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"To write prescriptions is easy, but to come to an understanding with people is hard."

-- Franz Kafka, "A Country Doctor"

Analgesics for Chronic Pain (CP)

- Pills most common method of CP treatment
- Pain meds can be a blessing for some in chronic pain, but not universally effective
- Analgesics effective for tissue injury (nociceptive pain) but less effective from damage to the nervous system (neuropathic pain)

Analgesics for Chronic Pain

- Short-term use of opioids is rarely worrisome
- Prolonged use increases side-effect risks
- Medications for treating chronic pain in and of themselves can cause a disability and a decrease in the ability to function in life

Limitations of Chronic Opioid Therapy

- Evidence for long-term analgesic efficacy is weak
  - Analgesia (pain relief)
  - Activities of Daily Living (physical and psychosocial functioning)
  - Adverse Events (untoward side effects)
  - The great majority patients on opioids chronically develop dependence

Medication Side-Effects

- Nausea, vomiting, constipation, swelling, urinary retention, and respiratory depression
- Tiredness & daytime sleepiness (fatigue)
- Internal organ problems (liver, kidney, etc.)
- Poor coordination and balance

Medication Side-Effects

- Cognitive (memory/concentration) difficulties
- Depression
- Hormonal imbalance (endocrine problems)
- Weight gain
- Sexual dysfunction

Measuring Opioid Usefulness

- Ultimate outcome of the use of opioid medication must be viewed in terms of:
  - Pain relief/reduction
  - Objective gains (function or increased activity)
  - Manageable side-effects
- It is not about the drug but about the benefit from use

Opioids

- A select group benefits from opioids, with resultant pain reduction and improved physical and psychological functioning
- Many do poorly with opioids, especially with escalating doses

Opioids Types

- Opioid agonists
  - Short Acting
  - Long Acting
  - Opioid Partial Agonists/Antagonists
    - buprenorphine (Buprenex®, Subutex®)
    - buprenorphine and naloxone (Suboxone®)

Important Terms

- Physical dependence
- Withdrawal
- Tolerance
- Addiction
- Hyperalgesia

Dependence

- Physical dependence is a normally induced state such that abrupt stopping medication results in withdrawal symptoms
- Psychological dependence occurs when the individual becomes emotionally tied to taking a specific drug and develops anxiety with planned drug cessation

Withdrawal

- Withdrawal is defined as a set of normal physiologic consequences (things that happen to your body) that occur as a response to abrupt cessation of a drug
- Symptoms consistent with withdrawal include increased heart rate, sweating, body aches, nausea, vomiting, diarrhea, and abdominal pain and mood changes

Tolerance

- Tolerance is a simple observation of requiring larger opioid doses to produce the same effect
- In other words, it takes more pills to get the same or less pain relief
- Increase dose may lead to side-effects & dependence

Addiction

- Addiction is an abnormal behavioral syndrome induced by a certain medication or drug in a susceptible patient
- Findings necessary to make a diagnosis of addiction include:
  - Abnormal behavior focused on acquiring the offending drug
  - Evidence of harm with the use of the drug
  - Continued drug use despite the individual's awareness of harm with use

Opioid Hyperalgesia

- Opioid-induced hyperalgesia (OIH) refers to a phenomenon whereby opioid administration results in a lowering of pain threshold, clinically manifest as apparent opioid tolerance, worsening pain despite accelerating opioid doses, and abnormal pain symptoms such as allodynia (pain from stimuli which are not normally painful)

Appropriate Opioid Use

- The issue of appropriate use of opioids in the treatment of Chronic Pain is complex, controversial, and timely

The Opioid Conundrum

- Ever increasing problem of increasing deaths and dysfunction from the inappropriate use of prescription opioids

- versus -

- Needs of patients for adequate pain control to facilitate comfort, activity, function, and return to work

The Opioid Conundrum

- For the medical practitioner and patient, achieving a balance across the spectrum of outcomes from pain alleviation and increased function as opposed to untoward side effects, aberrant drug-related behavior, drug addiction, drug abuse, drug diversion and potential death, remains problematic

For Which IWs are Opioids Appropriate?

- Assessment of the benefit and the risk of likelihood of abuse, misuse, or addiction
- Informed consent and opioid agreement including
  - Goals of treatment (benefits)
  - Expectations (physician and patient)
  - Risks and alternatives
- Monitoring the patient including UDT

Opioid Treatment Agreement

- You will not obtain any other prescription for controlled medication from another source/physician
- Our staff may communicate with any pharmacy or health care professional regarding your medications
- Medication only refilled during regular office hours
- Lost narcotic medication cannot be replaced
- Stolen narcotic medication MAY be replaced provided you obtain a police report and are seen in the office

Safely Managing Opioids in Chronic Pain

- Initiation and Titration of Chronic Opioid Therapy
  - Treatment individualized & always a trial
- Monitoring patients on opioids
  - Level of function
  - Progress toward predetermined goals
  - Presence of adverse events
  - Compliance (or lack of)

Risk Factors for Abuse

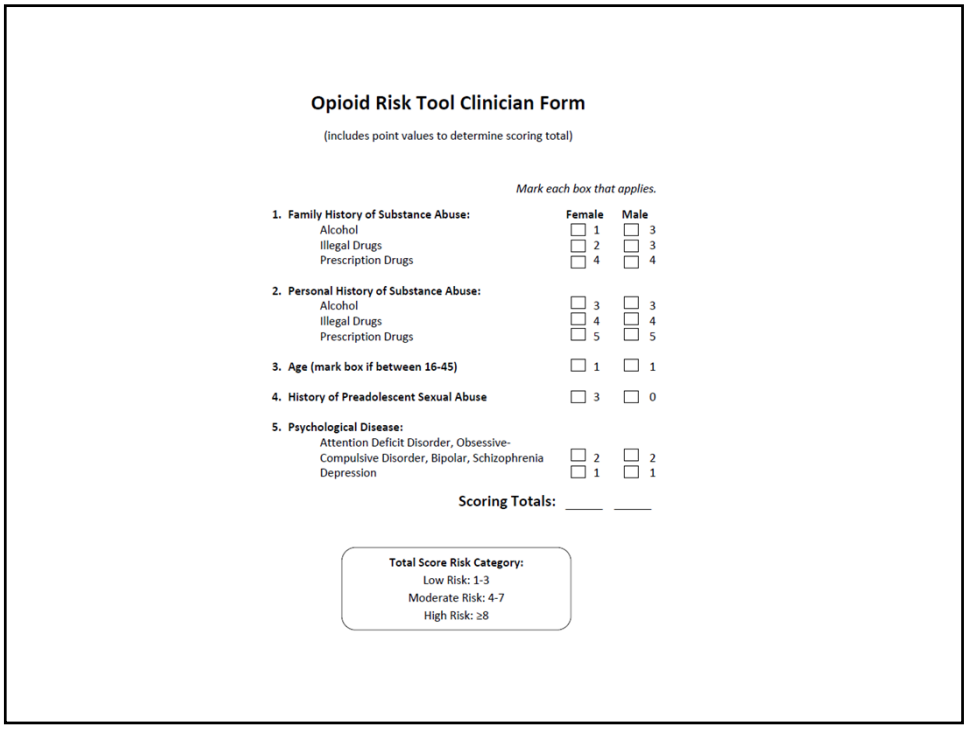
- Personal or family substance abuse history
- Adverse childhood experiences (ACE)
  - Neglect
  - Physical, emotional, sexual abuse
- Mental illness
- Psychological stress (chemical coping)

Identifying at Risk Patients

- Predictive tools
- Aberrant behaviors
- Urine drug testing
- Prescription monitoring programs
- Severity and duration of pain v. objective pathology
- Pharmacist communication
- Family and friends

Risk Assessment Tools

- ORT: Opioid Risk Tool
- SOAPP: Screener and Opioid Assessment for Patients with Pain
- DIRE: Diagnosis, Intractability, Risk, Efficacy
- COMM: Current Opioid Misuse Measure
- PMQ: Pain Medication Questionnaire
- DAST-10: Drug Abuse Screening Test



Opioid Risk Tool Clinician Form

(includes point values to determine scoring total)

Mark each box that applies.

	Female	Male
1. Family History of Substance Abuse:		
Alcohol	☐ 1	☐ 3
Illegal Drugs	☐ 2	☐ 3
Prescription Drugs	☐ 4	☐ 4
2. Personal History of Substance Abuse:		
Alcohol	☐ 3	☐ 3
Illegal Drugs	☐ 4	☐ 4
Prescription Drugs	☐ 5	☐ 5
3. Age (mark box if between 16-45)	☐ 1	☐ 1
4. History of Preadolescent Sexual Abuse	☐ 3	☐ 0
5. Psychological Disease:		
Attention Deficit Disorder, Obsessive-Compulsive Disorder, Bipolar, Schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring Totals:	____	____

Total Score Risk Category:
Low Risk: 1-3
Moderate Risk: 4-7
High Risk: ≥8

Treatment Approaches

- Limit/avoid opioid usage absent clear and continued efficacy
- Identify at risk IWs for delayed recovery
- Biopsychosocial functional restoration approach per the MTUS / ODG / ACOEM

Biomedical Model

- Explains pain through etiologic factors (e.g., injury) or disease whose pathophysiology results in pain
- Cause →→ Effect
- This classic biomedical approach to understanding and treating pain is incomplete

Biomedical Model

- Its exclusive application can result in
  - Unrealistic expectations on the part of the physician and patient
  - Inadequate pain relief
  - Excessive disability in those with pain that persists well after the original injury has healed
  - Unnecessary & preventable chronic pain syndrome

Biopsychosocial Model

- Recognizes that pain is ultimately the result of
  - Pathophysiology
  - Psychological state
  - Childhood and life experiences
  - Relationship/interactions with the environment
    - workplace, home, disability system, and health care providers

