucci, A., Pasqualucci, V., Galla, F., De Angelis, V., Marzocchi, V., Colussi, R., Paoletti, F., Girardis, M., Lugano, M., Del Sindaco, F. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone.*Acta Anaesthesiol Scand*; Sep 2000.

893. Nuti, C., Vassal, F., Mertens, P., Lemaire, J. J., Magnin, M., Peyron, R. Improved dexterity after chronic electrical stimulation of the motor cortex for central pain: a special relevance for thalamic syndrome.*Stereotact Funct Neurosurg*; 2012.

894. Chun-jing, H., yi-ran, L., hao-xiong, N. Effects of dorsal root ganglion destruction by adriamycin in patients with postherpetic neuralgia.*Acta Cir Bras*; Jun 2012.

895. Reddy, C. G., Dalm, B. D., Flouty, O. E., Gillies, G. T., Howard, M. A.,3rd, Brennan, T. J. Comparison of Conventional and Kilohertz Frequency Epidural Stimulation in Patients Undergoing Trialing for Spinal Cord Stimulation: Clinical Considerations.*World Neurosurg*; Apr 2016.

896. Wolter, T., Kiemen, A., Porzelius, C., Kaube, H. Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study.*Eur J Pain*; May 2012.

897. Duarte, Rui V., Andronis, Lazaros, Lenders, Mathieu W. P. M., De Vos, Cecile C. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation.*Quality of Life Research*; 2016.

898. Norbye AD, Omdal AV,Nygaard ME,Romild U,Eldøen G,Midgard R. Do Patients With Chronic Low Back Pain Benefit From Early Intervention Regarding Absence From Work?: A Randomized, Controlled, Single-Center Pilot Study.*Spine*; 2016.

899. Tavafian, S. S., Jamshidi, A., Mohammad, K., Montazeri, A. Low back pain education and short term quality of life: a randomized trial.*BMC Musculoskelet Disord*; Feb 28 2007.

900. Bendix, AF, Bendix, T, Lund, C, Kirkbak, S, Ostenfeld, S. Comparison of three intensive programs for chronic low back pain patients: a prospective, randomized, observer-blinded study with one-year follow-up.*Scandinavian journal of rehabilitation medicine*; 1997.

901. Devasahayam, Augustine Joshua, Lim, Cindy Khim Siang, Goh, Ming Rong, You, Jacinta Peng Lim, Pua, Pek Ying. Delivering a Back School Programme with a Cognitive Behavioural Modification: A Randomised Pilot Trial on Patients with Chronic Nonspecific Low Back Pain and Functional Disability.*Proceedings of Singapore Healthcare*; 2014.

902. Paolucci, T., Fusco, A., Iosa, M., Grasso, M. R., Spadini, E., Paolucci, S., Saraceni, V. M., Morone, G. The efficacy of a perceptive rehabilitation on postural control in patients with chronic nonspecific low back pain.*Int J Rehabil Res*; Dec 2012.

903. Szulc, Paweł, Wendt, Michał, Waszak, Małgorzata, Tomczak, Maciej, Cieślik, Krystyna, Trzaska, Tadeusz. Impact of McKenzie Method Therapy Enriched by Muscular Energy Techniques on Subjective and Objective Parameters Related to Spine Function in Patients with Chronic Low Back Pain.*Medical science monitor: international medical journal of experimental and clinical research*; 2015.

904. Dear, B. F., Titov, N., Perry, K. N., Johnston, L., Wootton, B. M., Terides, M. D., Rapee, R. M., Hudson, J. L. The Pain Course: a randomised controlled trial of a clinician-guided Internet-delivered cognitive behaviour therapy program for managing chronic pain and emotional well-being.*Pain*; Jun 2013.

905. Haas, M., Groupp, E., Muench, J., Kraemer, D., Brummel-Smith, K., Sharma, R., Ganger, B., Attwood, M., Fairweather, A. Chronic disease self-management program for low back pain in the elderly.*J Manipulative Physiol Ther*; May 2005.

906. Ruehlman, L. S., Karoly, P., Enders, C. A randomized controlled evaluation of an online chronic pain self management program.*Pain*; Feb 2012.

907. Brown, C. A., Jones, A. K. Psychobiological correlates of improved mental health in patients with musculoskeletal pain after a mindfulness-based pain management program.*Clin J Pain*; Mar 2013.

908. de Buck, Petronella DM, le Cessie, Saskia, van den Hout, Wilbert B, Peeters, Andreas J, Ronday, Herman K, Westedt, Marie-Louise, Breedveld, Ferdinand C, Vliet Vlieland, Theodora PM. Randomized comparison of a multidisciplinary job-retention vocational rehabilitation program with usual outpatient care in patients with chronic arthritis at risk for job loss.*Arthritis Care & Research*; 2005.

909. Abbasi, M, Dehghani, M, Keefe, FJ, Jafari, Hassan, Behtash, H, Shams, J. Spouse-assisted training in pain coping skills and the outcome of multidisciplinary pain management for chronic low back pain treatment: A 1-year randomized controlled trial.*European Journal of Pain*; 2012.

910. Martins, M. R., Gritti, C. C., dos Santos Junior, R., de Araujo, M. C., Dias, L. C., Foss, M. H., de Andrade, L. B., Rocha, C. E. Randomized controlled trial of a therapeutic intervention group in patients with fibromyalgia syndrome.*Rev Bras Reumatol*; May-Jun 2014.

911. Streibelt, Marco, Bethge, Matthias. Effects of intensified work-related multidisciplinary rehabilitation on occupational participation: a randomized-controlled trial in patients with chronic musculoskeletal disorders.*International Journal of Rehabilitation Research*; 2014.

912. Turner-Stokes, Lynne, Erkeller-Yuksel, Feza, Miles, Anne, Pincus, Tamar, Shipley, Michael, Pearce, Shirley. Outpatient cognitive behavioral pain management programs: a randomized comparison of a group-based multidisciplinary versus an individual therapy model.*Archives of physical medicine and rehabilitation*; 2003.

913. Brendbekken, Randi, Harris, Anette, Ursin, Holger, Eriksen, Hege R, Tangen, Tone. Multidisciplinary intervention in patients with musculoskeletal pain: a randomized clinical trial.*International journal of behavioral medicine*; 2016.

914. Van der Maas LC, Köke A,Pont M,et al. Improving the Multidisciplinary Treatment of Chronic Pain by Stimulating Body Awareness: A Cluster-randomized Trial.*Clin J Pain*; 2015.

915. Heutink, M., Post, M. W., Bongers-Janssen, H. M., Dijkstra, C. A., Snoek, G. J., Spijkerman, D. C., Lindeman, E. The CONECSI trial: results of a randomized controlled trial of a multidisciplinary cognitive behavioral program for coping with chronic neuropathic pain after spinal cord injury.*Pain*; Jan 2012.

916. Heutink, M., Post, M. W., Luthart, P., Schuitemaker, M., Slangen, S., Sweers, J., Vlemmix, L., Lindeman, E. Long-term outcomes of a multidisciplinary cognitive behavioural programme for coping with chronic neuropathic spinal cord injury pain.*J Rehabil Med*; Jun 2014.

917. Castel, A., Fontova, R., Montull, S., Perinan, R., Poveda, M. J., Miralles, I., Cascon-Pereira, R., Hernandez, P., Aragones, N., Salvat, I., Castro, S., Monterde, S., Padrol, A., Sala, J., Anez, C., Rull, M. Efficacy of a multidisciplinary fibromyalgia treatment adapted for women with low educational levels: a randomized controlled trial.*Arthritis Care Res (Hoboken)*; Mar 2013.

918. Casanueva-Fernandez, B., Llorca, J., Rubio, J. B., Rodero-Fernandez, B., Gonzalez-Gay, M. A. Efficacy of a multidisciplinary treatment program in patients with severe fibromyalgia.*Rheumatol Int*; Aug 2012.

919. Toussaint, L. L., Whipple, M. O., Abboud, L. L., Vincent, A., Wahner-Roedler, D. L. A mind-body technique for symptoms related to fibromyalgia and chronic fatigue.*Explore (NY)*; Mar-Apr 2012.

920. Olason, M. Outcome of an interdisciplinary pain management program in a rehabilitation clinic.*Work*; 2004.

921. Martin, J., Torre, F., Padierna, A., Aguirre, U., Gonzalez, N., Matellanes, B., Quintana, J. M. Impact of interdisciplinary treatment on physical and psychosocial parameters in patients with fibromyalgia: results of a randomised trial.*Int J Clin Pract*; May 2014.

922. I, Saral, D, Sindel, S, Esmaeilzadeh, HO, Sertel-Berk, A, Oral. The effects of long- and short-term interdisciplinary treatment approaches in .*Rheumatology international*; 2016.

923. Kim, Tae Hoon, Kim, Eun-Hye, Cho, Hwi-young. The effects of the CORE programme on pain at rest, movement-induced and secondary pain, active range of motion, and proprioception in female office workers with chronic low back pain: a randomized controlled trial.*Clinical rehabilitation*; 2014.

924. Monteiro-Junior, R. S., de Souza, C. P., Lattari, E., Rocha, N. B., Mura, G., Machado, S., da Silva, E. B. Wii-Workouts on Chronic Pain, Physical Capabilities and Mood of Older Women: A Randomized Controlled Double Blind Trial.*CNS Neurol Disord Drug Targets*; 2015.

925. Patti, Antonino, Bianco, Antonino, Paoli, Antonio, Messina, Giuseppe, Montalto, Maria Alessandra, Bellafiore, Marianna, Battaglia, Giuseppe, Iovane, Angelo, Palma, Antonio. Effects of Pilates exercise programs in people with chronic low back pain: a systematic review.*Medicine*; 2015.

926. Gatchel, Robert J, McGeary, Donald D, Peterson, Alan, Moore, Mysti, LeRoy, Karen, Isler, William C, Hryshko-Mullen, Ann S, Edell, Tom. Preliminary findings of a randomized controlled trial of an interdisciplinary military pain program.*Military medicine*; 2009.

927. Castro-Sánchez, Adelaida María, Lara-Palomo, Inmaculada C, Matarán-Peñarrocha, Guillermo A, Fernández-de-las-Peñas, César, Saavedra-Hernández, Manuel, Cleland, Joshua, Aguilar-Ferrándiz, María Encarnación. Short-term effectiveness of spinal manipulative therapy versus functional technique in patients with chronic nonspecific low back pain: a pragmatic randomized controlled trial.*The Spine Journal*; 2016.

928. Tsauo, Jau-Yih, Chen, Wei-Hsiu, Liang, Huey-Wen, Jang, Yuh. The effectiveness of a functional training programme for patients with chronic low back pain–a pilot study.*Disability and rehabilitation*; 2009.

929. Sharma, Rahul, Agarwal, Dr.,Shagun. The effectiveness of a work style intervention on the recovery from chronic neck and upper limb symptoms in computer workers.*Journal of Physiotherapy*; March 2012.

930. Bruehl, Stephen, Husfeldt, Brenda, Lubenow, Timothy R, Nath, Heather, Ivankovich, Anthony D. Psychological differences between reflex sympathetic dystrophy and non-RSD chronic pain patients.*Pain*; 1996.

931. Roth, Randy S, Geisser, Michael E. Educational achievement and chronic pain disability: mediating role of pain-related cognitions.*The Clinical journal of pain*; 2002.

932. Tuzer, Verda, Bulut, Suheyla Dogan, Bastug, Bahar, Kayalar, Gülseren, Göka, Erol, Beştepe, Emrem. Causal attributions and alexithymia in female patients with fibromyalgia or chronic low back pain.*Nordic journal of psychiatry*; 2011.

933. Bair MJ, Poleshuck EL,Wu J,Krebs EK,Damush TM,Tu W,Kroenke K. Anxiety but not social stressors predict 12-month depression and pain severity.*Clin J Pain*; 2013.

934. Geisser, Michael E, Perna, Robert, Kirsch, Ned L, Bachman, Jan E. Classification of chronic pain patients with the Brief Symptom Inventory: Patient characteristics of cluster profiles.*Rehabilitation Psychology*; 1998.

935. Choi, Y., Mayer, T. G., Williams, M., Gatchel, R. J. The clinical utility of the Multidimensional Pain Inventory (MPI) in characterizing chronic disabling occupational musculoskeletal disorders.*J Occup Rehabil*; Jun 2013.

936. Keith G. Wilson, Ph.D.,Mariane Y. Eriksson,B.A.,Joyce L. D'Eon,Ph.D.,Samuel F. Mikail,Ph.D.,and Patricia C. Emery,B.A. Major Depression and Insomnia in Chronic Pain.*The Clinical Journal of Pain*; 2002.

937. Walton, D/M.,Putos,J.,Beattie,T.,& MacDermid,J. C. Confirmatory factor analysis of 2 versions of the Brief Pain Inventory in an ambulatory population indicates that sleep interference should be interpreted separately.*Scandinavian Journal of Pain.*; 2016.

938. Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., Cleeland, C. S. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain.*Clin J Pain*; Sep-Oct 2004.

939. de Andres Ares, J., Cruces Prado, L. M., Canos Verdecho, M. A., Penide Villanueva, L., Del Valle Hoyos, M., Herdman, M., Traseira Lugilde, S., Velazquez Rivera, I. Validation of the Short Form of the Brief Pain Inventory (BPI-SF) in Spanish Patients with Non-Cancer-Related Pain.*Pain Pract*; Sep 2015.

940. Naegeli, A. N., Tomaszewski, E. L., Al Sawah, S. Psychometric validation of the Brief Pain Inventory-Short Form in patients with systemic lupus erythematosus in the United States.*Lupus*; Nov 2015.

941. Raichle, K. A., Osborne, T. L., Jensen, M. P., Cardenas, D. The reliability and validity of pain interference measures in persons with spinal cord injury.*J Pain*; Mar 2006.

942. Greve, K. W., Bianchini, K. J. Should the Retention trial of the Test of Memory Malingering be optional?.*Arch Clin Neuropsychol*; Jan 2006.

943. Robinson, J. P., Burwinkle, T., Turk, D. C. Perceived and actual memory, concentration, and attention problems after whiplash-associated disorders (grades I and II): prevalence and predictors.*Arch Phys Med Rehabil*; Jun 2007.

944. Duckro PN, RONALD B. MARGOLIS AND RAYMOND C. TAIT. PSYCHOLOGICAL ASSESSMENT IN CHRONIC PAIN.*Journal of Clinical Psychology*; 1985.

945. Vowles KE, McCracken LM,O'Brien JZ. Acceptance and values-based action in chronic pain: a three-year follow-up analysis of treatment effectiveness and process.*Behav Res Ther*; 2011.

946. Carmody, T. P., Duncan, C. L., Huggins, J., Solkowitz, S. N., Lee, S. K., Reyes, N., Mozgai, S., Simon, J. A. Telephone-delivered cognitive-behavioral therapy for pain management among older military veterans: a randomized trial.*Psychol Serv*; Aug 2013.

947. Shpaner, M., Kelly, C., Lieberman, G., Perelman, H., Davis, M., Keefe, F. J., Naylor, M. R. Unlearning chronic pain: A randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy.*Neuroimage Clin*; 2014.

948. Berry, R., Verrier, M. J., Rashiq, S., Simmonds, M. K., Baloukov, A., Thottungal, J., McWilliams, L., Olechowski, C., Dick, B. D. A brief cognitive-behavioral intervention for sleep in individuals with chronic noncancer pain: A randomized controlled trial.*Rehabil Psychol*; May 2015.

949. Thorn, B. E., Day, M. A., Burns, J., Kuhajda, M. C., Gaskins, S. W., Sweeney, K., McConley, R., Ward, L. C., Cabbil, C. Randomized trial of group cognitive behavioral therapy compared with a pain education control for low-literacy rural people with chronic pain.*Pain*; Dec 2011.

950. Ang, D. C., Kaleth, A. S., Bigatti, S., Mazzuca, S., Saha, C., Hilligoss, J., Lengerich, M., Bandy, R. Research to Encourage Exercise for Fibromyalgia (REEF): use of motivational interviewing design and method.*Contemp Clin Trials*; Jan 2011.

951. Verwoerd, A. J., Luijsterburg, P. A., Koes, B. W., el Barzouhi, A., Verhagen, A. P. Does Kinesiophobia Modify the Effects of Physical Therapy on Outcomes in Patients With Sciatica in Primary Care? Subgroup Analysis From a Randomized Controlled Trial.*Phys Ther*; Sep 2015.

952. Lazaridou A, Kim J,Cahalan CM,Loggia ML,Franceschelli O,Berna C,Schur P,Napadow V,Edwards RR. Effects of Cognitive-Behavioral Therapy (CBT) on Brain Connectivity Supporting Catastrophizing in Fibromyalgia.*Clin J Pain*; 2017.

953. Fales, J., Palermo, T. M., Law, E. F., Wilson, A. C. Sleep outcomes in youth with chronic pain participating in a randomized controlled trial of online cognitive-behavioral therapy for pain management.*Behav Sleep Med*; 2015.

954. Mundt JM, Crew EC,Krietsch K,Roth AJ,Vatthauer K,Robinson ME,Staud R,Berry RB,McCrae CS. Measuring Treatment Outcomes in Comorbid Insomnia and Fibromyalgia: Concordance of Subjective and Objective Assessments.*J Clin Sleep Med*; 2016.

955. Miro, E., Lupianez, J., Martinez, M. P., Sanchez, A. I., Diaz-Piedra, C., Guzman, M. A., Buela-Casal, G. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial.*J Health Psychol*; Jul 2011.

956. Edinger, J. D., Wohlgemuth, W. K., Krystal, A. D., Rice, J. R. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial.*Arch Intern Med*; Nov 28 2005.

957. Thieme, K., Gromnica-Ihle, E., Flor, H. Operant behavioral treatment of fibromyalgia: a controlled study.*Arthritis Rheum*; Jun 15 2003.

958. Vlaeyen, J. W., Teeken-Gruben, N. J., Goossens, M. E., Rutten-van Molken, M. P., Pelt, R. A., van Eek, H., Heuts, P. H. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. I. Clinical effects.*J Rheumatol*; Jul 1996.

959. Williams, D. A., Cary, M. A., Groner, K. H., Chaplin, W., Glazer, L. J., Rodriguez, A. M., Clauw, D. J. Improving physical functional status in patients with fibromyalgia: a brief cognitive behavioral intervention.*J Rheumatol*; Jun 2002.

960. Martinez-Valero, C., Castel, A., Capafons, A., Sala, J., Espejo, B., Cardena, E. Hypnotic treatment synergizes the psychological treatment of fibromyalgia: a pilot study.*Am J Clin Hypn*; Apr 2008.

961. Castel, A., Perez, M., Sala, J., Padrol, A., Rull, M. Effect of hypnotic suggestion on fibromyalgic pain: comparison between hypnosis and relaxation.*Eur J Pain*; May 2007.

962. Linden, M., Scherbe, S., Cicholas, B. Randomized controlled trial on the effectiveness of cognitive behavior group therapy in chronic back pain patients.*J Back Musculoskelet Rehabil*; 2014.

963. Garcia, J., Simon, M. A., Duran, M., Canceller, J., Aneiros, F. J. Differential efficacy of a cognitive-behavioral intervention versus pharmacological treatment in the management of fibromyalgic syndrome.*Psychol Health Med*; Nov 2006.

964. Domenech, J., Sanchez-Zuriaga, D., Segura-Orti, E., Espejo-Tort, B., Lison, J. F. Impact of biomedical and biopsychosocial training sessions on the attitudes, beliefs, and recommendations of health care providers about low back pain: a randomised clinical trial.*Pain*; Nov 2011.