Functional Restoration Approach

- Multidisciplinary & Interdisciplinary
- Individualized
- Educational
- Functionally oriented (not pain oriented) to reengage in home and work activities
- Locus of control shifts to individual

Treatment Goals

- Provide each patient with education and a range of tools that assist them confidently and more effectively manage pain, increase function, and return to life activities including work

Education Issues

- Understanding the cause and meaning of pain
- Learning to live with chronic pain
- Locus of control within the person
- Becoming a person with a manageable pain problem rather than a chronic pain patient
- Education to prevent relapse (backsliding)

Physical Restorative Services

- Active & Functional
  - Improved body mechanics
  - Spine stabilization, stretching & strengthening
  - Aerobic conditioning
  - Aquatics therapy
  - Tai Chi, Yoga, Qi Gong, etc.
  - Flare-up management
  - Self-directed fitness program

Cognitive-Behavioral Treatment

- Interventions to change perception or emotional response to pain
  - Acceptance / Reduce negative thought patterns
- Cognitive restructuring, relaxation training, guided imagery, desensitization, & pacing
- Communication skills training
- Promotion of a self-management perspective
- Reduce anger and entitlement issues

Conclusions

- Use of opioids may be appropriate
  - Pathology that fits the problem
  - Improved level of function and increased ADLs
  - Decreased pain
  - Manageable side effects

Conclusions

- Balanced multimodal care
  - Use of opioids as part of complete pain care
  - Anticipation and management of side effects
- Maintain standard of care
  - History & physical exam
  - Follow-up
  - Referrals as needed
  - Measure functional outcomes
  - Documentation

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  http://www.ampainsoc.org/library/pdf/Opioid_Final_Evidence_Report.pdf
- Responsible Opioid Prescribing: A Physician's Guide by Scott M. Fishman, MD, Federation of State Medical Boards, 2012
  http://www.fsmb.org/pain-overview.html
- Opioid Prescribing Toolkit by Nathanial Katz, MD, Oxford University Press, 2011
- Opioid Clinical Management Guide by CARES Alliance
  http://www.caresalliance.org/

Internet Resources

- ***General Pain Sites***
  - PainEDU – *http://www.PainEDU.org*
  - painACTION – *http://www.painaction.com*
  - American Pain Society (APS) – *http://www.ampainsoc.org*
  - International Association for the Study of Pain (IASP) – http://www.iasp-pain.org
  - American Academy of Pain Medicine – http://www.painmed.org
- For a more complete list go to www.FeinbergMedicalGroup.com and click on References and then Internet Links

Internet Resources

- ***Laws or Legal Issues Regarding Opioid Treatment***
  - Federation of State Medical Boards – *http://www.fsmb.org*
  - Drug Enforcement Administration, Office of Diversion Control - *http://www.deadiversion.usdoj.gov*
  - The Legal Side of Pain – *http://www.legalsideofpain.com*
  - University of Wisconsin Pain & Policy Studies Group – *http://www.painpolicy.wisc.edu*
- ***Risk Assessment Tools***
  - PainEDU – *http://www.PainEDU.org*
- ***Resources for Chronic Pain Patients***
  - American Chronic Pain Association – *http://www.theacpa.org*

Opioids and Chronic Pain Treatment

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The proper use of opioids in the treatment of injured workers has come under increasing scrutiny in recent years. The problem is not just about issues surrounding opioids but also the importance of understanding about the person taking the opioid. To paraphrase Sir William Osler, it is more important to know about the person who has the disease than about the disease the person has.

We have come to understand that the traditional biomedical model fails miserably with certain individual with chronic pain including those where opioids are prescribed. We know recognize the importance of a biopsychosocial, whole-person approach as promoted in all evidence-based medicine opioid guidelines[1] [2] [3] [4] [5] [6] including the presumptively correct California DWC Medical Treatment Utilization Schedule (MTUS) Chronic Pain Medical Treatment Guideline[7]. The Introduction to this MTUS Guideline attempts to establish a conceptual framework for understanding and treating chronic pain including the prescription of opioids and other treatments.

The issue of appropriate current and future use of opioids in the treatment of Chronic Pain is complex, controversial, and timely.

On one side we have the ever increasing problem of increasing deaths and dysfunction from the inappropriate use of prescription opioids, and on the other we have the needs of patients for adequate pain control to facilitate comfort, activity and function. For the practitioner and patient, achieving a balance across the spectrum of outcomes from pain alleviation and increased function as opposed to untoward side effects, aberrant drug related behavior, drug addiction, drug abuse, drug diversion and potential death, remains problematic.

Scientific studies have shown a dramatic increase in accidental deaths associated with the use of prescription opioids and also an increasing average daily morphine equivalent dose (MED) for the most potent opioids over the past decade. Specifically, there has been a four-fold increase in prescribing of opioid analgesics which has been associated with a four-fold increase in opioid related overdose deaths

and a six-fold increase in individuals seeking treatment for addiction to opioid analgesics.[8]

In response to the increasing morbidity and mortality associated with the increasing use of opioids, the Centers for Disease Control and Prevention has released several recommendations[9] for healthcare providers. The recommendations include the notion that use of opioid medications for acute and/or chronic pain should only take place after a determination has been made that alternative therapies have not provided adequate pain relief. Additionally, the lowest effective dose of opioids should be used. Behavioral screening, patient agreements, random, periodic, and targeted urine testing for opioids and other drugs should be strongly considered in patients with noncancer pain, who has been treated with opioids for more than six weeks. If or when a patient's MED has increased to 120 mg per day or more, without substantial improvement in function and pain, the treating physician should seek advice from a pain specialist.

On February 6, 2009, the Food and Drug Administration (FDA) sent letters[10] to manufacturers of certain opioid drug products indicating that these drugs will be required to have a risk evaluation and mitigation strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol.

On April 19, 2011, in conjunction with the Office of National Drug Control Policy (ONDCP) release of the Obama Administration's Epidemic: Responding to America's Prescription Drug Abuse Crisis--a comprehensive action plan to address the national prescription drug abuse epidemic, FDA issued letters to application holders directing them to submit a REMS within 120 days and describing the elements that needed to be included in the REMS (REMS notification letters).[11] The central component of the Opioid REMS program is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants) and patients.

The Background introductory statement notes that Prescription drug abuse is the Nation's fastest-growing drug problem. While there has been a marked decrease in the use of some illegal drugs like cocaine, data from the National Survey on Drug Use and Health (NSDUH) show that nearly one-third of people aged 12 and over who used drugs for the first time in 2009 began by using a prescription drug non-medically.[12] The same survey found that over 70 percent of people who abused prescription pain relievers got them from friends or relatives, while approximately 5 percent got them from a drug dealer or from the Internet.[13] Additionally, the latest Monitoring the Future study—the Nation's largest survey of drug use among young people—showed that prescription drugs are the second most-abused category of drugs after marijuana.[14] In our military, illicit drug use increased from 5 percent to 12 percent among active duty service members over a three-year period from 2005 to 2008, primarily attributed to prescription drug abuse.[15]

In November 2011, the FDA announced[16] the availability of a draft document entitled ``Blueprint for Prescriber Education for the Long-Acting/Extended-Release Opioid Class-Wide REMS" (Blueprint)[17]. The draft Blueprint contains core messages intended for use by continuing education (CE) providers to develop educational materials to train prescribers of long-acting and extended-release opioids under the required risk evaluation and mitigation strategy (REMS) for these products (Opioid REMS).

The FDA Blueprint notes that Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioids are in a key position to balance the benefits of prescribing ER/LA opioids to treat

pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. It notes that "opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem." It is noted that public health experts estimate that more than 35 million Americans age 12 and older have reported non-medical use of opioid analgesics during 2010 - up from 29 million in 2002[18]. In 2009, nearly 342,000 emergency department visits were associated with nonmedical use of opioid analgesics[19]. In 2007, nearly 28,000 Americans died from unintended consequences of drug use, and of these, nearly 12,000 involved prescription drug pain relievers.[20] The number of prescriptions filled for opioid pain relievers - some of the most powerful medications available - has increased dramatically in recent years. From 1997 to 2007, the milligram per person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams, an increase of 402 percent.[21] In addition, in 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48 percent.[22] Further, opiate overdoses, once almost always due to heroin use, are now increasingly due to abuse of prescription painkillers.[23]

Use of opioids for chronic noncancer pain (CNCP) remains controversial.[24] A 2007 systematic review indicated no clear efficacy of chronic opiate therapy (COT) for chronic back pain because no studies have evaluated opiate use beyond 16 weeks[25] and data on the long-term effectiveness of opioids for CNCP are sparse, with inconclusive or mixed results.[26] [27] Surveys of CNCP patients receiving COT have shown that many continue to experience significant chronic pain and dysfunction.[28] [29] Studies have found high rates of addiction in CNCP patients receiving COT.[30] [31] Patients with mental health and substance abuse co-morbidities are more likely to receive COT than patients who lack these risk factors, a phenomenon referred to as *adverse selection*.[32]

Although extensive clinical experience suggests that opioids can improve pain and function in some patients,[33] [34] a significant proportion experience no improvement or worsening of symptoms.[35] Recent surveys of chronic noncancer pain patients receiving chronic opioid therapy have shown that many continue to experience significant chronic pain and dysfunction.[36] [37] Because opioid use is often associated with a variety of potentially serious adverse outcomes, including harms related to drug abuse and diversion.[38] [39]

Additionally, there have been increasing reports of problems associated with chronic opioid therapy. Although opiates remain an important tool in reducing pain, it is important that the prescribing physician appreciate the potential adverse effects that may occur with chronic opioid administration, such as immune dysfunction,[40] endocrine deficiencies[41] [42], sleep disorders[43] [44], and hyperalgesia[45] [46].

Tolerance to the analgesic effects of an opioid occurs after its chronic administration, a pharmacological phenomenon that has been associated with the development of abnormal pain sensitivity such as hyperalgesia. This clinical phenomenon causes the patient to experience pain that is significantly more intense than the pain anticipated from actual injury and is caused by 1) decreased tolerance of pain, 2) hypersensitivity of the nerves, and 3) the patient's expectation of the occurrence of pain. Studies have shown opiates produce a long-lasting hyperalgesia that increases in magnitude and duration with continued use.[47] [48] [49] [50]

Although it is true that physician acceptance of opioid analgesic usage has relaxed over the years, it remains important to evaluate each patient individually, to ensure effective treatment. In general, there is a belief today that opioids (despite their potential for problems) have a place in the physician's treatment armamentarium when other methods have failed and when the use of opioids use results in less pain, more function and manageable side-effects.

It is important to recognize that pain symptoms even with reported "benefit" (pain reduction/relief) with opioids is not an adequate basis for opioid prescription absent a pathological process consistent with the pain complaints. Opioids are used illicitly for non-pain purposes in our society for both pleasure and habituation (physical dependence and addiction). Considering the controversy and potential danger of opioids, their use must be weighed against the risks associated with use. In other words, the use of opioids for benign musculoskeletal conditions is not medically indicated or reasonable.

Assuming non-opioid treatment approaches have failed and that there is adequate pathology to support the use of opioids, the clinician must determine that the use of opioids is beneficial and that the benefits outweigh the risks.

The physician can make this determination using the Four "A's" of Pain Treatment Outcomes[51] which include: 1) adequate Analgesia (pain relief); 2) improved Activities of Daily Living (physical and psychosocial functioning); 3) manageable or no Adverse effects (untoward side effects); and 4) no evidence of Aberrant drug taking (addiction-related outcomes).

Special attention must also be paid to individuals who have a predilection to opioid overuse and abuse. This includes those with a prior history of substance abuse but also people with a history of adverse childhood experiences.

Adverse Childhood Experiences (ACE) including abuse (physical, emotional, sexual, etc.), neglect (physical, emotional, etc.), household dysfunction (violence, mental illness, drug abuse, etc., in the home), and exposure to traumatic stressors increase the likelihood of chronic disability and prescription drug abuse in adulthood.[52] [53]

The 2008 ACOEM Practice Guidelines updated Chronic Pain Chapter [54] (I was on the Panel and served as an Associate Editor), suggests that opioids should not be used when there is no evidence that they provide increased function in life. Further, it is also recommended that patients on chronic opioid therapy go through a weaning process to see whether the opioids truly make any difference in function and pain management.

In cases where opioids are to be used, they should provide cost effective benefit; less pain and more function with manageable side effects. We should not use a particular opioid when something less costly but just as efficacious is available or when there is an alternative available with lesser potential problems such as acetaminophen, NSAIDs, anti-neuropathics, anti-depressants, etc., or with functional restoration approaches including education, cognitive behavior therapy, meditation, exercise, and physical rehabilitation. In fact, there is good evidence of cost-effectiveness when a functional restoration approach is provided as an adjunct and concomitantly with medication and interventional approaches.

Once patients have demonstrated improvement in function and concomitant reduction in pain, it is medically reasonable to constantly seek to minimize the opioid dose. This should be done slowly and methodically, in conjunction with careful monitoring of the patient's clinical and functional status. Under such circumstances it is sometimes possible to completely wean the patient from opioids after several months.

If attempts at weaning are accompanied by increased pain and worsened functional performance, the medication dose can be reinstituted and, perhaps, weaning attempted again after the patient has stabilized.

If weaning remains problematic, it is only then that consideration be given to maintenance, long-term opioid use.

Patients considered for long-term opioid use must be made aware of risks and benefits including the aforementioned long term potential adverse effects of opioids: tolerance, addiction, hypogonadism (with secondary osteoporosis) and opioid induced hyperalgesia.

If long-term treatment with an opioid is undertaken for chronic pain, periodic monitoring is essential to optimize benefit and minimize risk during the course of treatment.[55] Patients maintained on chronic opioid therapy should review and sign a formal opioid agreement/contract, to include random urine drug screens.[56]

The Official Disability Guidelines[57] (I serve on the ODG Medical Editorial Advisory Board) has established criteria for using of opioids. Briefly, the use of opioids should be part of a treatment plan that is tailored to the patient. Reasonable alternatives to treatment should have been tried. Is the patient likely to improve and has the patient at risk for abuse or addiction? If opioids are not effective, dose escalation may not prove beneficial. Is there pathology to justify use of opioids? Is there psychiatric comorbidity in one of the diagnostic categories that have not been shown to have good success with opioid therapy: conversion disorder; somatization disorder; pain disorder associated with psychological factors (such as anxiety or depression, or a previous history of substance abuse)? Only one practitioner should be prescribing opioids. The lowest possible dose should be prescribed to improve pain and function. The physician should document ongoing review and documentation of pain relief, functional status, appropriate medication use, and side effects. Satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function or improved quality of life.

There are other Guidelines that provide similar recommendations which include:

- Institute For Clinical System Improvement (ICSC) Health Care Guideline: Assessment and Management of Chronic Pain[58], Fourth Edition, November 2009)
- Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain[59]
- Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain[60]
- Washington State Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain[61]
- The American Pain Society: Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain[62]

The reader is also encouraged to view and download a copy of the American Chronic Pain Association 2012 Resource Guide to Pain Medications & Treatment (I am the Senior Author)[63].

The group, Physicians for Responsible opioid Prescribing (PROP)[64] states: Our mission is to reduce morbidity and mortality resulting from prescribing of opioids and to promote cautious, safe and responsible opioid prescribing practices. PROP states: “COT may provide modest, variable short-term pain relief for some patients with chronic pain. Long-term benefits of COT for chronic pain have not been established. Potential medical and behavioral harms of opioids are an important concern, particularly at higher dosage levels and in higher risk or medically complex patients. While COT at lower doses may be a useful treatment for some patients, it should only be considered for carefully evaluated, closely monitored patients when a cautious, structured and selective approach is employed, and clear benefits for pain and function are documented. COT always entails risks for patients, their families and the

community, so vigilance and caution are essential."

In summary, while opioids can prove extremely effective in managing chronic pain in certain individuals, their use is fraught with serious problems.

Opioids should be prescribed with extreme caution and their sustained use must be justified by increased function, decreased pain and manageable side-effects.

The evidenced based medicine scientific literature strongly supports a Functional Restoration approach[65] to chronic pain treatment.

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Opioid related excerpts from the

2013 ACPA Resource Guide To Chronic Pain Medication & Treatment

The full Guide can be found at **http://www.theacpa.org**

OPIOID ANALGESIC PAIN RELIEVERS

THE OPIOID DILEMMA

Considerable controversy exists about the use of opioids for the treatment of chronic pain of non-cancer origin. Many health care professionals think that chronic pain is inadequately treated and that opioids can play an important role in the treatment of all types of chronic pain, including non-cancer pain. Others caution against the widespread use of opioids, noting problems with tolerance, loss of benefit with time, and escalating usage with decreasing function along with increasing side-effects in some individuals.

The use of opioids (or for that matter any treatment) makes sense when the benefits outweigh the risks and negative side effects. Benefit is suggested when there is an increase in the person's level of functioning, a reduction or elimination of pain complaints, a more positive and hopeful attitude, and when side effects are minimal or controllable.

Opioids are not harmless drugs. The dilemma with the long-term use of opioids is that while opioid treatment may be prescribed to reduce pain and improve function, the treatment may actually result at times in just the opposite.

It is well known that in the opioid naïve (someone new to opioid use) patient, the use of opioids may heighten the risk of accidental death from respiratory (breathing) depression.

It is well known that prolonged use of opioids may result in problems including tolerance, hyperalgesia (increased pain sensitivity), hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses, etc.), depression, impaired sleep patterns, and suppression of the immune system. The long-term use of opioids may also impair functional improvement in an individual's recovery from surgery or with long-standing musculoskeletal disorders.

Research shows that long-term use of large quantities of opioids may interfere with the body's natural pain relievers, the endorphins. Since physical activity is thought to promote release of endorphins, it is also possible that opioids could inhibit the body's own mechanism of reducing pain by causing a person to be less active. Additionally, long-term opioid use may cause depression in some patients, which may impede their ability to recover.

Fifty-one percent of all patients taking oral opioids experience at least one adverse event/effect. Approximately 20% of all patients taking oral opioids discontinue their use because of an adverse event or an associated side effect.

While tolerance may develop and the individual may be prescribed higher doses of opioids over time, there is still increased risk of death as the dose of opioids increases.

In an article published by the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, titled Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006, opioid poisoning was noted to be the second leading cause of injury death overall and the leading cause of injury death for people ages 35–54 years, surpassing both firearm- related and motor vehicle-related deaths in this age group. The number of poisoning deaths and the percentage of these deaths involving opioid analgesics increased each year from 1999 through 2006.

Due to the seriousness of this problem, the FDA is now requiring that special safety procedures called REMS (Risk Evaluation and Mitigation Strategies) be put into place to protect people. One of the components of REMS requires that patients who receive opioids must be given an informational brochure called a Medication Guide for the specific drug they receive each time they get a new prescription. The Medication Guide is designed to inform patients about the serious risks associated with the drug. It should be read each time a new prescription is received, even if the specific opioid being used has not changed, since there may be important new information added. The FDA is also working in cooperation with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to increase prescribers' knowledge about appropriate prescribing and safe use of opioids. There is renewed emphasis on home storage and safe disposal of unused medication to help patients protect their families and the continued availability of opioids to patients.

WHAT ARE OPIOIDS?

OPIOID AGONISTS

Opioids are morphine-like substances and have been available for centuries to relieve pain. The term opioid is derived from opium, which is an extract from the poppy plant. There are naturally occurring (opiate), synthetic (opioid), and semisynthetic forms.