965. Woods, Marc P, Asmundson, Gordon JG. Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial.*Pain*; 2008.

966. Flink, Ida K, Linton, Steven J. Pain, sleep and catastrophizing: The conceptualization matters: Comment on Wilt JA et al.“A multilevel path model analysis of the relations between sleep, pain, and pain catastrophizing in chronic pain rehabilitation patients”.2016.

967. Jensen, M. P., Gertz, K. J., Kupper, A. E., Braden, A. L., Howe, J. D., Hakimian, S., Sherlin, L. H. Steps toward developing an EEG biofeedback treatment for chronic pain.*Appl Psychophysiol Biofeedback*; Jun 2013.

968. Hassett, A. L., Radvanski, D. C., Vaschillo, E. G., Vaschillo, B., Sigal, L. H., Karavidas, M. K., Buyske, S., Lehrer, P. M. A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia.*Appl Psychophysiol Biofeedback*; Mar 2007.

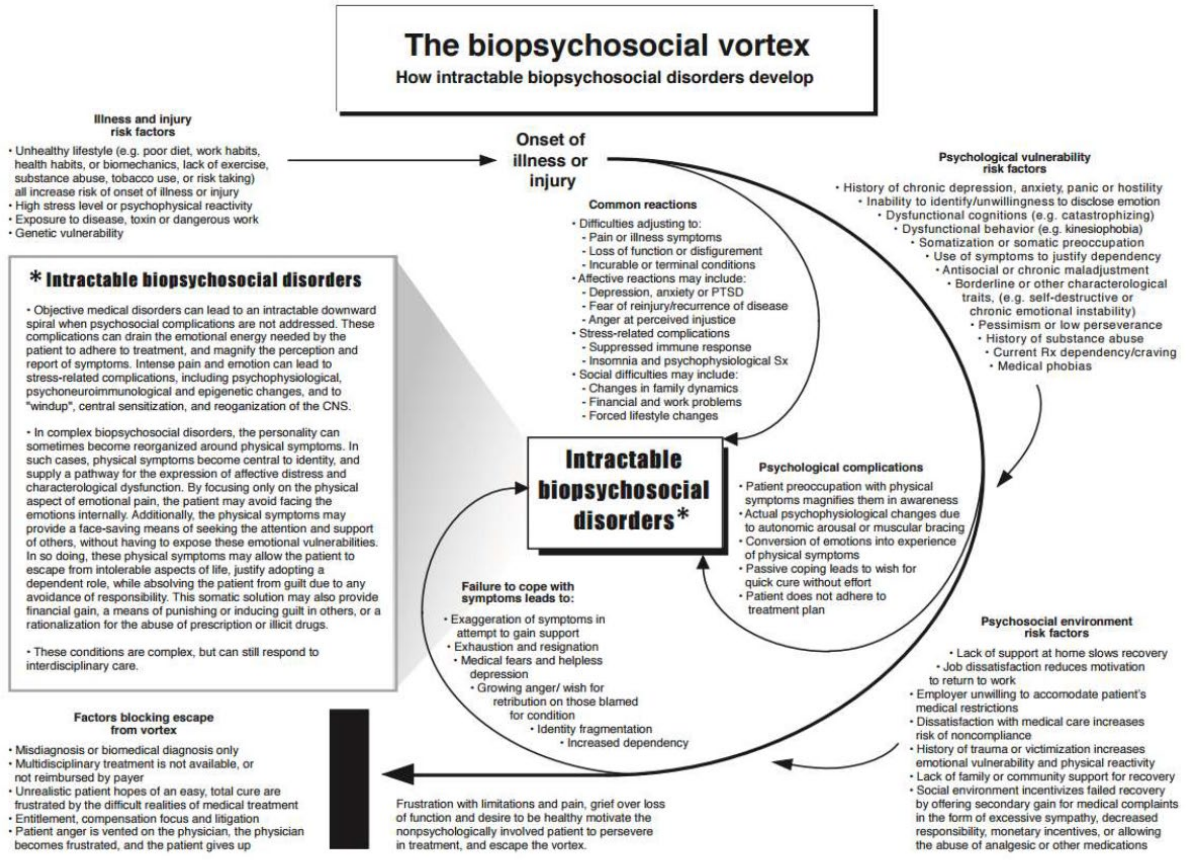
969. Neblett, R., Mayer, T. G., Brede, E., Gatchel, R. J. Correcting abnormal flexion-relaxation in chronic lumbar pain: responsiveness to a new biofeedback training protocol.*Clin J Pain*; Jun 2010.

970. Tan, G., Rintala, D. H., Jensen, M. P., Fukui, T., Smith, D., Williams, W. A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain.*Eur J Pain*; Feb 2015.

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Chronic Pain: Supplementary Material

FIGURE 1. THE BIOPSYCHOSOCIAL VORTEX



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[1]The biopsychosocial model was initially conceived as a new model for medicine, which could provide a means of integrating the biological aspects disease and illness with its psychological and social aspects. It was hoped that this new model could provide, "…a blueprint for research, a framework for teaching, and a design for action in the real world of health care" (Engel, 1977)(p 129). Since its inception, the biopsychosocial model has spawned a wealth of research and practice models, and is the model adapted into this guideline. At the same time, the biopsychosocial model itself is often presented as vague philosophical abstraction. One attempt to define the biopsychosocial model with greater specificity is the Vortex Paradigm (D. Bruns & Disorbio, 2009, 2014; D Bruns & Disorbio, 2015). This paradigm conceptualizes intractable medical conditions such as chronic pain as being precipitated by the cumulative effect of biological, psychological and social risk factors. The Vortex Paradigm suggests numerous falsifiable hypotheses that can be tested by multivariate methods. In a manner similar to the way heart disease can be predicted by a multivariate equation that includes cholesterol,

age, blood pressure, diabetes, genetics etc., the Vortex Paradigm would predict that return to function following injury can be predicted by a multivariate equation that includes biological severity, depression, catastrophizing, substance use disorder, personality disorder, job dissatisfaction, childhood trauma, secondary gain, etc.

In the clinical setting, the Vortex Paradigm would posit that biological, psychological and social variables may all contribute to the onset of an injury or illness. Once present, a significant biological condition may have direct psychological and social consequences, and these may interact with the patient's pre-existing biological, psychological and social strengths and vulnerabilities. As the level of biopsychosocial risk factors increases, the risk of decompensation (a "downward spiral") into an intractable chronic condition increases. When the patient presents to the physician, all of these variables are present, and a treatment plan should be developed regarding how to either actively treat or manage these concerns, to prevent them from delaying recovery.

TABLE 1. RED FLAGS FOR POTENTIALLY SERIOUS CONDITIONS ASSOCIATED WITH CHRONIC PAIN*

Disorder	Medical History	Physical Examination
Tumor and Neoplasia	Severe localized pain, often deep seated, non-radiating unrelenting boney pain History of cancer (at ***any*** point in a lifetime) Age >50 years Symptom consistent with disease in a specific organ system Cough Change in bowel habit, epigastric pain, early satiety Pain that worsens with use of specific body part Constitutional symptoms, such as recent unexplained weight loss, fatigue Pain that continues at night or at rest Development of new symptoms at a distant site to the original complaint not readily explained by that original problem (e.g., development of cough in a patient with shoulder pain) Pain non-responsive to usually effective treatments (e.g., low back pain not responding to evidence-based treatment guidance)	Pallor, reduced blood pressure, diffuse weakness Tenderness over boney landmark(s) and percussion tenderness corresponding to pain complaints Decreased range of motion due to protective muscle spasm New mass or tenderness Abnormal pulmonary examination (rales, rhonchi, decreased breath sounds) New findings at a distant site to the original complaints

Infection	Constitutional symptoms, such as recent fever, chills, or unexplained weight loss Recent bacterial infection (e.g., urinary tract infection); IV drug abuse; diabetes mellitus; or immunosuppression (due to corticosteroids, transplant, or HIV) History of recurring infections treated with antibiotics (e.g., repeated urinary tract infections) Foreign travel with exposure potential Insect bites	Fever, tachycardia, tachypnea, hypotension Elevated white blood cell count (may be decreased in elderly, immunocompromised or sepsis) Shift in the WBC differential towards immature cells ("left shift") Abnormal urinalysis Abnormal body part examination (e.g., pulmonary) Tenderness over boney landmarks
Progressive Neurologic Deficit	Severe spine and/or extremity pain Progressive numbness or weakness Complaints of new clumsiness of gait or impairment of hand function	Significant and progressive dermatomal and/or myotomal (motor) involvement Evidence of cauda equina syndrome–urinary retention or bowel incontinence Hyper-reflexia or other evidence of myelopathy
Intracerebral Pressure Increase or Mass or Vascular Lesion	Persistent or variable headache present on awakening Episodic severe headache Subtle loss of coordination or balance Cognition or other mentation difficulties History of cerebrovascular accident, or stroke-like symptoms, including transient	Papilledema upon fundoscopic exam. Possible mild neurologic findings Possible mental status changes
Rheumatologic Disease	Diffuse arthralgias, either a/symmetrical Joint swelling and/or prolonged morning stiffness Skin changes, lesions, or ulcers Oral ulcers Gastrointestinal diseases Fatigue, malaise Subtle mental status changes	Polyarticular joint effusions (usually with warmth) Synovitis, joint tenderness Range of motion reductions X-ray abnormalities consistent with erosive or degenerative pathology Elevated sedimentation rate (ESR) or C-reactive protein (CRP) Hematuria, proteinuria Other specific abnormalities as appropriate (e.g., ANA, RF, anti-DNA, C3, anti-Ro, anti-La, oral ulcers, pulmonary abnormalities,

		ophthalmological involvement, dermal abnormalities)
Psychosocial	Suicidal ideation Violent ideation Psychosis Substance abuse/opioid dependence Homelessness	Positive signs on psychological screening/testing Patient interview

*This list is not meant to be comprehensive; it is a review of the most common suggestive historical and examination findings.

TABLE 2. NONPHYSIOLOGIC PHYSICAL EXAMINATION SIGNS

Physical Examination Maneuver	**Definition of Nonphysiologic Sign**
1. Superficial tenderness	Discomfort on light palpation
2. Non-anatomic tenderness	Tenderness crossing anatomic boundaries
3. Axial loading	Pain elicited on pressing down on the occiput
4. Pain on simulated rotation	Pain or augmentation of pain on gentle rotation of the torso that does not rotate the lumbar spine
5. Distracted straight leg raise	Pain on straight leg raise when recumbent, but not when seated
6. Non-anatomic sensory complaints	Stocking/glove distributions of sensory changes
7. Non-physiological weakness	Cogwheeling, ratcheting or give-away weakness
8. Overreaction	Exaggerated response to stimulus, particularly if not reproduced when retested later

Adapted from Waddell G, McCulloch HA, Kummel E, Venner RM. Non-organic physical signs in low-back pain. *Spine*. 1980;5:117-25.

Numbers 1 and 2, 3 and 4, 6 and 7 were combined in the original criteria. As originally described, scores over 3 were felt to show high probability of symptom magnification or illness behaviors. Subsequently, even one sign was associated with greater morbidity in the acute LBP setting [(59)].

TABLE 3. DIAGNOSTIC CRITERIA FOR NON-RED FLAG CONDITIONS

Probable Diagnosis or Broad Category of Injury	Symptoms	Signs	Tests and Results
Nociceptive Pain	Variable depending on the specific injury. Typically non-radiating pain. May have symptoms related to a discrete injury (e.g., burn, fracture, tendon rupture). Weakness may be present, but generally is not related to neurological impairment, rather associated with pain avoidance other than, e.g., fractures, complete tendon tears.	Highly variable findings that depend on the injury, mechanism and extent of injury. May have normal examination or may have abnormalities that include focal skin, muscle, tendon, bone etc. abnormalities. Focal tenderness generally present. Avoidance of use of the affected body part Range of motion decrements may occur. Muscle weakness is typically fear-avoidant and partially/totally overcome by increased effort; exceptions include fractures and complete tendon tears. Normal sensibility, stretch reflex.	None for many disorders and most clinical presentations. Others may involve assessment with x-rays, other imaging studies such as CT, MRI that help define the presence and extent of injury. Rheumatological panels, ESR if concerns about those disorders
Neuropathic Pain	Burning, lancinating, independent of activity; weakness	May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch reflex abnormalities, neurotrophic skin changes	EMG/NCS Glucose tolerance testing, fasting glucose and/or hemoglobin A1c if concerns about diabetes mellitus Possible testing for alcohol (e.g., MCV, GGTP, hepatic enzymes) Rheumatological panels, ESR if concerns about those disorders
Central*	Highly variable findings depending on location and extent of injury (e.g., stroke, multiple sclerosis, spinal cord injury). For purposes of this table, this does not include	Highly variable findings depending on mechanism, extent of injury (may range from no objective findings to paralysis)	Brain MRI (occasionally spinal MRI) Somatosensory evoked potential studies – not indicated for radicular

Probable Diagnosis or Broad Category of Injury	Symptoms	Signs	Tests and Results
	disorders that may involve central sensitization from primary peripheral conditions due to neuroplasticity/neural reorganization, e.g., post amputation pain, irritable bowel syndrome, fibromyalgia. Burning pain perceived peripherally in region of CNS insult	Neurotrophic skin changes usually affecting ipsilateral upper and lower limb and maybe contralateral face	lesions but diagnostic for myelopathic injury/diseases EMG unlikely to be helpful, but often will be abnormal depending on location and extent of insult(s)
Peripheral	Burning pain in distal limbs (may have weakness)	Usually normal; may have symmetrical neurotrophic skin changes	EMG/NCS, blood studies (glucose, ESR, hepatic enzymes, MCV, rheumatological panels)
Radicular	Radiating, lancinating, burning pain Reduced sensibility along dermatomal distribution	Myotomal weakness Reduced stretch reflexes	MRI, EMG/NCS correlate with pain distribution, sensory and/or muscle/reflex deficits; for lumbar, positive straight leg raising present; for cervical, positive provocative maneuvers present
Complex Regional Pain Syndrome	Pain quality is similar to that described for "neuropathic," but involves a distal limb and extends beyond the distribution of a single peripheral nerve and is particularly severe	Asymmetrical use of extremities, swelling (or atrophy), mottling, temperature abnormalities, sudomotor findings, hair/nail/skin findings	Temperature discrepancy between limbs Bone scan $\geq$6 months after onset shows reduced uptake in affected extremity followed by increased radiotracer retention in peri-articular metaphysis of distal limb 3 hours later; 6 months after onset typical demineralization in long bones adjacent to joints distally on affected side Sweat studies

Probable Diagnosis or Broad Category of Injury	Symptoms	Signs	Tests and Results
Trigger Points/ Myofascial Pain (See guideline on Shoulder Disorders)	Non-radiating, usually unilateral pain most commonly periscapular (generally unilateral and in body part subjected to injury)	Muscle taut band or knot with referred pain on palpation Palpation reproduces patient pain Absence of widespread tender points	None Occasionally, rheumatological testing is helpful to demonstrate an alternative disorder
Tender Points/ Fibromyalgia*	Widespread non-radiating pain often with prior or current depression, other affective disorders, and/or other psychological issues; fatigue often present	Absence of "objective" findings on exam. Numerous largely symmetrical tender points were a prior diagnostic requirement. Tender point(s) in muscle nevertheless are often present, which when compressed reproduce patient's pain	No inflammatory markers in blood studies; normal MRI, EMG, x-rays; generally no antecedent physical trauma
Chronic Pain Syndrome**	Enduring or recurring pain persisting longer than typical for an associated condition Inadequate response to appropriate care Marked restriction in daily activities Excessive medication use and frequent use of medical services Excessive dependence on clinicians, spouse and/or family; withdrawal from social milieu, i.e., work or other social contacts	Marked alteration in behavior with frequent depression or anxiety Significant, reliable impairment of functional status inadequately explained by physical findings Evidence of possible psychological dysfunction such as anxiety, fear-avoidance, depression or significant pain or illness behaviors (may have "deconditioning" or poor aerobic endurance), passive-dependence	Psychological evaluation (including diagnostic testing as indicated) may be useful

*Chronic pain is defined as at least 3 months duration in this guideline.

**Non-occupational conditions included for completeness.

Adapted from AMA *Guides to Impairment Rating*, 6th edition [(683)] and Sanders et al. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. *Pain Prac*. 2005;5(4), 303-15 [(684)].

TABLE 4. GUIDELINES FOR MODIFICATION OF WORK ACTIVITIES AND DISABILITY DURATION

DISORDER	ACTIVITY MODIFICATIONS AND ACCOMMODATION	RECOMMENDED TARGET FOR DISABILITY DURATION*	
		Modified Duty Available	**Modified Duty Not Available**
Complex Regional Pain Syndrome (includes Types I and II)	Use extremity as normally as possible. Avoid aggravating activities involving extremity (e.g., forceful prolonged use, heavy lifting, walking or standing). Advance activities as soon as possible for better outcomes. Must be strongly individualized based on the severity of CRPS.	Mild 0-30 days Moderate 30-60 days Severe 60-90 days	Mild 0-30 days Moderate 60-90 days Severe 90-180 days
Peripheral Neuropathy	Generally no limitations required. For severe peripheral neuropathy, modifications may be needed to avoid significantly aggravating exposures (e.g., highly repeated forceful use of hand in distal upper extremity peripheral neuropathy).	Mild 0 days Moderate 0-7 days Severe 7-14 days	Mild 0-3 days Moderate 3-7 days Severe 7-21 days
Tender Points/ Fibromyalgia	Ideally, no limitations. May need graded increase in activity levels to regain normal function if significantly debilitated.	Activity limitations should be avoided.	Activity limitations should be avoided.

*Mild, moderate, and severe are defined by the degree to which the condition affects ADLs; e.g., mild involves little to no impairment in the impact on the patient's ability to perform ADLs, while severe involves marked impairment in the ability to perform ADLs. The clinician should make these determinations based on the presumed impairment specifically due to the underlying condition, noting that reported limitations in ADLs are often a function of psychological and occupational factors, which are typical in chronic pain. Where suspected, they should be ruled out or explicated in the process of determining what actual disability duration is warranted based on the specific underlying condition.

Disability durations are primarily consensus from the Evidence-based Practice Chronic Pain Panel. Disability durations also incorporate data used with permission from Reed Group, Ltd. Reed P. *The Medical Disability Advisor. Workplace Guidelines for Disability Duration, 5th Edition*. 2005. Westminster, Colorado: Reed Group, Ltd.

TABLE 5. CRPS DIAGNOSTIC CRITERIA FOR CLINICAL PURPOSES*

1. Continuing pain that is disproportionate to the inciting event.
2. At least one symptom in three of these four categories:
   - *Sensory:* hyperesthesia and/or allodynia
   - *Vasomotor*: temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - S*udomotor/edema:* edema and/or sweating changes and/or sweating asymmetry
   - *Motor/trophic:* decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. At least one sign at evaluation in two or more of the following categories:
   - *Sensory:* evidence of hyperesthesia to pinprick and/or allodynia to light touch, and/or temperature sensation, and/or deep somatic pressure and/or joint movement
   - *Vasomotor:* evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   - *Sudomotor/edema:* evidence of edema and/or sweating changes and/or sweating asymmetry
   - *Motor/trophic:* evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. *Diagnosis:* CRPS is excluded by the existence of conditions that better explain the signs and symptoms.

*Adapted from (181, 258, 249).