Most opioids are agonists, a drug that binds to a receptor of a cell and triggers a response by the cell. An agonist produces an action. It is the opposite of an antagonist, which acts against and blocks an action.

Examples of opioid agonists include morphine, hydromorphone, fentanyl, and oxycodone. There are a number of opioid receptors in the body that mediate analgesia. In 1975, it was discovered that the body generates its own (internal or endogenous) opioids (called endorphins, enkephalins, and dynorphins).

There are numerous opioids available by prescription (see chart below). The potency, speed of onset, and duration are unique to each drug. All of the opioids have similar clinical effects that vary in degree from one drug to another.

There are both short- and long-acting opioid formulations. Some opioids are used around-the-clock in scheduled doses, while others are used as needed for intermittent or breakthrough pain.

OPIOID MIXED AGONISTS/ANTAGONISTS

There are a number of opioid analgesics (pain relievers) that are partial agonists and mixed agonists/antagonists. The mixed agonists/antagonists are characterized as having an analgesic "ceiling" effect in which the analgesic benefit plateaus, and no further benefit is obtained by increasing the dose.

Given their antagonist nature, these medications can reverse the effects (analgesia and side effects) of full agonist opioids, such as morphine, fentanyl, hydromorphone, and oxycodone, and therefore should be used with caution in those taking a full agonist opioid. A partial agonist/antagonist is occasionally initiated in a person already taking an agonist opioid. The doses should be adjusted gradually to avoid symptoms of opioid withdrawal. In most cases, these two types of agents should not be used together.

Symptoms of withdrawal include sweating, gooseflesh or goose bumps (a temporary local change in the skin when it becomes rougher due to erection of little muscles, as from cold, fear, or excitement), runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your health care professional or pharmacist if you have these or other side effects.

OPIOID DELIVERY

Opioids are available orally (by mouth), intravenously, by intramuscular injection (although not recommended), via nasal spray, transdermally (through the skin), oral transmucosally (absorbed under the tongue and the inside of the cheek), buccally (absorbed via the inside of the cheek), sublingually (absorbed under the tongue), via suppository, an epidural (injection of an anesthetic into the lumbar area of the spine in the space between the spinal cord and the covering dura), and intrathecal drug delivery (injection into the sheath surrounding the spinal cord – also see discussion on Implanted Intrathecal Drug Delivery Systems - "Pain Pumps").

SHORT-ACTING AND LONG-ACTING OPIOID AGONISTS

Short-acting oral opioids, also called immediate-release (IR) opioids, often contain an opioid as the only active ingredient (e.g., morphine, hydromorphone, oxycodone, and oxymorphone), while others contain a combination of an opioid and a non-opioid such as acetaminophen or ibuprofen.

Examples of short-acting opioid combination products include:

- oxycodone with acetaminophen (Percocet®)
- oxycodone with aspirin (Percodan®)
- oxycodone with ibuprofen (Combunox®)
- hydrocodone with acetaminophen (Lorcet®, Lortab®, Vicodin®, Norco®)
- hydrocodone with ibuprofen (Vicoprofen®)
- tramadol hydrochloride with acetaminophen (Ultracet®)

Short-acting oral opioids, true to their description, exert a rapid-onset but short-lived therapeutic effect. These agents typically start working 15–30 minutes after administration, with peak analgesic effect within 1–2 hours. Sustained pain relief is maintained for only about 4 hours. They are a potent option for treating acute pain (e.g., from a serious athletic injury or after a root canal) and are usually prescribed for pain that is anticipated to last only a few days.

Because of their short half-life and rapid clearance from the body, short-acting opioids must be taken every 3–4 hours. Therefore, these drugs are not ideal for long-term therapy of chronic pain. Short-acting opioids may be effective, however, as an initial "trial" therapy in patients with moderate or severe chronic pain who have not previously received opioid treatment. In this case, short-acting agents are used to establish an individual patient's response and tolerance to opioid therapy and lay the groundwork for long-term dosing of long-acting opioid therapy.

In addition to their importance in managing acute pain and initiating therapy for chronic pain, short-acting agents can be used with a long-acting agent during long-term therapy as "rescue medication." Rescue medication may be necessary for addressing breakthrough pain that occurs despite ongoing, long-term analgesic treatment.

Long-acting (sometimes called slow-release) medications are the opioid treatment of choice for patients with continuous moderate to severe chronic pain. They have a more lasting therapeutic effect than short-acting agents. Long-acting formulations are described as having sustained, extended, or controlled release of drug and are abbreviated as SR, ER, or CR, respectively.

Examples of long-acting opioids include:

- morphine (oral sustained release, e.g., MS Contin®, Avinza®, Kadian®)
- oxycodone (oral controlled release, e.g., OxyContin®)
- oxymorphone (oral extended release Opana® ER)
- hydromorphone (oral extended release EXALGO®)
- methadone (oral) (e.g., Dolophine®, Methadose®)
- fentanyl transdermal system (Duragesic®)

The prolonged effects of these agents are due to their long half-lives or slow delivery into the body via controlled-release opioid preparations. Because of the slower release of active drug, long-acting opioids can provide prolonged, steady pain relief for 8–12 hours. Long-acting drug preparations are given at regularly scheduled times, such as every 12 hours. Hydromorphone EXALGO®) is a once-daily medication with reported sustained blood levels for 18-24 hours.

Slow-release tablets should be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed slow-release pills can lead to rapid release and absorption of a potentially fatal dose of the drug.

Examples of Medical Opioid Agonists*	
Codeine (with acetaminophen -Tylenol® with codeine No. 2, No. 3, No. 4)	Codeine is metabolized by the liver to morphine. Some individuals do not have the enzyme required to convert codeine to morphine, and therefore the medication is ineffective. Even though they do not receive benefit, they are still at risk for the associated side effects. Codeine often is associated with higher levels of nausea and vomiting and constipation compared to other opioids.
Dihydrocodeine bitartrate, Aspirin, Caffeine (Synalgos-DC®)	This combination drug of dihydrocodeine, aspirin and caffeine is rarely prescribed in chronic pain states.
Fentanyl (Actiq® lozenge, Fentora® buccal tablet and ONSOLIS™ buccal film, Abstral® buccal film, Duragesic® transdermal patch, Lazanda® nasal spray)	There have been reports of death and other serious side effects from overdoses while on fentanyl transdermal patches. Furthermore, patients that have not been on opioids (opioid naïve) should not be initially started on the fentanyl transdermal patch because of the inherent inaccuracies in dosing which can lead to an overdose. Exposure to heat (hot bath, heating pad, hot sun, etc.) can increase the speed of fentanyl release. The directions for using the fentanyl skin patch must be followed exactly to prevent death or other serious side effects from overdose. Do not cut fentanyl patches. Oral transmucosal fentanyl is available in multiple formulations for the treatment of breakthrough pain in cancer patients receiving opioid treatment and who have become tolerant to it. The FDA warns that serious adverse events, including deaths, can occur in patients treated with oral fentanyl. The deaths that have occurred were due to respiratory depression as a result of improper patient selection, improper dosing, and/or improper product substitution. Actiq® (oral transmucosal fentanyl lozenge on a plastic stick) is absorbed by swabbing the drug-containing lozenge over and under the tongue and between the cheeks and gums. It is contraindicated for acute postoperative pain and migraine headache.
Hydrocodone • With **acetaminophen** – Anexsia®, Lorcet®, Lortab®, Norco®, Vicodin®, Hycet®, Xodol®, Co-Gesic®, Zydone® • With **ibuprofen** – Reprexain™, Vicoprofen® • With **aspirin** – Azdone, Lortab ASA, Panasal	Hydrocodone is a short-acting opioid available only in combination with other ingredients, and different combination products are prescribed for different uses. Some hydrocodone products are used to relieve moderate to severe pain. Other hydrocodone products are used to relieve cough.
Hydromorphone (Dilaudid®, Dilaudid-5®, EXALGO®)*	EXALGO® tablets are an extended-release oral formulation.
Levorphanol (Levo-Dromoran®)	Levorphanol has the same properties as morphine with respect to the potential for habituation, tolerance, physical dependence and withdrawal syndrome. It is 4 to 8 times as potent as morphine and has a longer half-life.
Meperidine (Demerol®)	Due to its low potency, short duration of action, and unique toxicity (i.e., seizures, delirium, and other neuropsychological effects) relative to other available opioid analgesics, meperidine has fallen out of favor and is not recommended or typically used in chronic pain states.

Examples of Medical Opioid Agonists*

Methadone (Dolophine®, Methadose®)	Although methadone possesses analgesic properties, it must be used carefully and with a great deal of caution. It has a long half-life and can accumulate in the body which can lead to an overdose. It interacts with a large number of other medications, including OTC drugs. It is strongly recommended that the individual on methadone not use any OTC or herbal medications without clearing them with the prescribing health care professional. The addition of other commonly used pain medications (e.g., antidepressants, anticonvulsants, and NSAIDS) can increase the likelihood of methadone negatively influencing the heart's ability to conduct electrical signals properly. Prior to starting methadone, patients should undergo an electrocardiogram to check for any pre-existing heart abnormalities that may contraindicate its use. Methadone can also be associated with the development of central sleep apnea. Benzodiazepines should be utilized with extreme caution by individuals on methadone secondary to the synergistic negative respiratory and cardiac effects.
Morphine (Avinza™, Duramorph®, Kadian®, MS-Contin®, Oramorph SR®)*	Morphine is considered to be the prototypical opioid and is available in many formulations.
Oxycodone (OxyContin®, OxyIR®, Roxicodone™, Oxecta®) • Combunox® (containing ibuprofen, oxycodone) • Endocet® (containing acetaminophen, oxycodone) • Endodan® (containing aspirin, oxycodone) • Lynox® (containing acetaminophen, oxycodone) • Magnacet® (containing acetaminophen, oxycodone) • Narvox® (containing acetaminophen, oxycodone) • Percocet® (containing acetaminophen, oxycodone) • Percodan® (containing aspirin, oxycodone) • Perloxx® (containing acetaminophen, oxycodone) • Primlev® (containing acetaminophen, oxycodone) • Roxicet® (containing acetaminophen, oxycodone) • Roxiprin® (containing aspirin, oxycodone) • Taxadone® (containing acetaminophen, oxycodone) • Tylox® (containing acetaminophen, oxycodone) • Xolox® (containing acetaminophen, oxycodone)	Recently, the manufacturer of OxyContin® reformulated its product. The previous OxyContin® product contained an immediate-release component (38%) as well as an extended-release component (62%). The reformulated OxyContin® is 100% extended-release. The reformulated OxyContin® is harder to crush or chew and therefore serves as a better deterrent for abuse. The previous OxyContin® had an imprint of "OC" on the tablet, whereas the reformulated OxyContin® has an imprint of "OP." There is currently no generic for the reformulated OxyContin®, which is the only form available in the United States. With the older formulation, many patients experienced euphoria, which was essentially due to the initial high levels of the oxycodone in the blood. Often times the euphoria feeling has been equated with better pain control, although research has not shown this to be the case. The new tablet formulation takes longer to reach peak levels, which can be incorrectly associated with inadequate pain control.
Oxymorphone (Numorphan®, Opana® and Opana® ER)*	Opana® ER is an extended-release crush resistant oral formulation of oxymorphone.
Tapentadol (Nucynta®, Nucynta® ER)*	Tapentadol is an opioid with both opioid and nonopioid activity. The drug binds to opioid receptors and also inhibits the reuptake of the neurotransmitter norepinephrine. The dual mechanism of action inhibits the transmission of pain signals in both the ascending and descending pathways. In pre-clinical studies, this drug has a lower affinity than morphine for the opioid receptor. The short-acting formulation is approved for acute pain treatment, and the extended-release formulation is approved for continuous moderate to severe chronic pain. Tapentadol may have an improved GI side effect profile in comparison with other opioids.

Examples of Medical Opioid Agonists*	
Tramadol (Ultram®, Ultram® ER)* and Tramadol combined with acetaminophen (Ultracet™) considered a "weak" opioid	Tramadol is a weak opioid analgesic that acts on the central nervous system in two ways. It binds modestly to opioid receptors and thus produces some analgesia by the same mechanism as opioids. It also affects certain neurotransmitters in the brain to decrease the perception of pain. While a weak opioid, tramadol is not completely free of this risk and may trigger addiction even in those without a history of drug abuse or previous addiction. Tramadol reduces the respiratory rate to a lesser extent than opioids in overdoses and does not cause the sort of GI irritation produced by NSAIDs. Tramadol reduces the threshold for seizures, which may occur in overdose. Seizures may also be provoked in those with a history of seizure disorders, head trauma, etc., or in those taking other drugs that reduce the seizure threshold such as certain antidepressants. Since tramadol is a centrally acting synthetic analgesic, not an NSAID, it has no anti-inflammatory activity. Also unlike NSAIDs, tramadol does not have the potential to compromise the efficacy of certain antihypertensive agents (diuretics and ACE-inhibitors). Tramadol should be used cautiously, if at all, in patients with underlying liver and kidney disease.

*** Slow-release (e.g., extended-release, controlled-release, and sustained-release) oral opioid formulations should be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed slow-release pills can lead to rapid release and absorption of a potentially fatal dose of the drug.**

Examples of Medical Opioid Mixed Agonists/Antagonists	
Buprenorphine (Buprenex®, Butrans™ Transdermal, Subutex®) - also used for the treatment of opioid dependence	In addition to its use for the treatment of chronic pain, buprenorphine is used to help alleviate unpleasant withdrawal symptoms associated with opioid detoxification. Buprenorphine exhibits a ceiling effect, which means increasing the dose of buprenorphine beyond a certain point results in no additional pain control. Doses greater than 32 mg / day are ineffective. The ceiling effect demonstrated with buprenorphine offers advantages when compared to other medications used to manage addiction because there is a lower abuse potential, lower level of both physical dependence and withdrawal, and there is a decreased incidence of dose related side effects.
Buprenorphine/naloxone (Suboxone®) - also used for the treatment of opioid dependence	Buprenorphine/naloxone (Suboxone®) is a combination drug. Naloxone is a pure opioid antagonist, meaning it blocks the effects that opioid drugs have on the receptors. When given sublingually, naloxone has no significant effects on buprenorphine. However if Suboxone® is crushed or injected, naloxone will block the effects of buprenorphine. This characteristic discourages misuse. If Suboxone® is swallowed instead of dissolved under the tongue, the patient may experiences no effect due to the poor bioavailability and first pass metabolism. Naloxone inhibits respiratory depression, hypotension, sedation, and analgesia.
Butorphanol (Stadol®)	Available in injection or nasal spray formulations but not typically used for chronic pain treatment.
Nalbuphine (Nubain®)	Administered subcutaneously, intramuscularly or intravenously but not used for chronic pain treatment.
Pentazocine (Talwin®; with acetaminophen-Talacen®; with aspirin-Talwin® Compound)	Side effects are similar to those of morphine, but pentazocine may be more likely to cause hallucinations and other psychosis-like effects. Not used for chronic pain treatment.
Pentazocine/naloxone (Talwin® NX)	Talwin® NX is a combination of pentazocine and naloxone, an opioid antagonist. This oral formulation was developed to prevent tampering and reduce abuse. The goal of this drug design is to reduce the possible misuse of this medication when it is tampered with by crushing, chewing, or injecting. If the drug is taken as directed, the naloxone will not release and will pass through the body with no effect.

GENERAL OPIOID ADVERSE SIDE EFFECTS

Common opioid side effects, particularly with higher doses, include nausea, vomiting, constipation, thought and memory impairment, and drowsiness. The majority of these side effects can usually be treated with dose adjustments, wane over time (with the exception of constipation), or can be offset by other alternate medications. Psychostimulants (see below) can be useful in selected patients to treat mild sedation.

Approximately 40% of individuals taking opioid therapy for non-cancer pain experience constipation (less than three bowel movements per week) secondary to opioid treatment. Most individuals taking opioid medications will not develop tolerance to the side effect/adverse effect of constipation. Therefore, an effective preventive bowel regimen including diet changes and a stimulant laxative plus a stool softener will have to be maintained throughout the course of opioid treatment. Even individuals that utilize appropriate laxative therapy often still experience constipation that may impede the appropriate use of opioid pain medication and thus result in higher levels of pain, so attention to and prevention of this side effect is essential.

Non-pharmacological interventions that can be taken to assist with constipation include: 1) increasing dietary fiber intake, 2) increasing fluid intake, 3) increasing physical activity, and 4) encouraging daily bowel movements at the same time, often after a meal. Pharmacological treatments that can be utilized include stool softeners and stimulant laxatives. In cases that do not respond, other forms of laxative treatment can be considered. Bulk forming laxatives, such as psyllium, are often not useful and can actually worsen opioid-induced constipation by producing colon obstruction. New approaches to treating opioid-induced constipation are being developed. Currently, these new medications have only been FDA approved for the postoperative period and the treatment of opioid-induced constipation in patients with advanced illness.

Mild sedation and impaired judgment or coordination also should be anticipated. Until tolerance or a baseline is reached, the patient and family need to be warned against driving and the potential for falls.

Mild nausea is also common with opioid therapy. It can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be appropriate.

A side effect of long-term opioid use is a decrease in certain hormones, particularly sex hormones. This reduction may cause you to lose your ‘sex drive’, sometimes called libido. This tends to be associated with using these medications regularly for many years.

A serious side effect, particularly in opioid-naïve individuals (those who have not been taking opioids regularly), is respiratory depression (slowed rate of breathing or loss of urge to breathe). Tolerance to respiratory depression occurs with regular opioid use.

A genuine allergy to opioids is very rare. If an allergy does occur, opioids from another class should be chosen. For example, morphine, hydromorphone, oxycodone, and oxymorphone belong to the same class of opioid. Fentanyl and meperidine belong to a different class.

Summary of Possible Opioid Side Effects

- Central nervous system
    - A sense of emotional well-being and euphoria.
    - Drowsiness, sedation, and sleep disturbance.
    - Hallucinations.
    - Potential for diminished psychomotor performance.
    - Dysphoria and agitation.
    - Dizziness and seizures.
    - Aberrant behavior (see addiction definition below).
    - Hyperalgesia (see definition below).

- Respiratory system
    - Respiratory depression is rare but the most serious adverse effect and may result from toxicity.
    - Diminution of pain or pain relief by other modalities may exacerbate respiratory depression.

- Ocular system
    - Constriction of the pupil of the eye.

- Gastrointestinal system
    - Constipation, nausea and vomiting.
    - Delayed gastric emptying.

- Genitourinary
    - Urinary retention.

- Endocrine
    - Hormonal and sexual dysfunction.

- Cardiovascular
    - Decreased blood pressure.
    - Slowed heart rate.
    - Peripheral edema (swelling).

- Musculoskeletal system
    - Muscle rigidity and contractions.
    - Osteoporosis.

- Skin system
    - Itching is common and not an allergic reaction.

- Immune system
    - There are data suggesting that long term administration of opioids suppresses the immune system. Research is being conducted to determine its clinical significance.

- Pregnancy & Breast Feeding
    - All opioids cross the placenta.
    - No teratogenic effects have been observed.
    - Neonatal central nervous system depression can occur if opioids are used during labor; attention to peak times is essential.
    - Use with caution in breast feeding; appropriate timing of opioid dose administration is important for safe opioid use during breast feeding.

- Analgesic Tolerance
    - Decreased duration of analgesia and then decreased effectiveness.

- Withdrawal Syndrome
    - Withdrawal symptoms may occur with abrupt opioid cessation and can include runny nose, shivering, "gooseflesh," diarrhea, and dilation of the pupil of the eye.