TABLE 6. ADVERSE EFFECTS OF INJECTIONS

General complications of neuraxial injections, and of injections near the paravertebral muscles	Infection at site and remote (meningitis found in one German study following trigger point, facet, and epidural injections). Bleeding, including hematoma causing nerve compromise. Direct trauma to nerve, causing permanent damage or increased pain. Injection into the wrong space (artery, vein, inadvertent intrathecal, or thoracic cavity). This can lead to respiratory compromise, cardiac arrest, or pneumothorax.
Complications specifically related to the substance and amount injected (in addition to possible anaphylaxis)	Local anesthetics – seizures, cardiac collapse. Sympatholytics – hypotension, tachycardia, cardiac dysrhythmias. Corticosteroids* – endocrine dysfunction, diabetes, hypertension, dysphoria, immune compromise, phlebitis, muscle pain, osteoporosis, dependency, rarely nerve damage, etc.

	Baclofen* – anxiety, blurred vision, ataxia, coma, depression, dizziness, dysarthria, dystonic reaction, hallucinations, headache, respiratory depression, seizures, stroke, etc. Botulinum toxins – weakness, paralysis, respiratory compromise, diplopia, dizziness, injection site reaction.

*These adverse effects are mostly temporary aggravations and dependent on dose and frequency.

TABLE 7. SELECTION CRITERIA FOR IMPLANTABLE SPINAL CORD STIMULATORS FOR CRPS

1. Clear diagnosis of CRPS based on criteria that include objective measures, such as the Consensus Criteria.

2. Poor response to conservative treatment generally for at least 6 months,** including treatment in an experienced interdisciplinary clinic with proven good outcomes that included elements of a functional restorative program (i.e., at minimum including progressive strengthening, aerobic, image/mirror therapy exercises and CBT; also having trialed bisphosphonates, glucocorticosteroids, NSAIDs, anti-depressant(s) and gabapentinoids) and for which the patient demonstrated good motivation.

3. Remedial surgery inadvisable or not feasible.

4. Major psychiatric disorders have been treated with expected responses. Somatization disorder not amenable to treatment will disqualify the patient for use of invasive procedures, as the risk of the procedure is higher than the expected success rate. The candidate should have a successful independent, psychological evaluation and a structured interview performed by a psychologist specialized in chronic pain management including appropriate psychometric testing (see Appendix 1). (The psychological evaluation should be performed by a practitioner who is not employed by the requesting or treating physicians).***

5. Willingness to stop inappropriate drug use before implantation.

6. No indication that secondary gain is directly influencing pain or disability complaints.

7. Ability to give informed consent for the procedure.

8. Successful results of at least 50% pain reduction from a trial of a temporary external stimulator of approximately 2-3 days and reduction of use of opioid medication or other medication with significant adverse effects or functional improvement such as return to work that may be evaluated by an occupational or physical therapist prior to and before discontinuation of the trial.

*Adapted from (685,686,687).

**Some authors advocate earlier intervention; however, quality evidence is lacking.

***Presence of depression is common in patients with chronic pain, requires evaluation and may require treatment. Depression that is particularly severe may require treatment prior to assessing appropriateness of SCS; however, the presence of depression does not preclude SCS.

TABLE 8. DIFFERENCES BETWEEN PSYCHOLOGICAL SCREENING AND ASSESSMENT

Psychological Screening	Psychological Assessment
Brief	Comprehensive
Part of a routine visit	Requires a dedicated visit
Designed for early detection of psychosocial complications and identify patients in need of psychological referral	Designed to integrate the results of multiple psychological measures with patient history, medical findings and clinical observations
Narrowly defined scope of assessment	Typically a multidimensional assessment
May be administered by clinicians, support staff with appropriate training, or self administered	Requires interpretation by a psychologist or physician with training in these assessments
Positive finding determined by cutoff score	Positive finding determined by standardized scores which typically produces a percentile rank
Positive finding indicates a need for further psychological assessment	Goal is to reach a definitive conclusions about diagnosis, make determinations about patient disposition, develop treatment plan, and respond to referral questions

TABLE 9. FUNCTIONAL SUMMARY OF ACTIVITIES OF DAILY LIVING (ADLS)

Functional (ADL) Summary	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual
Sitting												
Standing												
Walking												
Climbing stairs												
Walking over uneven ground												
Repetitive neck motions												
Static neck posturing												
Stooping / Twisting (waist)												
Bending / Twisting (neck)												
Squatting												
Kneeling												
Repetitive use of upper extremity (right)												
Repetitive use of upper extremity (left)												
Grasping/Gripping (right hand)												
Grasping/Gripping (left hand)												
Keyboard/Mousing												
Forceful use of upper extremity (right)												
Forceful use of upper extremity (left)												
Fine Manipulation (right hand)												
Fine Manipulation (left hand)												
Pushing & Pulling (right)												
Pushing & Pulling (left)												
Pushing & Pulling (both)												
Reaching (at waist level)												
Reaching (at shoulder level)												
Reaching (above shoulder level)												
Lifting waist to shoulder (lbs.)												
Lifting waist to floor (lbs.)												
Carrying weight in both hands (lbs.)												
Carrying weight in one hand (lbs.)												
ROM of affected area												
% use of affected extremity												

TABLE 10. FUNCTIONAL SUMMARY OF WELL-BEING/QUALITY OF LIFE

Well-Being/QOL & ADL Function Summary	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual	Goal	Actual
Adaptability												
Self-sufficiency												
Self-esteem												
Healthy relationships												
Values based living												
Effective stress management												
Use of wellness techniques												
Increased energy (less fatigue)												
Sleep quality												
Impact of mood symptoms												
Connection to emotions												
Body awareness												
Thought awareness												
Upholding healthy boundaries												
Engaging in hobbies and/or self-care												
Socialization												
Level of irritability												
Level of increased participation/engagement												
Changes in fear of reinjury/Kinesiophobia												
Changes in depression												
Changes in anxiety												
Changes in IADLs*												

APPENDIXES

APPENDIX 1. PSYCHOLOGICAL AND BIOPSYCHOSOCIAL ASSESSMENT TOOLS

Pain-related disability is an exemplary biopsychosocial condition, with psychological and psychosocial concerns occurring concurrently with physical concerns [44,583,584]. To assess this condition, health professionals working in both research and clinical settings frequently gather data via a variety of biopsychosocial questionnaires and related assessment methods. The questionnaires used may be developed using a variety of methods, and can be employed as a systematic means of assessing a patient's pain, physical symptoms, functioning, quality of life, satisfaction with care, cognition, mood, behaviors, and history – essentially any information that the patient can report, and may reveal important information about risk factors, diagnoses, or treatment outcomes. The potential value of these questionnaires was exemplified in a systematic review of the research on psychological test, suggesting validity and reliability that is comparable to that of medical tests [688]. These assessments are important, because if biopsychosocial complications go unrecognized and are not addressed, they may interfere with treatment outcome.

The goal of this appendix is to provide information that will promote the understanding of the use of biopsychosocial questionnaires. The tests listed here include both ones commonly used for screening, to assess outcomes in clinical settings or randomized controlled trials, as well as ones that are used in psychological evaluations. The test descriptions are provided for informational purposes.

Biopsychosocial assessment measures can be divided into three broad categories: screening, outcome assessment, and psychological evaluation. Measures intended for each of these

uses tend to have certain characteristics, and awareness of these differences is beneficial when selecting a measure for a particular use. These three categories of measures can be described as follows:

1. **Screening measure.** A screening measure is a succinct instrument, sometimes as short as one or two questions. It is intended for administration to either an entire population, or an entire cohort of patients with a given condition. The frequency of utilization is typically in the initial exam and/or once a year. The objective of most screening measures is optimization of sensitivity, but not specificity. As a result, screening measures are able to identify at-risk populations, but as they are not able to suggest a diagnosis, a positive screening score is an indication for further diagnostic assessment. Screening measures are often administered by persons with minimal training, and the results are determined by a cutoff score (see Table 8).
2. **Outcome measures**. Outcome measures are unique in that they are intended to assess aspects of a patient's condition that are matters of concern, and that could potentially be changed by treatment. To accomplish this, an effective outcome measure should contain only changeable "state" items, as opposed to items assessing unchanging aspects of the condition. For example, if an outcome measure was intended to assess a patient's response to treatment for pain, a "state" item such as "My pain is so bad that I spend most of the day laying down" assesses a symptom that could be changed by effective treatment. In contrast, an unchanging item such as "I have had back pain for years" is a defining indication of chronic pain. However, this item is a historical fact and not something that any treatment could change. An outcome measure's power to detect change is a function of the degree to which it assesses relevant and changeable aspects of the patient's condition. An outcome measure is scored using an ipsative method which compares the patient to him/herself (e.g. "Is your score today better or worse than when you started?") (see Table 8).
3. **Psychological tests.** Psychological tests are part of the standard for the biopsychosocial assessment of chronic pain, and are generally indicated by either a positive psychological screening test or by clinical indications. The majority of psychological tests intended for clinical assessment utilize multidimensional assessment, and also have one or more validity measures that assess any tendency to magnify, minimize or otherwise distort symptom reports. Because of this, psychological tests are generally much longer than a typical screening test or outcome measure. These measures can be divided into multiple subcategories (see Table 8).
    - **Standardized vs. nonstandardized tests:** The majority of psychological tests intended for clinical assessment are "standardized" (see below) which allows test results to be compared to norms to produce a percentile rank. Most of these measures have scientific peer reviews that are published by the Buros Institute, and are protected by test security (e.g. not posted on the internet, and requiring a credentials check to obtain) which reduces the risk that they can be manipulated. These are interpreted by a psychologist and/or physician with appropriate training. In contrast, some nonstandardized psychological measures are freely available (e.g., The Pain Catastrophizing Scale, the CES-D, PROMIS measures, the Pain Anxiety Symptom Scale, the Pain Self Efficacy Scale) and scoring keys for the scales are freely found. These measures are commonly used in research settings. In contrast to the tests above, while these measures offer a brief assessment of a specific dimension, they are generally not standardized, lack validity measures, and do not offer a

comprehensive overview of biopsychosocial risk factors. These latter measures require less expertise to administer and interpret than standardized multidimensional tests.

- **Psychological vs. Biopsychosocial vs. Neuropsychological tests:** Psychological tests may also be subdivided by the domain to be assessed. The traditional division between these tests was that of psychological measures that assessed factors related to mental health diagnoses (e.g., mood, personality, psychosis, addiction), and neuropsychological measures that assess brain functioning (e.g., memory, ability to learn, knowledge). More recently, biopsychosocial measures have been developed to assess not only psychological variables, but also assess a patient's biological symptom complaints, perception of and beliefs about a medical condition, how a patient copes with a medical condition, any psychological reaction to a medical condition, and social support or secondary gain that could influence the outcome of medical treatment.

The comprehensive assessment of the patient with chronic pain most commonly involves a biopsychosocial assessment. The biopsychosocial evaluation of the patient focuses on interpreting the patient's physical symptoms and complaints within a psychosocial context. A biopsychosocial evaluation may consist of a clinical interview alone. However, the standard for the assessment of chronic pain includes the use of standardized psychological testing. Psychological tests are used for a variety of purposes, including measurement or description of patient traits, diagnosis, tracking change with treatment, and attempting to predict treatment outcome. While pain and disability are widely regarded as being biopsychosocial phenomena, the interrelationships between pain, functioning, physical symptoms, psychological, social and other diagnostic and outcome variables in patients with chronic pain is complex. Professionals utilizing these assessment instruments should be familiar with the strengths and limitations of the chosen assessment method.

Definitions

Cutoff score: A test score used to determine what is a low, average, high, or very high score. Cutoff scores may be determined by data or by reference to diagnostic criteria, or they may be arbitrary.

Ipsative assessment: Comparing a patient's current status to his or her past status (e.g., patient reports being able to function better than before). This is often done in treatment research, and is a well-established method of looking at changes in group scores.

Normative assessment: Comparing a patient to a reference group called a "norm group" (e.g., patient reports more difficulties with functioning than 92% of patients in rehabilitation). Normative scores allow a determination that a particular patient has a high or low score. Any scale capable of normative assessment can also perform ipsative assessment. The most common means of normative assessment used by psychological tests is the T-score.

Norm Group: A reference group to which a patient's score is compared. A general rule of thumb for norm groups used by psychological tests can be stated metaphorically in the following manner: If you are judging apples, comparing apples to apples is better than comparing apples to oranges. The closer the norm group is to the patient's status and situation, the more relevant the resulting score.

Reliability: The ability of a test or scale to produce consistent results, e.g., if a test is given twice in a short time frame, the results should be very similar.

Standardized Test: A standardized test has the following characteristics:

- Standard test administration materials
- Manual/user guide containing
  - Documentation of purpose and uses of test
  - Documentation of test norms and norm groups
  - Instructions for calculating standardized scores (which compares the patient's score to the norm group)
  - Method for interpreting standardized scores
  - Documentation of test reliability and validity
  - Documentation of test development process

T-score: The most commonly used standardized score on psychological tests. A t-score has a mean of 50 and a standard deviation of 10.

Validity: The extent to which a test or scale actually measures what it purports to measure. A common validity concern when psychological tests are used to assess medical patients is that many of these tests use both psychological and medical symptoms to diagnosed psychiatric disorders, and this can lead to false positive findings. For example, if a test of depression includes items about weight change, sleep disturbance, and loss of libido, to what extent is it actually measuring the effects of pain, inactivity, or medication side effects as opposed to depression?

Validity measure: A measure on a test that attempts to assess whether a subject's responses are valid as opposed to being the product of illiteracy, random responding, oppositional behavior, faking, or other attempts to manipulate the results of the test.

Testing Concepts

Standards for Psychological Test Use

Biopsychosocial tests vary greatly with regard to what they are intended to assess and the degree to which they have met accepted testing standards. There are a multitude of clinical and forensic standards that pertain to the assessment of the patient with chronic pain [689]. There are also clearly defined standards for psychological tests, and term "standardized psychological test" indicates that it is a measure whose development sought to meet the criteria defined by a work called the *Standards for Educational and Psychological Testing* [690]. The *Standards* are endorsed by the American Psychological Association and numerous other governmental, professional, credentialing, educational, and advocacy bodies [585]. These standards provide specific guidelines regarding standardized tests, including test development, validity, reliability, norms, fairness issues, the appropriate use of testing, and documentation. A standardized test is evaluated and normed on a population sample, with the norm group ideally being composed of a sample accurately representing the population with regard to age, gender, education, socioeconomic status, racial groups, region, and medical condition. When a test has undergone a formal validation process as specified by *The Standards*, the results of this process are documented in a manual. Most standardized psychological tests are submitted to the Buros Institute for peer review and these reviews are published in the *Mental Measurements Yearbook*.

The *Standards* state that in order for a psychological test to effectively identify unusual levels of a symptom or trait in an individual, the test should be standardized. A standardized test has a standard set of questions and a standard method of administration, scoring, and test interpretation. The resulting raw score is generally converted to standardized scores, which are usually based on a comparison to one or more "norm" groups. These standards also make it clear that the test administrator must have training in test administration and interpretation in order to make meaningful and accurate conclusions. Moreover, the *Standards* also indicate that the standardized tests must be administered and interpreted in a similar method by any clinician who utilizes the tests. While this may seem self-evident, conducting standardized testing in a manner differently from the standard method, places doubt on the resulting test data and how it may be utilized in the evaluation, diagnosis, and treatment process. Overall, any psychological test is preferred to the extent that it is standardized.

Ipsative and Normative Assessment

Ipsative assessment is the simplest method of assessment and can be utilized to compare the individual's performance scores in a pre-post manner. Ipsative assessments are common in medicine and are illustrated by the following examples:

- Prior to treatment, patient could walk for 15 minutes on a treadmill, but after 4 weeks this increased to 30 minutes.
- Prior to treatment, patient endorsed 12 of 20 items on a depression checklist, but after 8 weeks of treatment endorsed only 6.
- Prior to treatment, patient reported a pain level of 6, but after a trial of NSAIDs pain reports decreased to 3.

Ipsative measures compare a patient's present scores to the patient's own previous scores. These types of comparisons allow the assessment of change by a patient, but do not indicate if a patient's scores are high or low. Ipsative measures of this type can be very effective in research, but since this method cannot identify high or low scores, it has limited applicability in clinical assessment.

In contrast to ipsative assessment, some psychological tests employ cutoff scores. To employ this approach, a patient's score is compared to cutoff levels that determine what is interpreted as a low, average, high, or very high score. Cutoff scores may be determined by data or by reference to diagnostic criteria, or they may be arbitrary.

In psychological assessment, the preferred method of assessment is called normative assessment. Normative assessment compares the patient's score on particular measure to a reference called a "norm group," whose average score is called the "norm." Through the use of norms, standardized scores can be calculated. Through this process, it becomes possible to make more precise statements about individual patients. In this manner, standardized tests scores provide a means of identifying whether a patient's symptomatic complaints are unusually high or low relative to the norm group. Normative assessments can also be used in an ipsative manner by comparing the patient both to a group and to his or her own prior performance. Overall, normative assessment provides more information than ipsative assessment, and the use of norms is one of the standards for clinical assessment advocated by the *Standards for Educational and Psychological Testing*.

The nature of the norm group is extremely important. Consider the difference that the three norm groups below make on the follow statement:

This patient in physical rehabilitation is reporting more difficulties with functioning than 92% of…

- healthy persons in the community
- patients in physical rehabilitation
- patients with asthma
- patients with schizophrenia

If the patient is undergoing assessment as part of a physical rehabilitation program, the comparison of the patient's score to healthy persons in the community indicates that the patient is reporting more problems with functioning than the average healthy person. In contrast, using other patients in rehabilitation as the norm group is probably more useful, as if this patients score was higher than that of 92% of other patients, then this is a patient with unusually severe complaints. Alternately, the meaning of the third and fourth comparisons make less sense.

The *Standards* also state that during the development of a test, due consideration should be given to matters of diversity. Consequently, the nature of a test's norms is especially important. If a test's norm group is not sufficiently diverse, the test results could be biased. On the whole, tests which use standardized scores based on norms are preferred. Further, the more relevant the norms are to the patient's medical, gender, race/ethnicity, age, and educational and other group status, the more meaningful the resultant score.

Validity, Reliability and Standardization

For a psychological test to be used in the clinical setting, three characteristics that need to be considered are the reliability, validity, and standardization of that test. Test reliability can be determined by a relatively straightforward process. Internal reliability refers to the degree to which the items on a scale are internally consistent with each other, as opposed to being prone to contradictory findings. Test-rest reliability or test stability refers to the degree to which two administrations of the same test produce the same results. A determination of reliability is an integral part of the development of a standardized test.

The phrase "Text X is a validated measure" is sometimes heard, but this phrase misrepresents and oversimplifies the concept of test validity. It is not correct to say that a test is valid, rather it should be stated that there is a certain level of evidence that a given test is valid for a particular purpose. Test validity is more complex, and can be conceptualized as consisting of three levels.

The first level of test validity is based on the nature of the diagnosis or condition that is being assessed. If a psychological or medical condition is known to have a certain number of symptoms, then it is generally preferable to have items assessing those symptoms. This level of validity, called content validity, may be determined by clinical judgment, or by a panel of experts. A second level of validity pertains to the degree to which a scale actually measures what it is supposed to measure. Thus, if a scale is a measure of depression, it should exhibit a positive correlation to other scales measuring depression, or to clinical judgments of depression. In general, most standardized tests have met these two levels of validity. However, as there are multiple forms of depression, such as major depression, bipolar

depression, dysthymia, and adjustment disorder with depression, a test may be designed to sample only certain aspects of depression. Consequently, while the results of various measures of depression sometimes disagree, this may be understandable if the nature of each instrument is understood.

The third level of validity has to do with the ability of the test to predict current or future diagnoses, traits, behaviors or medical outcomes. Depending on the measure, there may be a greater or lesser amount of evidence to support a particular clinical use. There is a promising and increasing body of evidence suggesting predictive abilities of standardized psychological tests, e.g., to predict the relative outcomes of surgery, multidisciplinary treatment, and other forms of medical treatment [120,691,692,693,694].