DEFINITION OF TERMS REGARDING OPIOIDS

Opioid-responsiveness is the ability to achieve pain relief with evidence of improved function without the development of unmanageable or intolerable side effects.

Opioid-induced Hyperalgesia is a syndrome of increased sensitivity to painful stimuli, worsening pain despite increasing doses of opioids, and pain that becomes more diffuse, extending beyond the distribution of pre-existing pain. This syndrome may reduce the clinical usefulness of opioids in treating chronic pain and require a reduction in dose or detoxification.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction seems to be the primary fear that limits opioid prescribing. This is a term that requires clarification. Addiction is the traditional term used to identify the irresistible craving for, loss of control over use of, compulsive use of, and continued use despite harm of certain types of drugs. Drugs capable of producing addiction do so by interacting with the biochemistry of the brain in such a way that the drug begins to seem essential – one feels a "need" for it as one does for food and water. While the media give the impression that the risk of addiction is inherent to the properties of opioids, experts in addiction generally recognize that it results from the interaction of the drug and various hereditary, psychological, and situational factors unique to the individual.

Addiction *should be distinguished from* **physical dependence** (see below). *Any person (or animal) that takes sufficient doses of certain types of drugs for a significant length of time can have withdrawal symptoms if the drug is suddenly stopped or reversed by another medicine. This shows the presence of physical dependence but does not constitute addiction*.

The risk of addiction is not well defined in chronic use. When it occurs, the drug is a liability rather than an asset to the person. There are four core elements in true addiction (the four C's):

- **C**ompulsive use and preoccupation with the drug and its supply,
- Inability to consistently **C**ontrol the quantity used,
- **C**raving the psychological effects of the drug, and
- **C**ontinued use despite adverse effects from the drug.

Compulsive use or preoccupation may be demonstrated by taking the drug because it is available (as opposed to taking it exactly as a health care professional has instructed), inappropriate "stocking up," having several health care professionals/pharmacists to guarantee a supply, and spending scarce resources on the drug.

Other examples of inappropriate use include selling the drug or changing the drug from pill to powder for injection or snorting.

Loss of control is demonstrated by the person who regrets his drunkenness and "pledges" to stop after two beers the next time; instead, he has six beers and behaves regrettably again. With pain medication, loss of control tends to take the form of using up a month's supply in a week, so that the person must go without the medication for a long time.

Examples of use despite adverse consequences may consist of smoking despite emphysema, drinking and driving despite convictions for driving under the influence, or using analgesics and tranquilizers despite their having an adverse effect on the ability to function, mood, and family relationships.

Craving, in this sense, does not mean taking a medicine as directed to relieve pain, but rather, an intense desire for a mental effect ("buzz", "high", or "trip") caused by a medicine.

People sometimes worry that they may become addicted to their opioid pain medications. The exact risk is not known, but factors which may increase your risk are if you or someone in your family have or have had a problem with drugs or alcohol in the past or you have a serious problem with anxiety, depression or other emotional health problem. People with a past history of adverse childhood experiences (including sexual abuse) during childhood or adolescence are also at risk; talk to your health care professional.

Let your health care professional know if you have ever had a problem with drugs or alcohol in the past or are currently using drugs or alcohol, or if many family members have this problem, as these are important in determining if opioid pain medications are right for you.

Similarly, let your health care professional know if you are concerned about becoming addicted to your opioid pain medications. Signs to be aware of include taking more medication than prescribed without checking with your health care professional first, loss of control over the medication, feelings of craving the medication or taking the medication for the euphoric (mental) effects rather than for pain relief.

Pseudo-addiction describes a syndrome of poorly or under-treated pain which in certain patients may be inaccurately labeled as having substance abuse or addiction. Patients develop feelings of anger and isolation, which lead to acting-out behavior. Inadequate pain management often leads to pseudo-addiction. It commonly involves an ineffective medication or inadequate medication prescribing either by excessive intervals between allowed doses or inadequate doses. Pseudo-addiction may come about because the healthcare provider may be inadequately educated about pain management or have an excessive fear of causing addiction.

Chemical Copers: Some individuals demonstrate inappropriate medication use but not to the level of addiction and are not likely to display a severity that rises to the level of compulsivity or loss of control. In addition, they are not likely to display behaviors indicative of drug cravings, which would convince a clinician to diagnose addiction. Simply put, chemical copers occasionally use their medications in non-prescribed ways to cope with stress. One example is using pain medications to fall asleep. A major hallmark of chemical coping is the overly central place in the person's life that is occupied by obtaining drugs for pain and a corresponding inflexibility about nondrug components of care. The use of medications becomes central in the chemical coper's life while other interests become less important. As a result, they often fail to move forward with psychosocial goals and are usually uninterested in treating pain non-pharmacologically; that is, they do not take advantage of other treatment options provided (i.e., functional restoration), such as exploring recommendations to see psychologists or physical therapists. Further, they remain on the fringe of appropriate use of their medication but are able to comply with their health care professional's opioid agreement enough to avoid being removed from treatment. Chemical copers often self-escalate their medication dosage when they are faced with stress and need to have their prescriptions refilled early.

Physical Dependence is a state of adaptation that is manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. In the management of acute pain, physical dependence usually does not develop because of the limited duration of opioid use. *Physical dependence is not addiction.*

Withdrawal involves developing signs of illness/discomfort when intake of the substance is abruptly stopped. *Withdrawal is not addiction.* Many people who have taken opioids or sedatives for more than a few doses will show some tolerance with use and withdrawal on abrupt drug cessation. In addition, numerous drugs can produce tolerance and withdrawal, yet do not produce addiction (e.g., epilepsy medications, some blood pressure drugs). Symptoms of withdrawal to monitor for include sweating, goose flesh, runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your health care professional or pharmacist if you have these or other side effects. Obtaining refills on time will prevent withdrawal.

Opioid Tolerance is a phenomenon or adaptation of the body over a period of time in which one or more effects of a drug become less with repeated use at the same dose (many patients call this becoming "immune" to the drug). For example, a person might feel drugged after the first pain pill; but with continued use, a person might require several pills to feel anything. With analgesics, the concern is that the individual will build up tolerance to the drug and therefore require more medication to achieve results. Unfortunately, in many cases, increasing doses of medications may lead to increased or unacceptable side effects. *Analgesic tolerance is not addiction.*

Although all of the questions are not yet answered, it is known that tolerance to the different side effects does not develop at the same rate. With opioids, for example, one rapidly becomes tolerant to the sedating effects of the drugs. It has been shown that cancer patients who take large but stable doses of morphine show little or no sedation. They do, however, continue to experience constipation if untreated, as patients will not develop tolerance to this side effect.

The real question, of course, is the extent to which tolerance develops to the *analgesic* effects of the drugs; that is, how soon do they lose their ability to reduce pain? This is unclear, and the answer seems different in different people and with different types of pain. Some people seem to benefit from the same dose of an opioid for years, while others rapidly increase the dose and still have unsatisfactory relief. Older patients may not become tolerant as quickly to the analgesic effects of opioids as younger patients.

Pseudo-tolerance is the need to increase medications such as opioids for pain when other factors are present such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interactions, addiction, and/or deviant behavior.

Functional Impairment and physical inactivity are additional concerns that make health care professionals reluctant to provide chronic opioids. It is well known that a sedentary life decreases blood flow, impedes healing, decreases muscle tone, and contributes to depression, bone loss, and fatigue. Clearly, some people become inactive and passive on opioids, while others become more active. It may be that some are able to obtain good analgesia without taking enough to produce intoxication, while others are not able to do so.

Drug Misuse refers to the intentional or unintentional incorrect use of opioids in a manner other than that prescribed.

Opioid Abuse is the intentional incorrect use of opioids in a manner other than that prescribed. Another definition of abuse is any use of an illicit drug with the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness, e.g.,

getting high. A licit (legal) substance such as alcohol can be abused. It is a federal crime to take a controlled substance that has not been prescribed for oneself.

Diversion is allowing others to have access to your prescribed opioids. Diversion can be as simple as sharing one's medications with family members or friends on an occasional basis or can represent a conscious decision to distribute or sell them to others. Another definition of diversion is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale or distribution. It is a federal crime to divert opioids from the person for whom they have been prescribed.

THE EVIDENCE FOR OPIOID USE

The American Pain Society (http://www.ampainsoc.org) and the American Academy of Pain Medicine (http://www.painmed.org) issued the following document: Evidence Review: APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain which can be found at http://www.ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf.

This document notes that "Several published guidelines and consensus statements recommend judicious use of opioids in appropriately selected patients with chronic noncancer pain who have not responded to other treatments and analgesic medications. Nonetheless, there remains uncertainty about the optimal use of opioids for chronic noncancer pain. Some patients do not experience significant improvements in pain or function even on high doses of opioids. In addition, opioids are associated with a variety of potentially serious adverse events, as well as aberrant drug-related behaviors (see glossary), including abuse (see glossary), addiction, and diversion."

The actual American Pain Society and the American Academy of Pain Medicine Opioid Treatment Guidelines: Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain can be found at

http://download.journals.elsevierhealth.com/pdfs/journals/1526-5900/PIIS1526590008008316.pdf

The abstract of the article is as follows:

Abstract: Use of chronic opioid therapy for chronic noncancer pain has increased substantially. The American Pain Society and the American Academy of Pain Medicine commissioned a systematic review of the evidence on chronic opioid therapy for chronic noncancer pain and convened a multidisciplinary expert panel to review the evidence and formulate recommendations. Although evidence is limited, the expert panel concluded that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain. However, opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. The recommendations presented in this document provide guidance on patient selection and risk

stratification; informed consent and opioid management plans; initiation and titration of chronic opioid therapy; use of methadone; monitoring of patients on chronic opioid therapy; dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy; prevention and management of opioid-related adverse effects; driving and work safety; identifying a medical home and when to obtain consultation; management of breakthrough pain; chronic opioid therapy in pregnancy; and opioid-related polices. Perspective: Safe and effective chronic opioid therapy for chronic noncancer pain requires clinical skills and knowledge in both the principles of opioid prescribing and on the assessment and management of risks associated with opioid abuse, addiction, and diversion. Although evidence is limited in many areas related to use of opioids for chronic noncancer pain, this guideline provides recommendations developed by a multidisciplinary expert panel after a systematic review of the evidence.