Beyond validity and reliability, the *Standards for Educational and Psychological Testing* set more stringent criteria for the assessment of individuals in the clinical setting [585]. According to the *Standards*, in order for a psychological test to fairly assess individual patients, that test should be standardized. That means that in addition to evidence of reliability and validity, the test should have standardized test form/materials, instructions, scoring, norms, and interpretation, as this helps to reduce the error variance introduced by nonstandard assessment methods. All of this information and the test development process and evidence of validity and reliability should be documented in a test manual. Standardization makes it possible to scientifically determine if a particular patient's score is unusually high or low. In general, for clinical assessment, a standardized test is preferred.

Psychological Screening

Current preventive medicine policies recommend screening for a number of medical and psychological conditions. While medical screening is usually accomplished by examination or medical tests, psychological screening is usually accomplished by questionnaire. Under Federal healthcare regulations, the psychological conditions most commonly screened for are depression, substance use, and nicotine dependence [6]. With regard to patients with chronic pain, most opioid guidelines recommend psychological assessment of substance use vulnerability prior to long term opioid treatment [12]. Additionally, comprehensive chronic pain guidelines recommend screening patients with chronic pain for psychosocial contributions to pain [13,14,695], and common psychological conditions to screen for also include anxiety, somatization, dysfunctional cognitive styles (e.g. catastrophizing), or perception of disability / low functionality [17].

The American Psychological Association has noted that while the terms psychological screening and psychological assessment are sometimes used interchangeably, it is important to distinguish between them [16]. The differences between psychological screening and assessment are summarized in Table 8.

Screening tests are designed in such a way as to be short and highly sensitive, at the cost of low specificity. For example, if we think of body temperature as a medical screen, a temperature of 101 F can suggest that something is wrong, without providing any specific information about diagnosis. Similarly, a positive depression screen suggests that the patient is reporting being distressed, without telling us if the patient has diagnosable depression, and if so, if the depression is due to an injury, a bad marriage, or bipolar disorder. Consequently, like medical screens, the purpose of a psychological screen is not to provide a definitive diagnosis but rather to indicate a need for further assessment.

For the treating clinician, brief psychological screening questionnaires may provide information that can help to identify patients with psychological conditions. When psychological screening assessments are positive, or when there are other indications of psychological dysfunction or uncorroborated medical symptoms, a comprehensive psychological evaluation is indicated.

Psychological and Biopsychosocial Outcome Measures

In contrast to screening measures that are intended to identify patients in need of further assessment and treatment, outcome measures are intended to assess the patient's response to treatment. Like screening measures, outcome measures are brief, and may be administered by clinicians, support staff with appropriate training, or self-administered. Outcome measures may be administered in three different ways: pre-post, serial, and post hoc (i.e., occurring after the treatment).

A pre-post assessment is an ipsative assessment method that compares a patient's baseline level of functioning at the start of treatment to their functioning when treatment has concluded. A pre-post assessment is required to determine the degree to which any treatment actually produced change, and plays a critical role in determining treatment efficacy. A strength of pre-post assessment is that by identifying patients with severe pre-treatment symptoms, even a moderate level of functionality post-treatment is an indication that the patient benefited greatly from treatment. This assessment method helps to control for severity of the medical condition, and can be useful for clinicians who treat patients with catastrophic injuries.

Serial assessment is an ipsative method similar to pre-post assessment, except that while pre-post assessment occurs at the beginning and end of treatment, serial assessment is ongoing and occurs at regular intervals (e.g., once a week, once a month, etc.). A potential use of serial assessment is that it can help to determine when a patient is not benefitting from treatment, and more broadly when *maximum medical improvement* occurs. Maximum medical improvement (MMI) is said to occur when a patient's progress in treatment plateaus, and where it is believed that the patient is unlikely to make gains from further treatment. One method to determine the endpoint of treatment is to use the serial assessment of a relevant functional measure, as the scores may be plotted and graphically illustrate when a treatment plateau occurs.

In theory, serial assessment is an excellent means of determining undertreatment (i.e., stopping treatment when scores are still improving) and over treatment (i.e., continuing to treat after the response to treatment has plateaued). In practice however, there are a number of major threats to the validity of serial assessment.

The first threat to the validity of serial assessment has to do with floor and ceiling effects. To understand the problem created by these effects, consider a hypothetical measure of functioning we will call The Weightlifting Test. Suppose The Weightlifting Test had the following items:

After performing your exercises in the gym, answer the following questions True or False:

1. I am able to lift 40 pounds.
2. I am able to lift 42 pounds.
3. I am able to lift 44 pounds.
4. I am able to lift 46 pounds.

5. I am able to lift 48 pounds.
6. I am able to lift 50 pounds.

This hypothetical Weightlifting Test will make fine discriminations in a patient's level of functioning from 40-50 pounds, and within that range would be a valid measure and reliable measure. But below the "floor" of 40, improvement in strength from 10 to 30 pounds will not register on this measure. Similarly, improvement in strength from 80 to 100 pounds will not register either, as that change is above the "ceiling" of the instrument. When changes are occurring below the floor or above the ceiling on an instrument, this measure is no longer valid, as it will wrongly appear that the patient's condition is not changing when that is actually not the case. Note that instruments constructed using Item Response Theory (e.g., PROMIS) usually have fewer problems with floor/ceiling effects, as this test development method excels at controlling this.

A second threat to the validity of our hypothetical test has to do another source of error called a content validity problem. To illustrate this problem, suppose a patient's Weightlifting Test score remained at a constant 46 pounds for four weeks. This would appear to suggest that the patient is no longer benefitting from that treatment. However, during this same period, while strength remained unchanged, the patient may have made gains in range of motion. The problem is that as the content of the items of The Weightlifting Test do not assess range of motion, The Weightlifting Test is not a valid measure of changes in range of motion. This is called a content validity problem, and when it occurs in this context a patient's progress may appear to plateau, when actually it is still progressing on a different dimension.

There are also other threats to the validity of serial assessment. These include that many treatments have a typical time required to produce an effect (e.g., after 30 minutes of exercise a patient may not be any stronger). Consequently, patients may initially exhibit a baseline plateau before the benefits of the treatment are seen, and this baseline plateau does not indicate termination of treatment. In other cases, patients may exhibit a treatment plateau not because they are at MMI, but because they are not getting the treatment that they need. Overall, while serial assessments potentially have value in assessing response to treatment, there are numerous ways that it can produce erroneous results.

In contrast to pre-post and serial assessments, post hoc assessments are administered on one occasion after treatment has concluded. Post hoc measures most commonly assess matters such as patient satisfaction with care, but may also assess patient disposition following care, such as did the patient return to work? In some cases, post hoc measures attempt to simulate a pre-post assessment by utilizing patient recollection (e.g., "Do you think you are better now than when you started?"). However, as treatment may have begun months and sometimes years in the past, patient recollections of their own baseline level of functionality may not be reliable.

Finally, in some economic models, patient outcomes are used to incentivize clinicians (e.g., "pay for performance"). Alternately, whether or not a patient has responded positively to treatment at some point in time is sometimes used to make determinations regarding whether or not more treatment is indicated. Pre-post and post hoc outcome assessment methods often tap different aspects of medical treatment outcome, and a comprehensive outcome assessment protocol would include both.

The Psychological Evaluation Process

Due to the prevalence of psychological conditions observed in patients with chronic pain, it is important to psychologically assess the patient to ensure that these conditions are identified and addressed in the treatment process. However, clinical biases and an over-reliance on subjective perceptions from both the treating professional and patient can lead to inaccurate diagnosis and treatment failure. Objective psychological tests can be helpful in this regard, by providing a system of checks and balances for any biases in treating professional's clinical impressions. Thus, appropriate psychological tests provide a means to make the evaluation and treatment process more objective.

For the treating clinician, brief psychological questionnaires can provide information that can help to identify patients with psychological conditions (see Table A4c). In conjunction with an interview and examination, these questionnaires can facilitate a comprehensive assessment of the patient. When these screening assessments are positive for emotional distress, or when there are other indications of psychological dysfunction or uncorroborated medical symptoms, a comprehensive psychological evaluation is indicated and they also reveal therapeutic targets and the likely need for brief educational interventions about pain.

When patients are referred for a psychological assessment, the referral should include a specific clinical rationale. Psychological assessment is distinct from neuropsychological assessment. Neuropsychological assessment relies primarily on measures of cognitive ability, memory and concentration to assess patients with brain injury or disease. In contrast, psychological assessment focuses on the assessment of personality, mood, psychosis, emotional trauma, social conflicts, and the patient's beliefs about and reports of pain and other somatic symptoms. In relatively straightforward cases, extensive psychological testing is not always needed. The clinical interview though provides a mechanism for screening those individuals who are a higher risk for psychological concerns (e.g., substance use disorder, past psychological history, chronic physical concerns, not progressing as anticipated, or lack of objective medical evidence that supports the individual's symptoms). When these risk factors are present, the patient is likely a candidate for standardized psychological testing.

The professional performing the psychological evaluation is generally a psychologist with PhD, PsyD, or EdD credentials, or in some states may be a mental health professional. A physician with MD/DO credentials and proper training may perform the initial comprehensive evaluation. These professionals should have experience in diagnosing and treating chronic pain disorders in injured workers. Screening and outcome measures are commonly administered by a variety of professions. In contrast, standardized psychological and neuropsychological tests are most commonly administered by psychologists with a PhD, PsyD, or EdD degree. Standardized psychological and neuropsychological tests can also by administered by physicians or mid-level professionals with appropriate training or supervision, but, for some tests, documentation of appropriate training is required to access standardized measures protected by test security.

When psychological assessments are conducted, generally at least two standardized psychological tests are required to assess the same concern. One psychological test may not measure all of the variables that need to be assessed, thus additional tests may be needed to address all of the referral concerns. In general, evaluations utilizing shorter, one-dimensional tests (those that measure only one psychological concern) require the use of a

greater number of tests, while the reliance on larger, multi-dimensional tests tend to result in fewer tests being needed. That said, a general rule for psychological testing is to use the minimum number of tests necessary to adequately assess the identified concern or referral question(s). Additionally, psychological tests should not be given without consideration of the referral question(s) to be answered or psychological concern(s) that need to be ruled in or out. The use of additional psychological tests is not indicated if they do not objectively measure the identified clinical issue(s), are redundant measures of clinical concerns that have already been assessed or are not validated for clinical assessment. A systematic review found that the variables of pain, functioning, depression, anxiety, somatization, passive coping, job dissatisfaction, low education, and longer time off of work are associated with a poor outcome from lumbar surgery [(587)]. Expert consenus has also identified a number of other less well researched variables [(57)]. Presurgical psychological evaluations for lumbar surgery should assess these variables, in addition to a more general assessment of psychopathology.

The test descriptions are provided for informational purposes only in Tables A1–A3. These are not exhaustive lists, and are not intended to make recommendations. Additionally, this information is not intended to direct payers regarding which tests should be covered for diagnostic purposes. Furthermore, the information is not intended as a guiding document for legal concerns. Each area represents multiple complex issues that are governed by different state and federal regulations [(689)]. The final decision about which tests to use must be left to the evaluator, and the science is not at a point where it can be stated that a specific test is preferable for any purpose. Within each section, tests are listed in alphabetical order.

If the psychological evaluation is being conducted in order to qualify the patient for a specific treatment protocol or surgery, the psychologist should not be employed by the organization or practice performing that service. An exception to this would be multidisciplinary programs, where the psychological assessment and treatment are both part of an integrated program. Users should also be aware of the potential for test data to become forensic evidence either during or after the treatment process. While this appendix is not intended to provide professional direction regarding the complexities of the forensic process, the test user must understand that psychological test results as well as the test user's interpretation of the data have a significant potential for being introduced into the legal process with the chronic pain population. Consequently, it is important to recognize this potential when conducting the evaluation.

The release of personal health information in a psychological evaluation should be mindful of the HIPAA Minimum Necessary Standard. This standard states that the clinician should exercise reasonable efforts not to disclose more than the minimum amount of information needed to accomplish an intended purpose. When the results of a psychological evaluation are being released to another clinician for treatment purposes, this standard does not apply. However, in Worker Compensation settings, the results of a psychological assessment may be available to the employer, especially if the patient is in litigation. When this is the case, the Minimum Necessary Standard may apply to sensitive psychological information.

Identifying Invalid Test Protocols

Unlike research settings, information gathered from psychological tests in the clinical setting is not anonymous, but specific to the individual. This information serves an important role in

making clinical decisions pertaining to treatment or disability awards. Because of this, the individual may be incentivized to bias the information provided. Consequently, clinical tests often include validity measures that assess any reporting biases on the part of the patient.

There are a variety of patient behaviors that could invalidate the results of a psychological test or other self-report measure [586]. A patient may provide distorted or incorrect information for a variety of reasons, including secondary gain in the form of money, attention, access opioid or other medications, or work avoidance. Alternately, some patients may fail to answer out of concerns about the limits of confidentiality, embarrassment, confusion, or illiteracy. While some psychological tests are more subtle, others are totally transparent to the patient and the results can be manipulated with ease. To control for this, many psychological tests employ validity indices. Validity indices generally fall into one of five categories:

1. validity measures designed to detecting exaggerating, "simulation" or "faking bad";
2. validity measures designed to detecting minimizing, "dissimulation" or "faking good";
3. validity measures designed to detect random, inconsistent, or bizarre responding; and
4. validity assessment that tests for contradictory responses.

A further consideration that can sometimes invalidate a test is a failure to respond (leaving items blank), which can suggest either a lack of motivation, difficulty with comprehension, fatigue, or a resistance to answering certain questions.

Psychological screens and outcome measures as a rule do not have validity measures. In contrast, psychological assessments usually include validity measures. When validity indices are absent, the test administrator may not be able to determine if the test taker is minimizing, exaggerating, or otherwise distorting responses. When there are strong incentives for the patient to manipulate the test responses, such as financial gain, access to opioid prescriptions, access to other desired treatments, or work avoidance, transparent assessment protocols without validity measures should be avoided. Overall, the use of standardized psychological tests that incorporate measures to assess the validity of patient responses is strongly suggested when performing psychological assessments, as an important part of a psychological assessment is determining any biases that might influence how a patient presents information. It should be noted that psychological test results should always be used in combination with an interview, medical records and other sources of information when evaluating a patient.

What Psychosocial Variables Need to Be Assessed?

As noted in the section on Psychological Evaluation in the Chronic Pain Guideline, there are a number of reasons why a patient may be referred for psychological assessment. While some concerns, such as depression and anxiety, are commonly assessed, more specific concerns to be assessed are determined by the nature of the referral. When psychological tests are used, the clinician (usually a psychologist) is responsible for the selection and use of appropriate test instruments that adequately and objectively assess noted clinical concerns [57] [16].

Several psychosocial variables have been identified as predicting surgical outcomes (see Table A1) [587,691,693,696,697,698,699]. The evaluation of these variables is indicated when

performing presurgical psychological evaluations prior to lumbar surgery. The Den Boer and Celestin studies concluded that the outcome of lumbar surgery was determined by a set of multiple biopsychosocial variables – pain, functioning, depression, anxiety, somatization, passive coping, job dissatisfaction, low education, and longer time of work – suggesting that when more of these factors are present, the worse the prognosis or surgical outcome.

TABLE A1. GLOSSARY OF PSYCHOLOGICAL SCREENING MEASURES FOR DEPRESSION AND ANXIETY

Test	Description
Screening Tools for Depression or Anxiety ***These brief tools are intended for the assessment of depression and anxiety and can be used by the clinician to screen for affective distress. They should not be used for diagnostic purpose.***	
BDI II **5-10 minutes**	**Beck Depression Inventory II*** http://www.pearsonclinical.com/psychology/products/100000159/beck-depression-inventoryii-bdi-ii.html *Measures:* Assesses depression using items incorporating a broad range of cognitive, affective and physical depressive symptoms *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores; widely used clinically and in research *Comments:* Has scoring software. Scale includes physical symptoms that could be attributable to depression, illness, or medication adverse effects(588,589,590,591,592). The BDI for Primary Care (BDI-PC) is a shorter version of the BDI II and considered to be independent of physical function (592). It produces only a yes/no indication for depression. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
CES-D **3-5 minutes**	**Center for Epidemiological Studies Depression Scale** http://cesd-r.com/ *Measures:* Depression *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Not copyrighted, freely available, has been widely used in research. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
HDI **3-5 minutes**	**Hamilton Depression Inventory** https://www.tjta.com/products/tst_020.htm

	Measures: A brief measure self-report inventory that assesses depressive symptomatology. *Validity measures:* None *Norms and Validation:* Uses community norms *Comments:* Has scoring software A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
HDS or HAM-D **3-5 minutes**	**Hamilton Rating Scale for Depression** http://healthnet.umassmed.edu/mhealth/hamd.pdf *Measures:* A brief rating scale filled out by the professional that assesses a broad range of cognitive, affective, and physical depressive symptoms *Validity measures:* None *Norms and Validation:* Uses cutoff scores *Comments:* Since the professional fills out this measure, results may be affected by interviewer bias. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
STAI-AD **10 minutes**	**State-Trait Anxiety Inventory for Adults** http://www.mindgarden.com/145-state-trait-anxiety-inventory-for-adults Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press. *Measures:* Assess both anxious states and anxious tendencies without reliance on physical symptoms *Validity measures:* None *Norms and Validation:* Community norms, with male and female subgroup norms by age group. *Comments:* Used in a considerable amount of research. A positive screen for anxiety indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing. This screen distinguishes anxiety from depression. It is available in multiple languages.
Zung Depression Scale **3-5 minutes**	**Zung Depression Scale** http://healthnet.umassmed.edu/mhealth/zungselfrateddepressionscale.pdf *Measures:* A brief measure of depression that assesses a broad range of cognitive, affective, and physical depressive symptoms *Validity measures:* None *Norms and Validation:* No norms used, only estimated cutoffs whose applicability to medical patients is uncertain.

	Comments: Widely used in research. Scale includes physical symptoms that could be attributable to depression, illness, or medication side effects. Not copyrighted, freely available. A positive screen for depression indicates that the person should be referred to a clinical psychological for additional evaluation and potential psychological testing. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.

*Proprietary.

TABLE A2. GLOSSARY OF PSYCHOLOGICAL SCREEN MEASURES FOR ASSESSING PAIN AND FUNCTION

Test	Description
Brief Functional Assessment Tools ***These brief tools are intended for the assessment of functioning, and can be used to track progress in treatment. These tools should not be used for diagnostic purposes.***	
Oswestry **4-6 minutes**	**Oswestry Low Back Pain Disability Questionnaire** Fairbank JCT & Pynsent, PB (2000) The Oswestry Disability Index. *Spine*, 25(22):2940-2953. *Measures:* Problems with functioning *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Intended for assessing disability secondary to back pain and injury. This commonly used measure of functioning in research studies is known to be sensitive to assessing change. Original version has been shown to be an effective research outcome measure, but there are also several modified versions. Cutoff scores derived for original Oswestry should not be applied to modified versions. Not copyrighted, freely available. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
PDQ **3-4 minutes**	**Pain Disability Questionnaire** http://www.integrativepainsolutions.net/pain_disability_questionnaire.pdf *Measures:* Assesses disability associated with pain *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Brief tool that appears to be a very sensitive measure of disability associated with pain (700). One study found that it predicted rehabilitation outcome (701). Not copyrighted, freely available.

	A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
POP **3-5 minutes**	**Pain Outcomes Profile** http://www.aapainmanage.org/resources/tools/pain-outcomes-profile/ *Measures:* Assesses pain and pain interference with a variety of activities *Validity measures:* None *Norms and Validation:* Cutoff scores. Norms have not been released at time of publication. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
Roland and Morris Disability Questionnaire **3-4 minutes**	**Roland and Morris Disability Questionnaire** http://www.rmdq.org/ *Measures:* Problems with functioning *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Intended for assessing disability secondary to back pain and injury. Commonly used measure of functioning in research studies. Not copyrighted, freely available. *Languages:* English and Arabic, Chinese, Croatian, Czech, Danish, Dutch, Flemish, French, German, Greek, Hindi, Hungarian, Iranian, Italian, Japanese, Kannada, Korean, Marathi, Norwegian, Polish, Portuguese, Romanian, Russian, Spanish, Swedish, Tamil, Telugu, Thai, Tunisian, Turkish, and Urdu. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
<u>Brief Pain Assessment</u> ***These brief screening measures are intended for pain assessment and can be used by the clinician to track changes in pain, but should not be used for diagnostic purposes.***	
BPI–Long Form **15-25 minutes**	**Brief Pain Inventory – Long Form** http://www.npcrc.org/files/news/briefpain_long.pdf *Measures:* Assesses pain, pain variation, pain distribution, and degree to which pain interferes with functioning. Also includes a variety of questions about pain quality, response to treatment, and open-ended questions to which the patient can respond. *Validity measures:* None. *Norms and Validation:* No norms or cutoff scores. *Comments:* Only assesses problems with functioning associated with pain as opposed to physical limitations.

Brief Pain Inventory – Short Form **4-6 minutes**	**Brief Pain Inventory – Short Form** http://www.npcrc.org/files/news/briefpain_short.pdf *Measures:* Assesses pain, pain variation, and pain distribution through drawing. Also assesses degree to which pain interferes with functioning. *Validity measures:* None. *Norms and Validation:* No norms or cutoff scores. *Comments:* Only assesses problems with functioning associated with pain as opposed to physical limitations.
MPQ **Short Form** **3-5 minutes**	**McGill Pain Questionnaire** http://prc.coh.org/pdf/mcgill%20pain%20questionnaire.pdf *Measures:* Assesses sensory, affective, and evaluative dimensions through the use of verbal descriptors of pain experience as opposed to pure pain intensity. *Validity measures:* None. *Norms and Validation:* Cutoff scores. *Comments:* Some debate over what the scale is actually measuring; may not be useful for tracking changes in pain intensity due to treatment. *Languages:* English and Amharic (Ethiopian), Arabic, Chinese, Czech, Danish, Dutch, Finnish, Flemish, French, German, Greek, Hungarian, Italian, Japanese, Norwegian, Polish, Portuguese, Slovak, Spanish, and Swedish.
NRS **< 1 minute**	**Pain Numerical Rating Scale** http://www.rehabmeasures.org/pdf%20library/numeric%20pain%20rating%20scale%20instructions.pdf *Measures:* Pain intensity. *Validity checks:* None. *Norms and Validation:* No norms or cutoffs; used in thousands of research studies. *Comments:* Recommended by JCAHO. Extremely easy to use, most often administered verbally. Proven usefulness in ipsative assessment, but has not been normed. Complete lack of standardization with literally thousands of variations. No defined instructions with regard to what constitutes a 10 (e.g., worst pain imaginable), time frame (e.g., pain now vs. pain last week), location (overall pain vs. pain in one body site), scaling (e.g., 1-10, 0-10, 1-100). Verbal rating may not be presented the same way each time.
VAS **<1 minute**	**Pain Visual Analog Scale** https://www.painedu.org/downloads/nipc/pain%20assessment%20scales.pdf D. Gould et al. Visual Analogue Scale (VAS). *Journal of Clinical Nursing* 2001; 10:697-706 *Measures:* Pain intensity.

	Validity checks: None. *Norms and Validation:* No norms or cutoffs; used in thousands of research studies. *Comments:* Proven usefulness in ipsative assessment, but has not been normed. Complete lack of standardization with literally thousands of variations. No defined instructions with regard to what constitutes the highest pain level, time frame, location, and visual presentation (e.g., are numbers listed, line length, horizontal or vertical line). More difficult for some people to use than numerical scales. May be more sensitive to small changes in pain than numerical scales. Used extensively in research. Given that it must be administered in a printed form, is more likely to be presented the same way each time than a verbal Numerical Rating Scale.
Quebec Back Pain Disability Questionnaire **5 minutes**	**Quebec Back Pain Disability Questionnaire** http://scale-library.com/pdf/quebec_back_pain_disability_scale.pdf *Measures*: 20 daily activities that are categorized into 6 types of activities. These activities are bed/rest, sitting/standing, ambulation, movement, bending/stooping, and handling of large/heavy objects. This measure is for low back pain and limitations in functioning. This is a self-administered screen. *Validity*: Construct, Convergent, Content and Face *Scores*: Broken into 5 groups: mild, moderate, severe, very severe, and extreme perceived disability. Movement from a higher group to a lower group suggests improvement. Mild and Moderate Scores are considered Group A= likely to be fully back to work within 1 year with the same employer. All remaining groups are Group B. Group B patients are identified as needing a biopsychosocial approach. This means a multidisciplinary treatment approach, including cognitive behavioral therapy. *Comments*: Freely available. Can be used as a screen and an outcome measure. It is meant to be given at the beginning of treatment.
PHQ **5 minutes**	**Patient Health Questionnaire** http://www.phqscreeners.com/sites/g/files/g10016261/f/201411/english_0.pdf *Measures*: The PHQ is a self-administered version of the PRIME-MD. It screens for somatization and self-evaluation of severity of physical and mood symptoms. There are several versions of the PHQ: PHQ, PHQ-4, PHQ-7, PHQ-9, and PHQ-15. *Validity*: Cross-sectional, Construct, Criterion *Norms and validation:* No norms. Cut-off scores are used. *Comments*: The PHQ is freely available. It is currently in different languages: Czech, Danish, Dutch, English, Finnish, French, German, Hebrew, Hungarian, Italian, Korean, Malay, Mandarin, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, and Traditional Chinese. Can be used as a screen and outcome measure.

Neck Disability Index **5 minutes**	**Neck Disability Index (NDI)** http://academic.regis.edu/clinicaleducation/pdf%27s/ndi_with_scoring.pdf *Measures:* Assesses neck functioning. Measures activity limitation, participation restriction, and impairment within ICF classification. Self-administered. It is a validated variation of the Oswestry. It is intended to use with individuals with chronic neck pain, musculoskeletal pain, whiplash injuries, and cervical radiculopathy. *Validity:* Construct *Norms and validation:* Uses cut-off scores. *Comments:* Is useful for predicting progression from acute to chronic neck dysfunction. The NDI may have floor/ceiling effects. The user of the NDI should supplement with another outcome measure. A higher score indicates more reported functional impairment. Can be used as a screen and outcome measure.
Upper Limb Functional Index **5 minutes**	**Upper Limb Functional Index (ULFI)** https://www.worksafe.vic.gov.au/__data/assets/pdf_file/0003/10956/upper_extremity.pdf *Measures:* Assesses functioning related to upper extremities through 20 items. It is a self-administered screen. Questions are answered on a Likert-scale ranging from extreme difficulty to no difficulty. *Validity:* Construct *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The ULFI can be used to assess initial functional, treatment progress and treatment outcome. Can be hand scored. There is an online score calculator found at: https://www.thecalculator.co/health/upper-extremity-functional-index-(uefi)-calculator-955.html
Lower Extremity Functional Scale **5 minutes**	**Lower Extremity Functional Scale (LEFS)** http://www.mccreadyfoundation.org/documents/lefs.pdf *Measures*: Self-administered screen comprised of 20 items related to function of the lower limb only. There are no screens for anxiety or depression. It is reported to be used to measure initial function, treatment progress and outcome. *Validity*: Construct and concurrent. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* This item is freely available. The LEFS can be hand scored. An online score calculator is found at: https://www.thecalculator.co/health/lower-extremity-functional-scale-(lefs)-calculator-1020.html

	Higher scores indicate less functional difficulty. Is validated for patients with TKA, ankle sprains, inpatient and outpatient lower extremity MSK conditions.
Lower Limb Questionnaire **5 minutes**	**Lower Limb Questionnaire** http://www.aaos.org/research/outcomes/lower_limb.pdf Measure: This is a self-administered screen comprised of 7 questions pertaining to lower limb function only. Validity: Content, construct, and concurrent. Comments: Developed by several professional orthopedic organizations. This screen is freely available. It can be used as a screen and outcome measure.
Foot and Ankle Ability Measure **5 minutes**	**Foot and Ankle Ability Measure (FAAM)** http://www.aptsnc.com/wp-content/uploads/2012/11/foot-and-ankle-ability-measure.pdf http://www.aaos.org/uploadedfiles/preproduction/quality/measures/foot%20and%20ankle%20ability%20measure.pdf *Measures:* Self-administered screen pertaining functioning of foot and/or ankle conditions. Has 29 items, with 8 items rated in a sports subscale and 21 items rated in an ADL subscale. Validated for individuals with diabetes and foot and/or ankle conditions. Items are rated on a Likert scale. Sport and ADL subscales are score separately. *Validity:* Content, construct *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The FAAM can be used to assess chronic ankle instability, heel pain/plantar fasciitis, RA and OA of the foot/ankle, sprains, and fractures. Lower scores indicate higher loss of function.
Patient-Specific Functional Scale **<5 minutes**	**Patient-Specific Functional Scale (PSFS)** *Measures:* Assesses functioning with an orthopedic condition. Has been validated for neck, upper extremity, and knee dysfunction. Measures activity limitation, participation restriction, and impairment within ICF classification. The total score is derived from the sum of activity scores. *Validity:* Construct, concurrent, divergent *Reliability:* High test-retest reliability *Norms and validation*: Concurrent, convergent. *Comments:* The PSFS is free. Floor effect is observed with knee dysfunction. Individuals generally identify activities where substantial impairment exists. There is no space on the scale for the individual to note deteriorating functioning. The PSFS has been used with the following conditions: joint replacement, knee dysfunction, low back pain, lower limb amputees, multiple sclerosis, neck dysfunction and whiplash, public symphysis, pain in pregnancy, spinal stenosis, and upper extremity musculoskeletal conditions. Can be used and a screen and outcome measure.

Orebro Musculoskeletal Pain Questionnaire **5-10 minutes**	**Orebro Musculoskeletal Pain Questionnaire (OMPQ)** *Measures:* Assess the risk than an injured worker will develop a long-term disability or failure to return to work following a musculoskeletal injury. It is comprised of 21 questions. It identifies psychosocial factors that impact on recovery and return to work. It is completed 4-12 weeks after the injury. *Validity:* Construct, concurrent, convergent, discriminant. *Reliability:* High test-retest, sensitivity, and specificity. *Norms and validation:* *Comments:* Can be used for all body regions, including spine, upper extremities, and lower extremities. Is useful for identifying potential risk factors so that early intervention can take place.

TABLE A3. GLOSSARY OF PSYCHOLOGICAL OUTCOME MEASURES FOR ASSESSING PAIN, MOOD, SLEEP DISTURBANCE, AND FUNCTIONING

Test	Description
PROMIS Measures ***These brief tests are intended for the assessment of pin, mood, sleep disturbance, and functioning, and can be used to track progress in treatment as well as outcome.***	
PROMIS-29 **Profile** **5-15 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?aspxautodetectcookiesupport=1#5 *Measures:* Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health and other national organizations. Short forms have 4-10 items. CATs have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved.

	PROMIS measures are available in English and Spanish, with additional language versions currently under development. Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-29 are found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/promis-29%20profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.
PROMIS-43 **15-25 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?aspxautodetectcookiesupport=1#5 *Measures:* Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health. Short forms have 4-10 items. CATs have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved. PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-43 is found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/promis-43%20profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.
PROMIS-57 **30-40 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?aspxautodetectcookiesupport=1#5

	Measures: Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health. Short forms have 4-10 items. CATs have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved. PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-57 is found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/promis-57%20profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.
NIH Toolbox **1-5 minutes**	**NIH Toolbox Measures** http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox *Measures:* Assesses cognitive, emotional, sensory, and motor functions. However, regarding pain, the NIH Toolbox recommends just two measures which are discussed below. Cook, K.F., Dunn, W., Griffith, J.W., Morrison, M.T., Tanquary, J., Sabata, D., Victorson, D., Carey, L.M., MacDermid, J.C., Dudgeon, B.J. and Gershon, R.C. (2013) 'Pain assessment using the NIH Toolbox', *Neurology*, 80(Issue 11, Supplement 3), pp. S49–S53. doi: 10.1212/wnl.0b013e3182872e80. *Validity measures:* Content, Concurrent, Cross-sectional *Norms and Validation:* No norms, uses cutoff scores *Comments:* The NIH Toolbox uses two measures to assess pain in adults. The first is a single question pertaining to rating pain-intensity on a 0-10 scale. The second is the PROMIS Pain Interference v1.0-Pain Interference 6a. This short-form measure has 6 items. The PROMIS Pain Interference v1.0 6a measure is found at:

	http://www.healthmeasures.net/administrator/components/com_instruments/uploads/promis%20sf%20v1.0%20-%20pain%20interference%206a%206-2-2016.pdf However, PROMIS has four pain interference measures in short form: 4a, 6a, 6b, and 8a. The number is associated with the number of items in each short form. All PROMIS pain short forms are found at: http://www.healthmeasures.net/search-view-measures?task=search.search PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free.
SF-36 **5-15 minutes**	**36-Item Short-Form Health Survey** http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html *Measures:* General physical and mental health *Validity measures:* Cross-sectional, Criterion, and Face *Norms and Validation:* SF-36 is the most familiar of a series of related instruments developed through the Medical Outcomes Study initiated by the RAND Corporation. Hypertension and other norms available for original SF-36, which had both acute and standard forms. SF36 v2 has uniform format, and standardized T scores using community norms. RAND 36-Item Health Survey 1.0 includes the same items as those in SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Other forms include the longer HSQ 2.0, and the shorter SF-20, SF-12, SF-12v2, SF-10 and SF-8. *Comments:* Has scoring software. Does not assess depression, anxiety, or somatization. Reading level varies between items, with some items as low as grade 2, and other items as high as grade 12 [(594)]. *Languages:* English and Spanish, German, French, Chinese, Japanese, and for persons from the following countries: Armenia, Bangladesh, Brazil, Bulgaria, Cambodia, Croatia, Czech Republic, Finland, Greece, Hungary, Iceland, Israel, Korea, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, Tanzania, Turkey, Wales (UK), and Vietnam. Comments: RAND Health developed the SF-36. RAND requires the user to obtain written permission for any changes made to the SF-36. Any publications with changes in the SF-36 and published must clearly note the changes made to the SF-36. It must also give written credit to RAND and that the SF-36 was developed as part of the Medical Outcomes Study.

Quebec Back Pain Disability Questionnaire **5 minutes**	**Dallas Pain Questionnaire** http://scale-library.com/pdf/dallas_pain_questionnaire.pdf *Measures*: Self-questionnaire specific to low back pain. Assess pain and function on daily living. There are four main areas that are assessed: daily activities, professional activities, anxiety/depression, and sociability. This is a self-administered screen. Questions are based on a five-point Likert scale. *Validity*: Face, content, criterion, construct. *Comments*: The scale is available in English and French. The scale is free. Can be used as a screen and outcome measure.
Dallas Pain Questionnaire **5 minutes**	**Dallas Pain Questionnaire** http://scale-library.com/pdf/dallas_pain_questionnaire.pdf *Measures*: Self-questionnaire specific to low back pain. Assess pain and function on daily living. There are four main areas that are assessed: daily activities, professional activities, anxiety/depression, and sociability. This is a self-administered screen. Questions are based on a five-point Likert scale. *Validity*: Face, content, criterion, construct. *Comments*: The scale is available in English and French. The scale is free.
Patient-Specific Functional Scale **<5 minutes**	**Patient-Specific Functional Scale (PSFS)** *Measures:* Assesses functioning with an orthopedic condition. Has been validated for neck, upper extremity, and knee dysfunction. Measures activity limitation, participation restriction, and impairment within ICF classification. The total score is derived from the sum of activity scores. *Validity:* Construct, concurrent, divergent *Reliability:* High test-retest reliability *Norms and validation*: Concurrent, convergent. *Comments:* The PSFS is free. Floor effect is observed with knee dysfunction. Individuals generally identify activities where substantial impairment exists. There is no space on the scale for the individual to note deteriorating functioning. The PSFS has been used with the following conditions: joint replacement, knee dysfunction, low back pain, lower limb amputees, multiple sclerosis, neck dysfunction and whiplash, public symphysis, pain in pregnancy, spinal stenosis, and upper extremity musculoskeletal conditions. Can be used and a screen and outcome measure.
Neck Disability Index **5 minutes**	**Neck Disability Index (NDI)** http://academic.regis.edu/clinicaleducation/pdf%27s/ndi_with_scoring.pdf *Measures:* Assesses neck functioning. Measures activity limitation, participation restriction, and impairment within ICF classification. Self-administered. It is a validated variation of the Oswestry. It is intended to use with individuals with chronic neck pain, musculoskeletal pain, whiplash injuries, and cervical radiculopathy. *Validity:* Construct

	Norms and validation: Uses cut-off scores. *Comments:* Is useful for predicting progression from acute to chronic neck dysfunction. The NDI may have floor/ceiling effects. The user of the NDI should supplement with another outcome measure. A higher score indicates more reported functional impairment. Can be used as a screen and outcome measure.
Quick DASH **5 minutes**	**QuickDASH (Disabilities of the Arm, Shoulder, and Hand)** http://dash.iwh.on.ca/quickdash *Measures*: Uses 11 items to assess physical function and symptoms in people with musculoskeletal issues in the upper extremity musculoskeletal concerns. It focuses on disability/symptom rating. *Validity: Construct* *Norms and validation:* No norms. Cut-off scores are used. Significant differences in scores with individuals Reporting severe symptoms. *Comments*: Can be hand-scored or scored with an e-tool. The Quick DASH is free provided it is not placed into any product or is sold. Can be used as a screen and outcome measure.
Simple Shoulder Test **5 minutes**	**Simple Shoulder Test (SST)** http://www.orthop.washington.edu/?q=patient-care/articles/shoulder/simple-shoulder-test.html *Measures*: Utilizes 11 questions to ask about the individual's functioning regarding the shoulder only. This is a self-report tool. *Validation*: Face and cross-sectional *Norms and validation:* No norms. Uses cut-off scores. Comments: It is freely available.
Upper Limb Functional Index **5 minutes**	**Upper Limb Functional Index (ULFI)** https://www.worksafe.vic.gov.au/__data/assets/pdf_file/0003/10956/upper_extremity.pdf *Measures:* Assesses functioning related to upper extremities through 20 items. It is a self-administered screen. Questions are answered on a Likert-scale ranging from extreme difficulty to no difficulty. *Validity:* Construct *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The ULFI can be used to assess initial functional, treatment progress and treatment outcome. Can be hand scored. There is an online score calculator found at:

	https://www.thecalculator.co/health/upper-extremity-functional-index-(uefi)-calculator-955.html
Western Ontario Rotator Cuff Index **5 minutes**	**Western Ontario Rotator Cuff Index (WORC)** *Measures:* Assesses rotator cuff function and pain only. It has 21 questions that are visual analog scale items organized into 5 categories: quality of life (Qol), sports/recreation, work, lifestyle, and emotions. Items are rated on a Likert scale. *Validity:* Construct, concurrent, criterion *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* Has been found empirically to be more response than the SST, QuickDASH, DASH, and SF-36. A higher score is associated with lower level of functioning.
Patient-Rated Elbow Evaluation **5 minutes**	**Patient-Rated Elbow Evaluation** http://srs-mcmaster.ca/wp-content/uploads/2015/05/english-pree.pdf Measure: A self-administered questionnaire that asks individuals to rate elbow pain and function. There are no assessment measures of anxiety or depression. Validation: Concurrent, Face, and Content Comments: This screen is freely available.
Lower Extremity Functional Scale **5 minutes**	**Lower Extremity Functional Scale (LEFS)** http://www.mccreadyfoundation.org/documents/lefs.pdf *Measures*: Self-administered screen comprised of 20 items related to function of the lower limb only. There are no screens for anxiety or depression. It is reported to be used to measure initial function, treatment progress and outcome. *Validity*: Construct and concurrent. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* This item is freely available. The LEFS can be hand scored. An online score calculator is found at: https://www.thecalculator.co/health/lower-extremity-functional-scale-(lefs)-calculator-1020.html Higher scores indicate less functional difficulty. Is validated for patients with TKA, ankle sprains, inpatient and outpatient lower extremity MSK conditions.
Lower Limb Questionnaire **5 minutes**	**Lower Limb Questionnaire** http://www.aaos.org/research/outcomes/lower_limb.pdf Measure: This is a self-administered screen comprised of 7 questions pertaining to lower limb function only. Validity: Content, construct, and concurrent.