Taking opioids may or may not be in one's best interest. The literature does not provide simple, clear guidelines for those who must face day-to-day pain.

The exact relationship between higher opioid dosage and risk is not yet clear, but a troubling pattern of increased deaths associated with prescription opioid use has emerged during the same period that average doses significantly increased.

The fact that opioids reduce the natural drive to breathe is a serious concern. In addition, opioids become particularly dangerous when used in conjunction with other medications that can also depress respiration — sedative-hypnotics, benzodiazepines, antidepressants, and muscle relaxants — or with alcohol.

The FDA has implemented a risk evaluation and mitigation strategy (REMS) for extended release and long-acting opioids as part of a federal initiative to address prescription drug abuse, misuse, and overdose. The REMS requires manufacturers to provide prescriber and patient education on the safe use of these drugs. Affected opioid drugs, which include brand name and generic products, are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Further information can be found at:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

or http://www.er-la-opioidrems.com/IwgUI/rems/home.action

KEY STEPS TO USE OPIOIDS SAFELY

1. **Keep your doctor informed.** Inform your health care professional about any past history of substance abuse. All patients treated with opioids for pain require careful monitoring by their health care professional for signs of abuse and addiction, and to determine when these analgesics are no longer needed.

2. **Follow directions carefully.** Opioids are associated with significant side effects, including drowsiness, constipation, and depressed breathing depending on the amount taken. Taking more than is prescribed could cause severe respiratory depression or death. Even if you are taking what the doctor prescribed, side effects should be reported. Do not crush, break, or dissolve pills. This can alter the rate at which the medication is absorbed and lead to overdose and death.

3. **Reduce the risk of drug interactions.** Do not mix opioids with alcohol, antihistamines, barbiturates, or benzodiazepines. All of these substances slow breathing, and their combined effects could lead to life-threatening respiratory depression.

4. Prevent theft and diversion. Do not store your opioids in the medicine cabinet or where others have access to the medications. The best strategy is to store your medications in a locked box.

5. Keep track of when refills are needed to prevent going without medications, leading to withdrawal. Discuss refill strategies with your prescriber ahead of time. Some pain clinics will not fill prescriptions without a visit to the clinic. Other clinics will not fill prescriptions on Friday afternoons or weekends/evenings.

OPIOIDS & THE GOALS OF PAIN MANAGEMENT

There has been disagreement as to whether the goal of pain management should be to reduce pain or to improve the way people function in their daily lives. The consensus of the members of the American Pain Society is that the primary goal in treating chronic pain patients with opioids is to **increase the level of function** rather than just to provide pain relief.

It may be that this argument is not meaningful. When people are truly comfortable, they usually resume activities that they had previously avoided. If a person with pain fails to do this, it suggests that symptom relief has not occurred, even though the person may believe that the medications "take the edge off." Clearly, maximizing quality of life entails both factors: minimizing suffering and maximizing function.

Pain management is essentially rehabilitation. The person experiencing pain and the family must ask to what end they want to be rehabilitated. What does rehabilitation mean to each of them? Webster defines rehabilitation as "*to restore to useful life through education and therapy."* If a person's goal is solely to reduce pain, then he or she may overlook the more important (and attainable) goal of rehabilitation. The essence of rehabilitation and maintaining wellness is for the person to take an <u>active</u> part in the recovery process.

It is important to mention that taking opioids precludes certain types of employment, even though one is tolerant and does not have side effects. People should be aware of the rules currently put forth by Federal and State authorities.

MONITORING YOUR MEDICATION USE

Healthcare professionals who prescribe opioids are required to monitor for pain and any unusual drug-related behaviors as part of caring for their patients. .

The most relevant areas for monitoring have been termed the Four A's:

1) Analgesia (pain relief – often measured by a 10-point rating scale).
2) Activities of daily living (physical, psychological, and social functioning).
3) Adverse or side effects.
4) Aberrant or abnormal drug-related behaviors.

Some of the following questions may help clarify how appropriately opioid pain medications are being used, and whether they are helping or harming the person's well-being:

- *Is the person's day centered around taking medication?* If so, consultation with the health care professional may clarify long-term risks and benefits of the medication and identify other treatment options.

- *Does the person take pain medication only on occasion, perhaps three or four times per week?* If this is the case, then the likelihood of addiction is low.

- *Have there been any other chemical (alcohol or drug) abuse problems in the person's life?* If so, then it is important to inform the health care professional, who will need to take that into consideration when prescribing. Often, patients with a previous history of substance abuse disorders are not ideal candidates for consideration for opioid treatment for pain management.

- *Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed?* If so, that suggests the pain medication is failing to promote rehabilitation. Daily activity is necessary for the body to produce its own pain relievers, to maintain strength and flexibility, and to keep life full and meaningful. Encourage the person with pain to request recommendations from a health care professional for a graduated exercise program.

- *Is the person in pain able to function (work, household chores, and play) with pain medication in a way that is clearly better than without?* Chances are that the pain medication

is contributing to wellness. Most people who are addicted to pain medications or other substances (excluding nicotine) do not function well. They are often undependable and forgetful.

The following may be signs that a person is being harmed more than helped by pain medication.

- Sleeping too much or having days and nights confused.
- Decrease in appetite.
- Inability to concentrate or short attention span.
- Mood swings (especially irritability).
- Lack of involvement with others.
- Difficulty functioning due to drug effects.
- Use of drugs to regress rather than to facilitate involvement in life.
- Lack of attention to appearance and hygiene .

While it is impossible to make generalized guidelines for when to provide opioids on a regular, ongoing basis, the person and his/her family can often help to determine whether these agents are useful. If family members see that the person with pain has lost control of his or her life, is less functional, and is more depressed when taking or increasing the dose of opioids than they were before, they should seek help.

Most research suggests that family members over-report the patient's pain, but they also may be the only ones who can accurately determine whether the person's life, mood, function, attitude, and comfort have changed for the better or worse. The person taking the medication may be so aware of the discomfort produced when they miss doses of pills that they incorrectly conclude that they need the medication. This severe pain may in fact only represent withdrawal due to physical dependence, as opposed to a persistent need for analgesic therapy.

What is the place of opioid pain medication? There is no question of the usefulness of opioids in acute pain and cancer pain. We do not yet know when they are most helpful in chronic use. Benefit is suggested when there is a significant increase in the person's level of functioning, reduction/elimination of pain complaints, a more positive and hopeful attitude, and the side effects can be managed safely. Patients should not have the expectation of prolonged opioid use without concomitant benefits.

OPIOID TREATMENT AGREEMENT

Patients have an important responsibility with respect to opioids to ensure that both they, as well as others, will be able to have access to opioids in the future. When opioids are prescribed, patients are usually requested to formally communicate their agreement with the written

therapeutic plan (Opioid Treatment Agreement – sometimes termed an Opioid Contract or Opioid Therapy Plan), and, in particular, their understanding that the goal of opioid therapy is not the elimination of pain but, rather, its reduction to the point where measurable and meaningful increases in function are apparent. This would also include agreeing that they will obtain opioids only from one pharmacy and one medical provider, abstain from using other sedatives without express permission from the health care professional prescribing the opioids, and not engage in activities that would be interpreted as representing misuse or diversion of their medication.

The majority of persons who abuse opioids obtain the drug from friends or family members, often without the knowledge of the person for whom the medication is prescribed. Opioids used in this way, or sold or purchased illicitly, are unacceptable and would constitute misuse and abuse that would void the opioid treatment agreement, resulting in loss of prescribed opioids. Further, it is important to take the opioid exactly as prescribed by the health care professional with respect to dose and to timing between doses.

The discussion of safe storage and disposal not only helps to prevent theft and subsequent abuse but also prevents accidental overdose by children and cognitively impaired family members. Patients should always be aware of how many refills and how many pills remain in their prescription.

Part of an opioid treatment agreement also includes random urine drug testing.

A sample Opioid Treatment Agreement is available at the following location http://www.lni.wa.gov/ClaimsIns/Files/OMD/agreement.pdf (Washington State Department of Labor and Industries Medical Treatment Guidelines).

A sample informed consent agreement form is available from the American Academy of Pain Medicine: **Long-term Controlled Substances Therapy for Chronic Pain SAMPLE AGREEMENT** at http://www.partnersagainstpain.com/printouts/A7012CT6.pdf.

URINE DRUG TESTING (UDT) / URINE DRUG SCREENING (UDS)

Urine drug testing (UDT) or urine drug screening (UDS) is often ordered by the physician prior to starting opioids and at random intervals during treatment. UDT is used to check that the medications prescribed are being taken and that non-prescribed and/or illicit drugs are not used. Typically, urine tests include screening for prescription opioids, benzodiazepines, cocaine, heroin, amphetamines, and marijuana.