	Comments: Developed by several professional orthopedic organizations. This screen is freely available. It can be used as a screen and outcome measure.
Foot and Ankle Outcomes Questionnaire **5-20 minutes**	**Foot and Ankle Outcomes Questionnaire** http://www.aaos.org/research/outcomes/foot_ankle.pdf Measures: Pain and functioning related to the foot and ankle only. The questions ask about the individual's pain and functioning in the past week. This screen was developed by the American Academy of Orthopedic Surgeons and other organizations. Although the screen indicates it is related to outcomes, a review of the screen demonstrates that is focused on the individual's current level of pain and functioning. Validation: Convergent and structural Reliability: Internal consistency and test-retest Comments: This questionnaire is freely available in English. It can be given multiple times throughout the treatment process to measure treatment progress and outcomes.
<u>Psychological Assessment Tests</u> ***These are brief standardized biopsychosocial tests.***	
BBHI 2 **7-12 minutes** **6th grade**	**Brief Battery for Health Improvement 2** http://www.pearsonclinical.com/psychology/products/100000162/brief-battery-for-health-improvement-2-bbhi-2.html *Measures:* Standardized measures of pain, functioning, depression, anxiety, and somatization. Multidimensional pain assessment measures pain intensity, distribution, variability, and tolerability. *Validity measures:* Validity checks for exaggerating, minimizing, and random responding. Items left blank invalidate one scale at a time. *Norms and Validation:* Computerized report references multiple norm groups as indicated, with the primary norms being physical rehabilitation norms (composed of half acute and half chronic pain patients), and community norms. Additional subgroup norms for injury-related pain distribution (head injury, neck injury, upper extremity injury, back injury, lower extremity injury), chronic pain subgroup norms, and subgroup norms for rehabilitation patients recruited to fake good and fake bad. Derived from the BHI 2 test. *Comments:* Has scoring software that plots changes in scores over time with repeat administrations. Uses 17 critical items to screen for concerns such as suicidal ideation, compensation focus, addiction, satisfaction with care, psychosis, home life problems, and sleep disorders. *Languages:* English and Spanish
BSI **10-12 minutes** **6th grade**	**Brief Symptom Inventory** Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory (BSI): An introductory report. Psychological Medicine, 13, 595–605. doi:10.1017/S0033291700048017

	Measures: Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress *Validity measures:* None *Norms and Validation:* Uses community and psychiatric patient norms; derived from SCL-90-R test *Comments:* Has scoring software that plots changes in scores over time with repeat administrations
BSI 18 **3-5 minutes** **6th grade**	**Brief Symptom Inventory 18** http://www.pearsonclinical.com/psychology/products/100000638/brief-symptom-inventory-18-bsi-18.html *Measures:* Brief standardized measure of depression, anxiety, and somatization *Validity measures:* None *Norms and Validation:* Uses *oncology* patient norms; derived from SCL-90-R test *Comments:* Norms most appropriate for chronic pain associated *with malignancy*. Unclear how norms apply to injury-related pain. Has scoring software that plots changes in scores over time with repeat administrations.
MPI or **WHYMPI** **8-10 minutes** **Reading level unknown**	**Multidimensional Pain Inventory or Westhaven Yale Multidimensional Pain Inventory** https://www.va.gov/painmanagement/docs/whympi.pdf *Measures:* Contains 12 brief standardized measures divided into three groups which assess dimensions of the chronic pain experience, patients' perception of others' response to their pain, and participation in daily activities. Offers separate assessment of limitations in functioning/pain interference. Classifies patients as dysfunctional, interpersonally distressed or adaptive coper. *Validity measures:* None *Norms and Validation:* Developed originally with veterans (majority were male). Current norms based on a broad cross section of patients in the U.S. and Sweden with chronic pain, including back pain, pelvic pain, metastatic disease pain, lupus, and other conditions. *Comments:* Has a substantial research base in chronic pain. Does not assess anxiety or depression. Recent Version 3 of the scale is shorter. Reading level unknown. *Languages:* English, Spanish, French, Dutch, Italian, Japanese, Chinese, Portuguese, Finnish, Icelandic, and Swedish versions
P3 **12-15 minutes** **8th grade**	**Pain Patient Profile** http://www.pearsonclinical.com/psychology/products/100000657/pain-patient-profile-p-3.html *Measures:* Standardized measures of depression, anxiety, and somatization *Validity measures:* Validity measure checks for random or bizarre responding, but does not assess minimizing/exaggerating symptoms

	Norms and Validation: Community and chronic pain norms *Comments:* Has scoring software that plots changes in scores over time with repeat administrations *Languages:* English and Spanish
SF-36 **6-8 minutes** **Variable reading level**	**36-Item Short-Form Health Survey** http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html *Measures:* General physical and mental health *Validity measures:* None *Norms and Validation:* SF-36 is the most familiar of a series of related instruments developed through the Medical Outcomes Study initiated by the RAND Corporation. Hypertension and other norms available for original SF-36, which had both acute and standard forms. SF36 v2 has uniform format, and standardized T scores using community norms. RAND 36-Item Health Survey 1.0 includes the same items as those in SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Other forms include the longer HSQ 2.0, and the shorter SF-20, SF-12, SF-12v2, SF-10 and SF-8. *Comments:* Has scoring software. Does not assess depression, anxiety, or somatization. Reading level varies between items, with some items as low as grade 2, and other items as high as grade 12 [(594)]. *Languages:* English and Spanish, German, French, Chinese, Japanese, and for persons from the following countries: Armenia, Bangladesh, Brazil, Bulgaria, Cambodia, Croatia, Czech Republic, Finland, Greece, Hungary, Iceland, Israel, Korea, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, Tanzania, Turkey, Wales (UK), and Vietnam.
SCL-90-R **12-15 minutes** **6th grade**	**Symptom Checklist 90 – Revised** http://www.pearsonclinical.com/psychology/products/100000645/symptom-checklist-90-revised-scl-90-r.html Measures: Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress Validity measures: None Norms and Validation: Four norm groups available: adult psychiatric outpatients, adult psychiatric inpatients, adult non-patient, and adolescent non-patient; derived from SCL-90-R test Comments: Has scoring software that plots changes in scores over time with repeat administrations

TABLE A4. GLOSSARY OF PSYCHOLOGICAL ASSESSMENT TESTS USED FOR THE BIOPSYCHOSOCIAL EVALUATION OF PATIENTS WITH CHRONIC PAIN

Test Acronym Length Reading Level	Description
These are brief standardized biopsychosocial tests.	
BBHI 2 **7-12 minutes** **6th grade**	**Brief Battery for Health Improvement 2** http://www.pearsonclinical.com/psychology/products/100000162/brief-battery-for-health-improvement-2-bbhi-2.html *Measures:* Standardized measures of pain, functioning, depression, anxiety, and somatization. Multidimensional pain assessment measures pain intensity, distribution, variability, and tolerability. *Validity measures:* Validity checks for exaggerating, minimizing, and random responding. Items left blank invalidate one scale at a time. *Norms and Validation:* Computerized report references multiple norm groups as indicated, with the primary norms being physical rehabilitation norms (composed of half acute and half chronic pain patients), and community norms. Additional subgroup norms for injury-related pain distribution (head injury, neck injury, upper extremity injury, back injury, lower extremity injury), chronic pain subgroup norms, and subgroup norms for rehabilitation patients recruited to fake good and fake bad. Derived from the BHI 2 test. *Comments:* Has scoring software that plots changes in scores over time with repeat administrations. Uses 17 critical items to screen for concerns such as suicidal ideation, compensation focus, addiction, satisfaction with care, psychosis, home life problems, and sleep disorders. *Languages:* English and Spanish
BSI **10-12 minutes** **6th grade**	**Brief Symptom Inventory** Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory (BSI): An introductory report. Psychological Medicine, 13, 595–605. doi:10.1017/S0033291700048017 *Measures:* Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress *Validity measures:* None *Norms and Validation:* Uses community and psychiatric patient norms; derived from SCL-90-R test *Comments:* Has scoring software that plots changes in scores over time with repeat administrations

BSI 18 **3-5 minutes** **6th grade**	**Brief Symptom Inventory 18** http://www.pearsonclinical.com/psychology/products/100000638/brief-symptom-inventory-18-bsi-18.html *Measures:* Brief standardized measure of depression, anxiety, and somatization *Validity measures:* None *Norms and Validation:* Uses *oncology* patient norms; derived from SCL-90-R test *Comments:* Norms most appropriate for chronic pain associated *with malignancy*. Unclear how norms apply to injury-related pain. Has scoring software that plots changes in scores over time with repeat administrations.
MPI or **WHYMPI** **8-10 minutes** **Reading level unknown**	**Multidimensional Pain Inventory or Westhaven Yale Multidimensional Pain Inventory** https://www.va.gov/painmanagement/docs/whympi.pdf *Measures:* Contains 12 brief standardized measures divided into three groups which assess dimensions of the chronic pain experience, patients' perception of others' response to their pain, and participation in daily activities. Offers separate assessment of limitations in functioning/pain interference. Classifies patients as dysfunctional, interpersonally distressed or adaptive coper. *Validity measures:* None *Norms and Validation:* Developed originally with veterans (majority were male). Current norms based on a broad cross section of patients in the U.S. and Sweden with chronic pain, including back pain, pelvic pain, metastatic disease pain, lupus, and other conditions. *Comments:* Has a substantial research base in chronic pain. Does not assess anxiety or depression. Recent Version 3 of the scale is shorter. Reading level unknown. *Languages:* English, Spanish, French, Dutch, Italian, Japanese, Chinese, Portuguese, Finnish, Icelandic, and Swedish versions
P3 **12-15 minutes** **8th grade**	**Pain Patient Profile** http://www.pearsonclinical.com/psychology/products/100000657/pain-patient-profile-p-3.html *Measures:* Standardized measures of depression, anxiety, and somatization *Validity measures:* Validity measure checks for random or bizarre responding, but does not assess minimizing/exaggerating symptoms *Norms and Validation:* Community and chronic pain norms *Comments:* Has scoring software that plots changes in scores over time with repeat administrations *Languages:* English and Spanish
SF-36 **6-8 minutes**	**36-Item Short-Form Health Survey** http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html

Variable reading level	*Measures:* General physical and mental health *Validity measures:* None *Norms and Validation:* SF-36 is the most familiar of a series of related instruments developed through the Medical Outcomes Study initiated by the RAND Corporation. Hypertension and other norms available for original SF-36, which had both acute and standard forms. SF36 v2 has uniform format, and standardized T scores using community norms. RAND 36-Item Health Survey 1.0 includes the same items as those in SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Other forms include the longer HSQ 2.0, and the shorter SF-20, SF-12, SF-12v2, SF-10 and SF-8. *Comments:* Has scoring software. Does not assess depression, anxiety, or somatization. Reading level varies between items, with some items as low as grade 2, and other items as high as grade 12 [(594)]. *Languages:* English and Spanish, German, French, Chinese, Japanese, and for persons from the following countries: Armenia, Bangladesh, Brazil, Bulgaria, Cambodia, Croatia, Czech Republic, Finland, Greece, Hungary, Iceland, Israel, Korea, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, Tanzania, Turkey, Wales (UK), and Vietnam.
SCL-90-R **12-15 minutes** **6th grade**	**Symptom Checklist 90 – Revised** http://www.pearsonclinical.com/psychology/products/100000645/symptom-checklist-90-revised-scl-90-r.html Measures: Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress Validity measures: None Norms and Validation: Four norm groups available: adult psychiatric outpatients, adult psychiatric inpatients, adult non-patient, and adolescent non-patient; derived from SCL-90-R test Comments: Has scoring software that plots changes in scores over time with repeat administrations

TABLE A5. GLOSSARY OF STANDARDIZED PSYCHOLOGICAL TESTS USED FOR THE PSYCHOPATHOLOGY EVALUATION OF PATIENTS WITH CHRONIC PAIN

Test	Description
Psychological Assessment of Psychopathology ***These are comprehensive measures for assessing patients with psychopathology and who make threats***	
BHI 2	**See Table A6**
Hare Psychopathy Checklist – Revised	http://www.hare.org/scales/pclr.html Can be used to help assess the degree to which an individual exhibits severe antisocial traits in the form of a prototypical violent psychopath. May be useful if assessing patients who are making threats. Takes up to 3 hours of professional time.
MMPI-2	**See Table A6**
MMPI-2-RF	**See Table A6**

TABLE A6. GLOSSARY OF PSYCHOLOGICAL ASSESSMENT TESTS USED FOR THE BIOPSYCHOSOCIAL EVALUATION OF PATIENTS WITH CHRONIC PAIN

Test	Description
Comprehensive Chronic Pain Psychological Assessment ***These are comprehensive measures for assessing patients with chronic pain***	
BHI 2 **25-35 minutes** **6th grade**	**Battery for Health Improvement 2** http://www.pearsonclinical.com/psychology/products/100000095/battery-for-health-improvement-2-bhi-2.html **UPDATED INFORMATION INCLUDING NEW SCALES** http://www.pearsonclinical.com/psychology/products/100000095/battery-for-health-improvement-2-bhi-2.html *Measures:* Standardized measure includes 25 major scales and 40 minor scales that assess functioning, depression, anxiety, anger, somatization, job dissatisfaction, conflicts with physicians, family conflicts, trauma history, chronic maladjustment, borderline personality traits, dependent coping, perseverance and other variables. Multidimensional pain assessment includes measures of pain intensity, pain distribution, degree of correspondence of pain distribution with diagnostic category, pain variability, and pain intolerance. Assessment of pain cognitions includes measures of

	catastrophizing, kinesiophobia/fear avoidance, other dysfunctional pain cognitions, dysfunctional somatic cognitions, dysfunctional beliefs pertaining to analgesic medications and addictive history. Also assesses risk factors believed to be associated with a poor outcome following rehabilitation or surgical interventions, and severe risk factors such as suicidal ideation, violent ideation, entitlement, and compensation focus. *Validity measures:* Two bidirectional measures assess both exaggerating and minimizing, and one more assesses random/bizarre responding. Items left blank invalidate one scale at a time rather than the whole test. *Norms and Validation:* Computerized report references multiple norm groups as indicated, with the primary norms being physical rehabilitation norms (composed of half acute and half chronic pain patients), and general population/community norms. Additional subgroup norms for injury-related pain distribution (head injury, neck injury, upper extremity injury, back injury, lower extremity injury), chronic pain subgroup norms, and subgroup norms for rehabilitation patients recruited to exaggerate or minimize their reports. *Comments:* The development of this test was based on the "Vortex Paradigm" biopsychosocial theory. It has scoring software that plots changes in scores over time with repeat administrations *Languages:* English and Spanish
MBMD **20-30 minutes** **6th grade**	**Millon Behavioral Medicine Diagnostic** http://www.millon.net/instruments/mbmd.htm *Measures:* Total of 35 standardized scales include 5 psychiatric indications scales (anxiety, depression, cognitive dysfunction, emotional lability and guardedness), 11 coping scales, 6 negative health habits scales, 6 stress moderators scales, 5 prognostic scales, and 2 management scales. Scales intended to identify psychiatric and problematic behavioral comorbidities that may affect health management and compliance. *Validity measures:* One scale measures exaggerating, one minimizing; one bidirectional scale measures both exaggerating and minimizing, and one assesses random responding. *Norms and Validation:* Three patient norm groups, chronic illness (primarily heart disease, diabetes, HIV, neurological, 9% with chronic pain, but no identified physical rehabilitation patients), bariatric patient, and pain patient norms. *Comments:* Base rate scoring attempts to adjust test findings to approximate the actual base rates of psychological disorders observed in medical patients. Although the MBMD has pain norms, the general medical norms are used to score the test's pain prognosis algorithms, not the pain norms. Computer scored. *Languages:* English and Spanish.
MCMI I-V **25-30 minutes** **8th grade**	**Millon Clinical Multiaxial Inventory IV** http://www.millonpersonality.com/inventories/mcmi-iv/

	Measures: 24 standardized scales keyed to the DSM-5 diagnoses, including affective disorders, psychosis, and substance use, with separate scales for each type of personality disorder. *Validity measures:* One scale measures exaggerating, one minimizing; one bidirectional scale measures both exaggerating and minimizing, and one assesses random responding. *Norms and Validation:* Inpatient and outpatient psychiatric patients. *Comments:* Base rate scoring attempts to adjust test findings to approximate the actual base rates of psychological disorders in the psychiatric population. Computer scored. *Languages:* English and Spanish.
MMPI 2 **70-90 minutes** **6th grade**	**Minnesota Multiphasic Personality Inventory 2** https://www.upress.umn.edu/test-division/minnesotareport/minnesota-reports-overview *Measures:* Complex test with 126 official standardized scales, measuring a wide range of psychopathology. In addition to the 10 original MMPI clinical scales, scales were generated by a variety of methods (e.g., content analysis, factor analysis and others) and for a variety of purposes (assessing addictive tendencies and health concerns). Assesses depression, anxiety, somatization, addictive tendencies, psychosis, characterological tendencies, social support, and numerous other psychiatric conditions. *Validity measures:* Multiple validity measures assess patient responding. Three scales measure exaggerated, bizarre, or random responding; three measure minimizing; two measure contradictory responses. Also assessed is the number of items left blank on test, and percent left blank on each scale. *Norms and Validation:* Community norms. *Comments:* Computer scored. Several scales include physical symptoms that could be attributable to injury, illness, or medication side effects (595,596). This increases the risk of false positive psychological scores when medical patients report their symptoms. A long test, but despite its length does not measure several variables important for chronic pain assessment, including pain, functioning, and job dissatisfaction, so often needs to be paired with other tests. The most researched psychological test, a major revision (MMPI RF) is scheduled for release in 2008, and is substantially different from MMPI 2 (597,598,599,600,702). *Languages:* English, Spanish, [no longer available] and French versions.
MMPI 2 RF **40-50 minutes** **6th grade**	**Minnesota Multiphasic Personality Inventory 2 Revised Form** http://www.pearsonclinical.com/psychology/products/100000631/minnesota-multiphasic-personality-inventory-2-rf-mmpi-2-rf.html *Measures:* Revised version of the MMPI-2 with 51 standardized scales, measuring a wide range of psychopathology. Assesses somatic/cognitive dysfunction, emotional dysfunction, thought dysfunction, behavioral dysfunction, interpersonal functioning, and interests.

	Validity measures: Nine validity measures assess patient responding. Five scales measure exaggerated responding; two measure minimizing; two measure contradictory responses, and one assesses non-responsiveness. Also assessed is the percent left blank on each scale. *Norms and Validation:* Norms on 20 groups are available, including chronic pain and spine surgery candidates. *Comments:* Computer scored. Substantially shorter than the MMPI-2, but still longer than all other tests reviewed here. While it has many psychometric improvements over the MMPI-2 [(703)], the MMPI 2 RF has been critiqued as having more of a psychiatric focus than the MMPI 2, and thus less capable of assessing medical patients [(704)] *Languages:* English, Spanish and French versions.
MMPI 3 **30-40 minutes** **5th grade**	**Minnesota Multiphasic Personality Inventory 3** *https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Personality-%26-Biopsychosocial/Minnesota-Multiphasic-Personality-Inventory-3/p/P100000004.html* *Measures:* Revised version of the MMPI-2 RF with 52 standardized scales, eliminating scales that were out of date and adding five new ones. The MMPI-3 is the newest revision of the MMPI and includes the Restructured Clinical Scales of the MMPI-2 RF: Demoralization, Somatic Complaints, Low Positive Emotions, Antisocial Behavior, Ideas of Persecution, Dysfunctional Negative Emotions, Aberrant Experiences and Hypomanic Activation. Additionally, the MMPI-3 includes a multidimensional assessment of coping strategies that involve either internalization (e.g. worrying) vs externalization (e.g acting impulsively) of distress. The MMPI-3 also has three measures pertaining to thought disorder and one pertaining to mood elevation, along with various other measures of cognitive dysfunction, emotional dysfunction, and interpersonal dysfunction. *Validity measures:* Eleven validity measures assess patient responding. Five scales measure exaggerated responding; two measure minimizing; three measure contradictory responses, and one assesses nonresponsiveness. Also assessed is the percent of items left blank on each scale. *Norms and Validation:* Norms on 20 groups are available, including general population norms, forensic disability claimants norms and spine surgery candidates norms. In contrast with the MMPI-2 RF, the MMPI-3 is somewhat less pain oriented and does not have chronic pain norms. *Comments:* Computer scored. Available in English and Spanish. Ben-Porath YS, Heilbrun K, Rizzo M. Using the MMPI-3 in Legal Settings. *J Pers Assess*. Mar-Apr 2022;104(2):162-178. doi:10.1080/00223891.2021.2006672 Hall JT, Menton WH, Ben-Porath YS. Examining the Psychometric Equivalency of MMPI-3 Scale Scores Derived From the MMPI-3 and the MMPI-2-RF-EX. *Assessment*. Jun 2022;29(4):842-853. doi:10.1177/1073191121991921 Tylicki JL, Gervais RO, Ben-Porath YS. Examination of the MMPI-3 over-reporting scales in a forensic disability sample. *Clin Neuropsychol*. Oct 2022;36(7):1878-1901. doi:10.1080/13854046.2020.1856414

	Whitman MR, Tylicki JL, Mascioli R, Pickle J, Ben-Porath YS. Psychometric properties of the Minnesota Multiphasic Personality Inventory-3 (MMPI-3) in a clinical neuropsychology setting. *Psychol Assess*. Feb 2021;33(2):142-155. doi:10.1037/pas0000969
PAI **50-60 minutes** **4th grade**	**Personality Assessment Inventory** http://www.wpspublish.com/store/p/2893/personality-assessment-inventory-pai *Measures:* Standardized assessment of a broad cross-section of affective, characterological and psychotic conditions with 18 major scales and 31 subscales. *Validity measures:* One scale measures exaggerating, one minimizing, one random responding, and one assesses contradictory responses. *Norms and Validation:* Community and psychiatric norms. *Comments:* A comprehensive personality test that is significantly shorter than MMPI 2. Some scales, and in particular the somatization scale, include physical symptoms that could be attributable to injury or medication side effects. This increases the risk of false positive psychological scores when medical patients report their symptoms.
Hare Psychopathy Checklist – Revised	**Hare Psychopathy Checklist – Revised** http://www.hare.org/scales/pclr.html Can be used to help assess the degree to which an individual exhibits severe antisocial traits in the form of a prototypical violent psychopath. May be useful if assessing patients who are making threats. Takes up to 3 hours of professional time.

TABLE A7. GLOSSARY OF NEUROPSYCHOLOGICAL PSYCHOLOGICAL MEASURES FOR ASSESSING PAIN AND COGNITIVE FUNCTIONING

Test	Description
Cognitive Functioning Assessment ***These tests are intended for cognitive assessment.*** Note: *Some chronic pain patients report being unable to perform cognitive workplace functions secondary to medication side effects, lack of sleep, pain severity, or emotional distress. Cognitive tests generally do not include validity measures. They are almost impossible to fake good, but easy to fake bad. Thus, the test administrator will often need to administer 1 to2 psychological tests that evaluate sincerity of test effort and to rule out the potential for symptom exaggeration.*	
GAMA **25-minute timed test**	**General Ability Measure for Adults** http://www.pearsonclinical.com/psychology/products/100000200/general-ability-measure-for-adults-gama.html *Measures:* Provides a culture-free estimate of general ability based on the scores on 4 subtest scales: matching, analogies, sequences, and construction.
RBANS-Update **20- 30 minutes**	**Repeatable Battery for the Assessment of Neuropsychological Status-Update** http://www.pearsonclinical.com/psychology/products/100000726/repeatable-battery-for-the-assessment-of-neuropsychological-status-update-rbans-update.html?origsearchtext=rbans Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *The Journal of Clinical and Experimental Neuropsychology* 20, 310–319. *Measures:* Cognitive decline in individuals who have experienced stroke, head injury, dementia, or neurological injury or disease. Measures neuropsychological status in format and content similar to Wechsler tests. It measures attention, language, memory, and visuospatial/constructional abilities. *Validity:* Concurrent, criterion, construct *Norms and Validation:* Age, genders norms, uses *Comments:* The RBANS is a standardized test which assesses a variety of types of cognitive functioning. It has two forms of the test: A and B. The RBANS-Update can provide a measure of daily functioning.

	<u>Tests of Cognitive Ability</u> **These standardized neuropsychological tests are intended to evaluate multiple types of cognitive of functioning.**
WASI-II **15-30 minutes**	**Wechsler Abbreviated Scale of Intelligence-II** http://wechslertest.com/ *Measures:* Provides an abbreviated measurement of adult intelligence. These abbreviated scores are estimates of functioning since only the full administration of the WAIS-IV can provide full functioning scores. *Validity: Concurrent, criterion, construct* *Comments*: Can select either two-subtests or four-subtests to administer. Test administration time approximately 15 minutes for 2 subtests; 30 minutes for 4 subtests.
WAIS-IV **60-90 minutes**	**Wechsler Adult Intelligence Scale IV** http://wechslertest.com/ *Measures:* Adult intellectual ability and cognitive strengths and weaknesses. WAIS-IV and WMS-IV are the only co-normed ability-memory instruments. *Validity:* Criterion, construct, concurrent, predictive, convergent, and divergent. *Norms and Validation measures:* Co-normed with the WMS-IV. Age norms *Comments:* The WAIS-IV is a standardized test that evaluates cognitive and performance functioning. It has high internal consistency and re-test reliability. It can provide an estimate of premorbid intellectual functioning.
WMS-IV **45-60 minutes**	**Wechsler Memory Scale IV** https://www.pearsonclinical.ca/en/products/product-master/item-110.html *Measures:* Assessment of learning and memory functioning of older adolescents and adults. Measures visual and auditory memory, immediate vs. delayed memory, and free recall vs. cued recall as well as recognition. *Validity:* Criterion, construct, concurrent, predictive, convergent, and divergent. *Norms and Validation:* Co-normed with the WAIS-IV. Age norms. *Comments:* The WMS-IV is a standardized test that evaluates cognitive and performance functioning. It has excellent internal consistency and re-test reliability. It can provide an estimate of premorbid intellectual functioning.

WRAT-4 **35-45 minutes**	**Wide Range Achievement Test 4** http://www.pearsonclinical.com/education/products/100001722/wide-range-achievement-test-4--wrat4.html *Measures:* Basic academic skills of reading, spelling, and math computation. This edition has a new measurement of reading achievement. Age-based norms have been extended into age 94. Has excellent internal consistency and reliability. Has been validated against multiple other cognitive psychological tests.

TABLE A8. GLOSSARY OF PSYCHOLOGICAL ASSESSMENT TESTS USED FOR THE SYMPTOM EXAGGERATION AND MALINGERING OF PATIENTS WITH CHRONIC PAIN

Test	Description
Standardized Psychological Assessment for Symptom Exaggeration and Malingering ***These are comprehensive measures for assessing symptom exaggeration in patients with chronic pain. A minimum of two effort tests must be used to better assess for suboptimal effort or malingering.***	
MPS **20 minutes**	**Malingering Probability Scale** http://www.wpspublish.com/store/p/2869/malingering-probability-scale-mps *Measures*: Assessment of symptom exaggeration or malingering of psychological conditions of depression, anxiety, PTSD, schizophrenia *Norms*: Gender, age, educational level and region. Validation: Specifically validated with workers' compensation claimants.
SIMS **15 minutes**	**Structured Inventory of Malingered Symptomology** http://www4.parinc.com/products/product.aspx?productid=sims *Measures*: Assesses for malingered psychopathology and cognitive concerns. 75 true/false items. It evaluates malingered psychosis, low intelligence, neurologic impairment, affective disorders, and amnestic disorders. An overall score for probable malingering is obtained. Is used to evaluate disability and workers' compensation issues. *Validity*: Cross-validation, concurrent, criterion, discriminant. *Reliability:* Excellent, test-retest. *Norms and validation:* Norms for cognitively intact individuals as well as specific clinical groups with cognitive impairment, aphasia, traumatic brain injury, and dementia.

	Comments: Cut-off scores for three groups: malingerers, psychiatric, and non-clinical. The SIMS can be hand or computer scored.
TOMM **15-20 minutes**	**Test of Memory Malingering** http://www.mhs.com/product.aspx?gr=cli&id=overview&prod=tomm *Measures*: Used to assess whether an individual is falsifying symptoms of memory impairment. Assesses faking of memory complaints. Does not assess malingering of pain or musculoskeletal disability symptoms. Hand or computer scored. *Validity:* Construct, concurrent, convergent, divergent. *Norms and validation:* Norms for cognitively intact, cognitively impaired, and malingering individuals. *Comments:* Cutoff scores are used to evaluate for feigned cognitive impairment. Excellent specificity for individuals with chronic pain. Sensitivity is increased with usage of the Albany Consistency Index (ACI).

APPENDIX 2. PICO QUESTIONS

Complex Regional Pain Syndrome

1. Is there evidence for using nonspecific inflammatory markers for diagnosing chronic pain with a suspicion of a rheumatological disorder?
2. What evidence supports use of antibodies to diagnose a specific rheumatological disorder?
3. Is ANSAR testing recommended to diagnose CRPS?
4. Is sweat production testing recommended for diagnosing CRPS?
5. Is bone scanning recommended for diagnosing CRPS?
6. Is there evidence supporting cytokine testing for diagnosing CRPS?
7. What is the evidence to support QSART for diagnosing CRPS?
8. Is there evidence supporting surface EMG for diagnosing CRPS?
9. Does the evidence support using functional EMGs for diagnosing CRPS?
10. Does the evidence support using MRI for diagnosing CRPS?
11. Is there evidence for using Local Anesthetics for diagnosing CRPS?
12. Are X-rays recommended for diagnosing CRPS?
13. What evidence supports use of SPECT/PET for diagnosing chronic pain?
14. Is thermography recommended for diagnosing chronic pain?
15. What is the evidence regarding reduced activity/bed rest and CRPS?
16. How does aerobic exercise impact CRPS?
17. What is the evidence supporting strengthening exercises and CRPS?
18. What evidence exists for stretching exercises and CRPS?
19. Is there evidence to support aquatic therapy for CRPS?
20. What is the evidence regarding desensitization techniques and CRPS?
21. What is the evidence regarding yoga and CRPS?
22. What is the evidence regarding tai chi and CRPS?

23. What evidence supports pain exposure physical therapy and CRPS?
24. Is there evidence supporting mirror therapy and CRPS?
25. What is the evidence regarding graded motor imagery and CRPS?
26. What is the evidence regarding virtual reality therapy and CRPS?
27. What is the evidence regarding visual illusions and CRPS?
28. Are oral NSAIDS effective for CRPS?
29. Are topical NSAIDS effective for CRPS?
30. Is acetaminophen effective for CRPS?
31. What evidence supports the use of low-dose naltrexone for CRPS?
32. Is there evidence for the use of antidepressants for CRPS?
33. Is there evidence for the use of duloxetine for CRPS?
34. What evidence exists for the use of selective serotonin reuptake inhibitors (SSRIs) for CRPS?
35. What evidence supports the use of anticonvulsants for CRPS?
36. Is the short term use of gabapentin or pregabalin recommended for CRPS?
37. What evidence exists for the use of bisphosphonates for CRPS?
38. What evidence exists for the use of mycophenolate for CRPS?
39. Is there evidence for the use of calcitonin for CRPS?
40. Are oral glucocorticosteroids recommended for CRPS?
41. What evidence exists for ketanserin for CRPS?
42. Is there evidence supporting the use of magnesium sulfate for CRPS?
43. What evidence exists for the use of thalidomide or lenalidomide for CRPS?
44. What is the evidence for the use of DMSO and CRPS?
45. What evidence exists for using capsicum cream for CRPS?
46. What evidence supports EMLA cream and CRPS?
47. What evidence supports the use of lidocaine patches for CRPS?
48. What evidence supports the use of vitamin C for prevention of CRPS in patients with wrist fractures, extreme trauma or other high risk populations?
49. Is there evidence for N-Acetylcysteine (NAC) use for CRPS?
50. Is there evidence to support using opioids for CRPS?
51. Is there evidence for using ketorolac for CRPS?
52. What evidence supports use of cryotherapy for CRPS?
53. What evidence exists for heat therapy in CRPS?
54. What evidence exists for diathermy in CRPS?
55. Is there evidence for use of hyperbaric oxygen in CRPS?
56. Is there evidence for use of fluidotherapy in CRPS?
57. Is there evidence for using magnets or magnetic stimulation in CRPS?
58. Is an occlusal splint recommended for CRPS?
59. What is the evidence for use of acupuncture in CRPS?
60. What is the evidence surrounding myofascial release and CRPS?
61. What is the evidence surrounding reflexology and CRPS?
62. Is there evidence for use of External Radiation for Sympathetic Blockade for CRPS?
63. What evidence supports Infrared Therapy use in CRPS?
64. Is there evidence for the use of Low Level Laser Therapy for CRPS?
65. What evidence supports Manipulation in CRPS?
66. What evidence exists regarding High-voltage Galvanic Therapy for CRPS?
67. Is there evidence supporting use of H-Wave® Device Stimulation for CRPS?

68. What evidence exists for Interferential Therapy for CRPS?
69. Is there evidence supporting Iontophoresis for CRPS?
70. What evidence exists regarding Microcurrent Electrical Stimulation for CRPS?
71. Is there evidence to support PENS for CRPS?
72. What evidence exists for the use of Sympathetic Electrotherapy for CRPS?
73. What is the evidence for the use of TENS and CRPS?
74. Is there evidence to support use of Botulinum Toxin Injections for CRPS/
75. What evidence supports Intrathecal Baclofen for CRPS?
76. Is there evidence for the use of Intrapleural Bupivacaine Infusions in CRPS?
77. What evidence supports the use of Lidocaine Infusions in CRPS?
78. What evidence exists for Stellate Ganglion Blocks for CRPS?
79. What evidence exists for Bier Blocks for CRPS?
80. What evidence exists for Guanethidine Bier Blocks for CRPS?
81. What evidence exists for Bretylium Bier Blocks for CRPS?
82. What evidence exists for Phentolamine Bier Blocks for CRPS?
83. What evidence exists for Methylprednisolone Bier Blocks for CRPS?
84. Is there evidence for Reserpine Bier Blocks for CRPS?
85. What is the evidence for the use of Brachial Plexus Blocks and Infusions for CRPS?
86. Is there evidence to support the use of Spinal Cord Stimulators for short to intermediate term relief of CRPS?
87. What is the evidence supporting amputation in CRPS?

Fibromyalgia

1. What is the evidence for the use of Antibodies for diagnosing FM?
2. Is there evidence for the use of Non-specific Inflammatory Markers for diagnosing FM?
3. Is ANSAR testing recommended for diagnosing FM?
4. What evidence is available for using Functional MRIs for diagnosing FM?
5. Is there evidence for the use of SPECT/PET for diagnosing FM?
6. Are Needle EMG and/or Nerve Conduction Studies recommended for diagnosing FM?
7. Is there evidence to support use of Surface EMG for diagnosing FM?
8. What evidence supports use of Local Anesthetic injections for diagnosing FM?
9. Is there evidence for Functional Capacity Evaluations for diagnosing FM?
10. What is the evidence for Bed Rest and FM?
11. What is the evidence for Fear Avoidance Belief Training and FM?
12. What evidence supports Aerobic Exercise for FM?
13. Is there evidence for Strengthening, Stabilization and/or Resistance Exercise for FM?
14. What evidence supports Stretching Exercises for FM?
15. Is there evidence for Yoga and FM?
16. Is there any evidence supporting Pilates for FM?
17. What evidence supports Swimming for FM?
18. Is Aquatic Therapy (Not Swimming) recommended for FM?
19. Is there evidence to support Tai Chi for FM?
20. What is the evidence supporting Spa and Balneotherapy for FM?
21. Is there evidence to support the use of Whole Body Vibration for FM?

22. What evidence exists regarding the use of Oral NSAIDs for FM?
23. Is Acetaminophen recommended for FM?
24. What is the evidence for using Norepinephrine Reuptake Inhibitor Anti-depressant (TCAs) for FM?
25. Is there evidence for the use of Selective Serotonin Reuptake inhibitors (SSRIs) for FM?
26. Is there evidence for the use of Serotonin Norepinephrine Reuptake Inhibitors such as Duloxetine and Milnacipran for FM?
27. What evidence supports the use of Noradrenergic and Specific Serotonergic Antidepressants for FM?
28. Is there evidence for using Serotonin Receptor Antagonists for FM?
29. What is the evidence for use of Bupropion, Trazadone or Pramipexole for FM?
30. Is there evidence for using Atypical Anti-depressants for FM?
31. What evidence exists for the use of NMDA Receptor Antagonists for FM?
32. Is there evidence supporting use of Anti-convulsants for FM?
33. What evidence exists for the use of Glucocorticosteroids for FM?
34. Is there evidence to support the use of Dehydroepianrosterone (DHEA) for FM?
35. Is there evidence supporting the use of Calcitonin for FM?
36. What is the evidence for the use of Vitamin D for FM?
37. Is Melatonin recommended for use in FM?
38. Is there evidence for the use of Hormone Replacement Therapy (HRT) for FM?
39. Is Raloxifen recommended for FM?
40. Is there evidence to support the use of Oxytocin in FM?
41. Is Growth Hormone (GH) recommended for FM?
42. What evidence supports the use of Pyridostigmine for FM?
43. Is there evidence for the use of Ritanserin in FM?
44. What evidence exists for using 5-Adneosylmethionine for FM?
45. Is there evidence for the use of Creatine in FM?
46. What is the evidence for using Terguride in FM?
47. Is there evidence to support the use of Valcyclovir in FM?
48. What evidence supports the use of Sodium Oxybate in FM?
49. Is there evidence for the use of Zolpidem for FM?
50. What is the evidence for Coenzyme Q for FM?
51. Is there evidence for using Acetyl-1-Carnitine for FM?
52. What evidence exists for using Antidiencephalon for FM?
53. Is there evidence to support the use of Dolasetron for FM?
54. Is there evidence for Zopiclone in FM?
55. What is the evidence for Ondansetron for FM?
56. Is there evidence to support the use of Skeletal Muscle Relaxants for FM?
57. Is there evidence for the use of Alpha1-Antitrypsin for FM?
58. What evidence supports the use of Topical Medications and Lidocaine patches for FM?
59. What is the evidence for using Opioids in FM Patients?
60. Is there evidence for the use of Kinesiotaping and Taping in FM Patients?
61. What evidence supports the use of Magnets/Magnetic Stimulation in FM?
62. What I the evidence for Weight Reduction/Weight Management in FM?
63. Is there evidence for use of Dietary Interventions in FM?

64. Is there evidence to support Music Therapy in FM?
65. Is Homeopathy recommended for FM?
66. Is there evidence supporting Herbal, Alternative, Complementary or Other Preparations in FM?
67. Is there evidence for the use of Reiki Therapy in FM?
68. What evidence supports the use of Qigong I FM?
69. Is there evidence for use of Acupuncture in FM?
70. What evidence exists surrounding the use of Manipulation and Mobilization in FM?
71. Is there evidence supporting massage in FM?
72. Is there evidence for Myofascial Release in FM?
73. Is there evidence for Reflexology for FM?
74. Is there evidence to support Hot and/or Cold Therapies for FM?
75. What is the evidence for Hyperbaric Oxygen use in FM?
76. Is there evidence for Interferential or Ultrasound use in FM?
77. What evidence supports the use of Pulsed Electromagnetic Therapy for FM?
78. Is there evidence to support using Microcurrent Cranial Electrical Stimulation for FM?
79. Is there evidence for using Cortical Electrostimulation for FM?
80. What evidence exists for the use of Transcranial Direct Current for FM?
81. What evidence exists for the use of Transcranial Magnetic Stimulation for FM?
82. What evidence supports the use of Low Level Laser Therapy for FM?
83. Is there evidence supporting the use of Transcranial Electrical Nerve Stimulation (TENS) for FM?
84. What evidence exists for Other Electrical Therapies for FM?
85. Is there evidence for the use of Iontophoresis for FM?
86. What is the evidence for using Ganglion Blocks for FM?
87. Are Ketamine Infusions recommended for FM?
88. Are Lidocaine Infusions recommended for FM?
89. What us the evidence for the use of C2 Nerve Stimulation in FM?
90. Is there evidence for the use of Prolotherapy Injections in FM?
91. What is the evidence for Self-Management for FM?
92. What is the evidence for Body/Self-Awareness for FM?
93. Is there evidence for the use of Attention Modification in FM?
94. What is the evidence surrounding the use of Guided imagery in FM?
95. Is there evidence for the use of Mindfulness Intervention in FM?
96. What is the evidence for Acceptance and Commitment Training in FM?
97. Is there evidence to support Psychoeducational Treatment in FM?
98. Is there evidence supporting Written Pain Education and Disclosures in FM?
99. What evidence supports the use of Shared Decision Making in FM?
100. What is the evidence for Psychological Treatment/Behavioral Therapy in FM?
101. Is there evidence for using Rehabilitation for Delayed Recovery in FM?
102. Is there evidence for using Biofeedback in FM?
103. What evidence exists for the use of Relaxation/Meditation Training in FM?
104. Is there evidence for Functional Restoration in FM?
105. What evidence supports Work Conditioning, Work hardening, and Early Intervention Programs in FM?

106. What is the evidence regarding Interdisciplinary Pain Rehabilitation Programs in FM?
107. Is there evidence for Other “Ad Hoc” Functional Restoration Programs in FM?

Neuropathic Pain

1. Is there evidence supporting Laboratory tests for diagnosing Peripheral NP?
2. Is there evidence for Occupational Neurotoxin Exposure Measurements for diagnosing NP?
3. Is there evidence to support Antibody Testing for confirmation of Specific Disorders?
4. Is ANSAR Testing recommended to confirm Specific NP Disorders?
5. Are Non-specific Inflammatory Markers recommended for screening various Inflammatory Disorders?
6. Is Cytokine Testing recommended for diagnosing Chronic NP?
7. What evidence supports the use of Needle EMG and Nerve Conduction Studies to diagnose NP?
8. IS there evidence to support the use of Surface EMG to diagnose Chronic NP?
9. What evidence supports the use of Functional MRIs for diagnosing Chronic NP?
10. Is there evidence to support Local Anesthetic injections for diagnosing Chronic NP?
11. What evidence supports the use of SPECT/PET for diagnosing Chronic NP?
12. Are FCE’s recommended for diagnosing Chronic NP?
13. What is the evidence for Bed Rest and NP?
14. Is there evidence to support Aerobic Exercise for NP?
15. Is there evidence for Strengthening Exercise for NP?
16. What is the evidence for Aquatic therapy and NP?
17. What evidence supports Physical and/or Occupational Therapy for NP?
18. What evidence exists for the use of NSAIDS for Chronic NP?
19. Is there evidence for Acetaminophen for NP?
20. What evidence exists for the use of Tricyclics Tetracyclics and SNRI Anti-depressants for NP?
21. What is the evidence for Selective Serotonin Reuptake inhibitors for NP?
22. Is there evidence for using Antipsychotics for NP?
23. What evidence exists for use of Anti-convulsants for NP?
24. Is there evidence to support the use of Anti-virals for NP?
25. What evidence exists for the use of Homeopathy and Complementary Medicine for NP?
26. Is there evidence for the use of Clonidine for NP?
27. What is the evidence for using Dextromethorphan for NP?
28. Is there evidence for the use of Muscle Relaxants for Acute Exacerbation of NP?
29. What evidence supports the use of Magnesium for NP?
30. Is there evidence to support the use of Tumor Necrosis Factor-alpha Blockers for NP?
31. Is there evidence to support the use of Topical NSAIDs for Chronic NP where the target tissue is superficially located?
32. Is there evidence supporting Other Topical creams such as Ketamine, Amitriptyline and Combinations for NP?
33. What is the evidence surrounding the use of Capsaicin Patches for NP?
34. What evidence exists for using Lidocaine patches for NP?

35. Is Motor Cortex Stimulation recommended for NP?
36. Is there evidence for the use of Magnets or Magnetic Stimulation for NP?
37. What evidence exists for Taping and Kinesiotaping for NP?
38. Is there evidence for Self-application or Healthcare Provider Application of Cryotherapies for NP?
39. What is the evidence for the use of Diathermy for NP?
40. Is there evidence to use Ultrasound for NP?
41. What evidence exists for Provider-Based or Self-Application of Infrared Therapy for NP?
42. Is there evidence to support the use of Low Level Laser Therapy for NP?
43. What is the evidence surrounding Manipulation for NP?
44. Is there evidence for the use of Massage for NP?
45. What evidence supports the use Mechanical Massage Devices for NP?
46. Is there evidence for Myofascial Release for NP?
47. What is the evidence for Acupuncture/Electroacupuncture for NP?
48. Is there evidence to use Reflexology for NP?
49. Is there evidence for the use of High-voltage Galvanic Therapy for NP?
50. What evidence exists for H-Wave® Device Stimulation for NP?
51. Is there evidence for the use of Interferential Therapy for NP?
52. Is there evidence for Iontophoresis for NP?
53. What is the evidence for the use of Microcurrent Electrical Stimulation for NP?
54. Is there evidence to support the use of PENS for NP?
55. Is there evidence to support the use of TENS for NP?
56. What evidence exists regarding Repetitive Transcranial Magnetic Stimulation (rTMS) and NP?
57. What evidence exists for the use of Sympathetic Electrotherapy and NP?
58. Is there evidence for the use of External Radiation for Sympathetic Blockade for NP?
59. What evidence supports the use of Corticosteroids for NP?
60. Is there evidence for the use of Immunoglobulin for NP?
61. What evidence supports using Ketamine Infusions for NP?
62. Is there evidence to use Intrapleural Bupivacaine Infusions for NP?
63. Is there evidence supporting the use of Lidocaine Infusions for NP?
64. What is the evidence regarding Intravenous Phenytoin for NP?
65. What is the evidence regarding Intravenous Adenosine for NP?
66. Is there evidence to support the use of Monoclonal Antibody Injections for NP?
67. Is there evidence regarding Dorsal Ganglion Destruction for NP?
68. What evidence exists for Nerve Blocks and NP?
69. Is there evidence for Surgical Decompression for NP?
70. What is the evidence for Spinal Cord Stimulation for NP?
71. Is there evidence for Intrathecal Drug Delivery Systems for Chronic Nonmalignant NP?

Chronic Pain Rehabilitation

1. What is the evidence regarding Work Conditioning, Work Hardening, Early Interventional Programs and Back Schools for Chronic Pain?

2. Is there evidence to support Tertiary Pain Programs, Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Pain Programs, Chronic Pain Management Programs or Functional restoration programs for Chronic Pain?
3. Is there evidence for participatory Ergonomics Programs for Chronic Pain Patients?

Behavioral Chronic Pain

1. What evidence suggest Psychological Evaluation for Chronic Pain Patients?
2. Is there evidence to support Cognitive Behavioral Therapy for Chronic Pain Patients?
3. What is the evidence supporting Fear Avoidance Belief Training for Chronic Pain Patients?
4. Is there evidence for use of Biofeedback in Chronic Pain Patients?

APPENDIX 3. INTERNAL PAIN HISTORY

What do you hope to accomplish during this visit?

What are your concerns about the potential for further injury as you recover?

What are your expectations regarding your return to work and disability from this health problem?

What are your symptoms since we last talked?

- Where are the symptoms located?
- How bad is the pain, (e.g., on a 0 to 10 scale)?
- Do you have pain or stiffness?
- Do you have numbness or tingling?
- Do you have pain or other symptoms elsewhere?
- Have you lost control of your bowel or bladder?
- Do you have fever, night sweats, or weight loss?
- Are your symptoms constant or intermittent?
- What makes the problem worse or better?
- What is the day pattern to your pain?
- Better first getting out of bed in the morning, during the morning, mid-day, evening or while asleep?
- When is it worst?
- Do you have a problem sleeping?
- What position is most comfortable?
- Is there any pain with cough, sneezing, deep breathing, or laughing?
- Since these symptoms began, have your symptoms changed? How?
- How does having this pain affect your life?

Job

- Are you working at your regular job?
- How long do you spend performing each duty on a daily basis?
- What tasks are you doing on your modified or light job?

- Do you have assistance from other people or lifting devices?
- Are you on modified or light duty?
- What are your work hours and breaks?
- Do you rotate jobs?
- What is the hardest part of the job for you to do with your injury? Why?
- How much do you lift at work as a maximum? Usual lift?
- How often do you do those tasks?
- Describe work times, movement and breaks for sedentary jobs

Off-work Activities:

- What other activities (hobbies, workouts, sports) do you engage in, at home or elsewhere?
- Describe your current daily activities starting with waking up to bedtime.
- Do you go grocery shopping, prepare your own meals, do yard work and laundry?
- Family, sexual function
- How heavy?
- Lifting from what height?
- How large is(are) the objects?
- How often?
- Do you carry objects long distances?
- Do you sit for long periods of time?
- Any heavy or difficult lifting?

Interval Treatments and Activities

- What treatments and medications have you received (include complete medication review)?
- Did treatment help decrease your symptoms?
- What and for how long?
- Did it help?
- How?
- How often do you perform them? When?
- Do you feel that they help?
- Show me how you do them.
- Exactly what treatment did you receive or participate in physical (or occupational) therapy (detailed descriptions of all modalities and specific exercises used)?
- Are you doing physical (or occupational) therapy exercises at home?

Symptom Limitations

- How do these symptoms limit you?
- How long can you sit, stand, walk, and bend?
- Can you lift?
- How much weight (use items such as gallons of milk, groceries, etc. as examples)?
- How much can you push or pull?

- Do you need to lie down or rest during the day?
- What activities at home do you need help with?
- What activities do you perform in a typical day? Begin with waking in the morning and proceed to bedtime.
- What activities are you now unable to do? Why?

Is there any change in medical conditions, psychological, psychiatric, mental health, substance use, alcohol or tobacco disorder history?

What is the occupational psychosocial context?

- If you had to take a job again, would you go back to your current job?
- Do you like your job at this point?
- What is your relationship with your co-workers and supervisor and how do they treat you now?
- How do you get along with your supervisor now?
- How do you get along with your coworkers now?
- How do your coworkers help you if you need it at this point?
- How does your supervisor help you if you need help now?
- Is your employer concerned about you now?
- Are you facing any disciplinary or performance action now?

Assess whether there are problems at home/social life. Does the patient feel in control of most situations? Is there support?

- How do your family members get along with each other now?
- How do they help and support you now?
- Does your family treat you differently now?
- Have your roles at home changed because of your injury?
- How do your friends treat you differently?
- Do you get increased symptoms when you are dealing with problems with your family and friends? How often? When? Why?

Are there advocagenic (litigious) influences?

- Do you have a workers' compensation claim for this injury?
- Do you a lawsuit or other legal action involving this pain problem?
- Have you consulted anyone (union representative, etc.) about particular problems you may have experienced with your claim (not receiving benefits, etc.)?
- Do you have additional insurance coverages such as short- or long-term disability?
- Have you taken sick time for this problem?
- Did you talk with your lawyer about what you should say at the clinic?
- Do you have a lawyer? Have you ever been involved in a lawsuit?

APPENDIX 4. DEFINITION OF TERMS RELATED TO CHRONIC PAIN

Name	Origin of Definition	Definition
General Pain Terms		
Pain	IASP	"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." [35,45] Note that according to this definition, all pain, both acute and chronic, has both sensory and affective components. While pain is often treated as a sensory experience in the clinical setting, brain imaging studies have determined that pain is equally an emotional experience[22,46,47] with biopsychosocial dimensions. [2,20,22,23] Pain can be subdivided into two types (primary and secondary pain) and is produced by one or more of three different pain mechanisms (nociceptive, neuropathic, and nociplastic mechanisms).
Chronic Pain	IASP	Traditionally, pain that persists for longer than 3-6 months. [48] In the ICD-11, this has been standardized as persisting for longer than 3 months. [2]
Central Sensitization		An altered state of functioning in the pain sensory system. This is associated with increased excitability of neurons in nociceptive pathways in the central nervous system, resulting in hyperalgesia [49,50]. While central sensitization has sometimes been attributed to spinal mechanisms [51], other studies have focused on altered functioning of circuits in the brain [19,52,53].
Peripheral Sensitization		An altered state of functioning in the pain sensory system. This is associated with increased excitability of neurons in nociceptive pathways in the peripheral nervous system, resulting in hyperalgesia. Commonly due to inflammation. [21]
Functional Symptom		A controversial and ambiguous term that is sometimes used to refer to objectively poor functioning such as that due to deconditioning [17,18]. Alternately, this term is sometimes thought to imply that the symptom is the result of psychopathology, typically a conversion disorder [6], where emotional pain may be misperceived as being physical pain. The use of the term "functional symptom" is discouraged [2].
Pain Mechanisms		
Nociceptive Pain	IASP	Pain that is related to nociceptor activity that signals actual or potential damage to non-neural tissue. Nociceptive pain is the product of a normally functioning pain sensory system [33]. Along with neuropathic pain and nociplastic pain, nociceptive is one of the three mechanisms of pain identified in the IASP pain taxonomy. [32,33]

Name	Origin of Definition	Definition
Neuropathic Pain	IASP	Pain that is caused by an injury to or disease of the pain neural system. [33] Along with nociceptive pain and nociplastic pain, neuropathic pain is one of the three mechanisms of pain identified in the IASP pain taxonomy. [32,33]
Nociplastic Pain	IASP	Pain that is caused by dysfunction of the pain sensory neural system, producing hyperalgesia with minimal or no nociceptive input. [33] Nociplastic pain is thought to be closely associated with central sensitization, but may also involve peripheral nerve sensitization and other mechanisms. [32-34] Nociplastic pain is considered to be a disease that is strongly associated with inflammation, cognition and mood, and which dysregulates the pain sensory system, and causes hyperalgesia [2,20].
Psychogenic Pain	DSM I	An archaic term having its origins in DSM I. [5] Psychogenic pain is generally considered to be related to some form of psychopathology, such as a conversion disorder or factitious disorder. The latter of these is a rare condition involving a compulsion to assume a patient role *in the absence of any monetary, work avoidance or other incentive for doing so*. Historically, the term "psychogenic pain" has been used in a pejorative way to dismiss pain symptoms that are not easily understood [4], and because of that its use has been eliminated from DSM 5[4] and ICD11 [2]. This term is not informed by current pain science, and its use is discouraged [2].
Pain Diagnoses		
Pain Disorder	ICD 10 & DSM-IV	a.k.a. Persistent somatoform pain disorder, pain disorder exclusively related to psychological factors, and pain disorder with related psychological factors. Pain which cannot be fully explained by pathophysiology, and which is believed to be partially or entirely explained by psychological processes. This diagnosis was dropped by both ICD-11 and DSM 5, as it can have pejorative connotations, especially when combined with the term "somatoform". [2]
Somatic Symptom Disorder with Pain	DSM 5	Pain reports that are associated with *excessive* anxiety and/or beliefs about the seriousness of the condition that are *out of proportion* to objective findings. There is no consideration of the impact of mood or cognitions that are *not* out of proportion (i.e. if the condition is serious). This has been faulted as being based on research that was over 20 years old, continuing to think in terms of mind-body dualism, and not being informed by current pain science[2]. There is no clear way to reconcile this diagnosis with nociceptive or nociplastic pain mechanisms, or to crosswalk it to primary pain or secondary pain diagnoses.

Name	Origin of Definition	Definition
Chronic Secondary Pain (CSP)	IASP & ICD 11	A diagnostic construct developed by a collaboration of IASP and WHO for use in the ICD-11[16] and based on current pain science [1,25]. It is defined as pain that persists for longer than 3 months and is secondary to an underlying disease or injury. The six CSP diagnostic *categories* are cancer[26], headache / orofacial[27], musculoskeletal[28], neuropathic[29], posttraumatic / postsurgical[30], and visceral[31]. Chronic secondary pain is thought to be a symptom most closely associated with nociceptive and neuropathic pain mechanisms.
Chronic Primary Pain (CPP)	IASP & ICD 11	A diagnostic construct developed by a collaboration of IASP and WHO for use in the ICD-11[16] and based on current pain science [1,25]. It is defined as pain that 1) persists for longer than 3 months, 2) is associated with significant emotional distress (e.g. anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in ADLs or participation in social roles), and 3) the symptoms are not better accounted for as chronic secondary pain or other diagnosis. [2] The five CPP diagnostic *subcategories* are a) headache / orofacial, b) musculoskeletal, c) widespread pain and fibromyalgia, d) complex regional pain syndrome, and e) visceral pain. [2,20] Chronic primary pain is thought to be most closely associated with nociplastic pain mechanisms, and is considered to be a disease in and of itself affecting the pain sensory system. [2,20] As all pain has an affective component, both CPP and CSP are thought to be associated with mood and cognition as biopsychosocial conditions.
Factitious Disorder	ICD 10 & DSM-IV	A rare psychological condition diagnosed when a patient seeks medical care for primary gain, which means being a medical patient is inherently rewarding. For example, a patient with factitious disorder might prefer to spend time in a hospital as opposed to take a vacation, as hospital stays are more enjoyable. The medical condition may be feigned, or self-induced via intentional self-injury, consuming a toxic substance or other means. Motivation by secondary gain such as monetary compensation or work avoidance rules out factitious disorder.
Malingering	Not a diagnosis	In contrast with factitious disorder, malingering is the conscious and intentional fabrication of symptoms for the purpose of secondary gain. Because of that, malingering may be a criminal act, not a psychological condition that requires treatment. Because malingering may be criminal behavior, this is a determination for the Court to make.