Pain Management in the California Workers' Compensation System;

Lessons Learned from Other States

Alex Swedlow
California Workers' Compensation Institute

Exhibit 2

Pharmaceuticals in the California Workers' Comp System

Agenda

- The California Workers' Compensation System
- Lessons from Washington and Texas

Exhibit 3

Pharmaceuticals in the California Workers' Comp System

Agenda

- The California Workers' Compensation System
- Lessons from Washington and Texas

Exhibit 4

Pharmaceuticals in the California Workers' Comp System
Areas of CWCI Rx Research

1. Changing Role of Rx in Workers' Compensation
2. Repackaged Drugs
3. Sole Source (Brand) v. Multi-source (Generic)
4. Opioids & Schedule-II Rx
5. Compound Drugs
6. Drug Testing

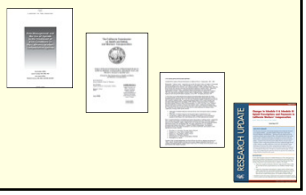


Exhibit 5

Pharmaceuticals in the California Workers' Comp System
Areas of CWCI Rx Research

Changing Role of Rx in CA Workers' Compensation

1. Growing use of pharmaceuticals
2. Reforms in pricing and fee schedules
3. Growing influence of pain management practices
4. Legislative, administrative and payer responses

Exhibit 6

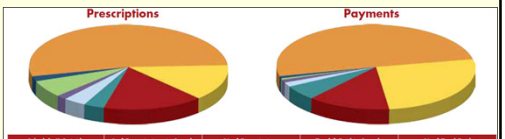
Pharmaceuticals in the California Workers' Comp System
Areas of CWCI Rx Research

Managing Pain Management
Rules and Regulations and Medical Management

- Pain Mgt Guidelines Implemented July 2009
  - Competing MTUS definitions and triggers
  - Hierarchy of medical evidence
  - Different levels of specificity
- Limits to Workers Comp Medical Management
  - Few supply- and demand-side controls
  - Liens
  - No 3rd party payer access to PDMP

Pharmaceuticals in the California Workers' Comp System

Opioid Prescription & Payments in CA Workers' Comp (2012)

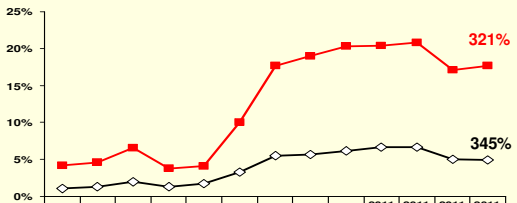


Schedule II Opioids	# of Prescriptions in Sample	% of Prescriptions	Total $ Paid in Sample	% of Total Paid
Oxycodone	175,985	53.0%	$49,978,919	50.7%
Fentanyl	45,434	13.7%	$26,136,655	26.5%
Morphine	54,458	16.4%	$12,982,949	13.2%
Oxymorphone	11,255	3.4%	$5,439,477	5.5%
Hydromorphone	12,271	3.7%	$1,534,618	1.6%
Tapentadol	5,514	1.7%	$1,224,551	1.2%
Methadone	20,803	6.3%	$543,605	0.6%
All Other	6,012	1.8%	724,806	0.7%
Total in Study Sample	331,732	100.0%	$98,565,580	100.0%

Pharmaceuticals in the California Workers' Comp System

Exhibit 8

Pharmaceutical Utilization & Cost Schedule-II Opioid Drugs[1]



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011 Q1	2011 Q2	2011 Q3	2011 Q4
Pcnt Scripts	1.1%	1.3%	2.0%	1.3%	1.7%	3.3%	5.5%	5.7%	6.2%	6.7%	6.7%	5.0%	4.9%
Pcnt Pymts	4.2%	4.6%	6.6%	3.8%	4.1%	10.0%	17.7%	19.0%	20.3%	20.4%	20.8%	17.1%	17.7%

[1] CWCI 2013. Calculations are on a calendar year basis

Pharmaceuticals in the California Workers' Comp System

Exhibit 9

Rx & Pain Management

Report to the Industry

What is the association between the use of opioids on low back pain on:

- Average Benefit Costs
  - Medical
  - Indemnity
- Loss of Productivity/Return To Work

CWCI 2008

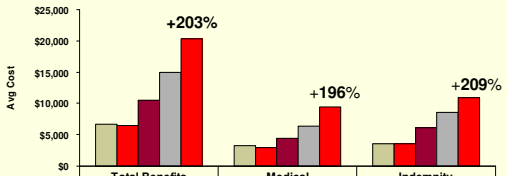
Morphine Equivalents Categories

Category	Average MEs in Category	Range of MEs in Category
No MEs	0	0
Level 1	124	3-240
Level 2	406	241-650
Level 3	1,207	651-2100
Level 4	14,870	2,101 and up

ME conversions based on American Pain Society Conversion Tables

CWCI 2008

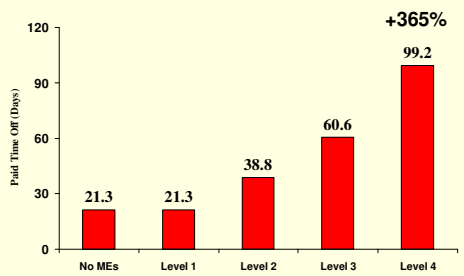
Adverse Outcomes: Increased Costs



	Total Benefits	Medical	Indemnity
No MEs	$6,733	$3,207	$3,526
Level 1	$6,499	$2,938	$3,561
Level 2	$10,550	$4,411	$6,139
Level 3	$14,950	$6,356	$8,594
Level 4	$20,389	$9,488	$10,901

CWCI 2008

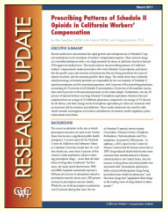
Adverse Outcomes: Reduced Productivity Paid Time Off Work



CWCI 2008

Pain Mgt and the Use of Opioids

Analysis of Prescribing Patterns Schedule II Opioids



CWCI March 2011

Analysis of:

1. Injury Characteristics
2. Physician Prescribing Patterns
3. Injured Worker Characteristics

PBM and ICIS Data:

- 16,890 Claims
- 9,174 Prescribing physician DEA code
- 233,276 Prescriptions
- Script, dosage and days
- Pharmaceutical characteristics
- DOS, billed and paid amount
- ER and EE characteristics

Analysis of Prescribing Patterns Schedule II Opioids

Top Injury Categories w/ Schedule II Opioids

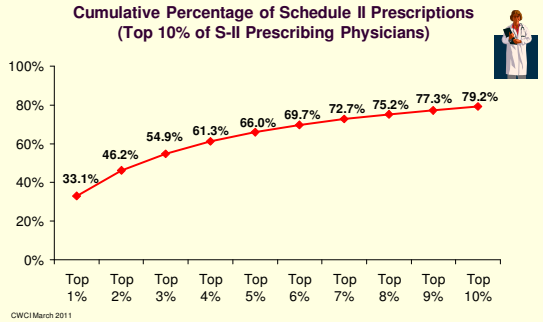
Diagnostic Category	Pcnt of S-II Opioid Claims	Pcnt of S-II Opioid Scrips	Pcnt of S-II Opioid Pymnts
Medical Back w/o Spinal Cord Involvmnt	**35.7%**	**47.1%**	**50.2%**
Spine Disorders w/ Spinal Cord or Root Involvmnt	11.3%	15.1%	16.1%
Cranial & Peripheral Nerve Dis	5.8%	6.8%	6.7%
Degen. Infect & Metabol Joint Dis	6.1%	6.1%	5.4%
Other Injuries, Poisonings & Toxic Effects	**5.5%**	**5.9%**	**6.8%**
Ruptured Tendon, Tendonitis, Myositis & Bursitis	6.9%	5.6%	5.2%
Sprain of Shoulder, Arm, Knee or Lower Leg	**6.8%**	**3.2%**	**2.8%**
Fracture, Dis of Shoulder, Arm, Knee or Lower Leg	6.3%	2.7%	1.6%
Other Mental Disturb	**1.2%**	**1.7%**	**1.5%**
Other Diagnoses of Musculoskeletal Sys	**1.5%**	**1.4%**	**1.1%**

Outside EBM Guidelines:

- 51% of Claims
- 60% of Prescriptions
- 62% of Payments

CWCI March 2011

Analysis of Prescribing Patterns Schedule II Opioids



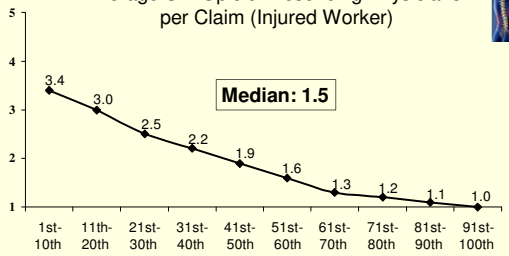
CWCI March 2011

Pharmaceuticals in the California Workers' Comp System

Exhibit 16

Analysis of Prescribing Patterns Schedule II Opioids

Average S-II Opioid Prescribing Physicians per Claim (Injured Worker)



CWCI March 2011

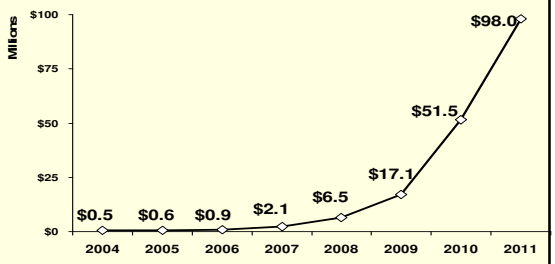
Pain Management

Drug Testing

- High levels of testing associated with increasing opioid and S-II utilization
- Rationale for drug testing:
  - Protocols?
  - Type of test?
  - Timing and frequency?
  - Medical necessity?
- Consequences:
  - Injured worker
  - Physician
  - Employer
  - Claims administrator

Exhibit 18

Drug Testing: Calendar Year Payments ($M)



CWCI 2013

Controlled Substance Utilization Review and Evaluation System (CURES)

CURES Background

- 1939 Bureau of Narcotic Enforcement (BNE) creates PMP mandated through the Health and Safety (H&S) Code
- September 2009, CURES program was enhanced with a web-based Prescription Drug Monitoring Program (PDMP) processing 913,874 patient activity reports.
- CURES receives over 5 million records each month from more than 6,700 licensed pharmacies.
- CURES is working with departmental IT to allow for the exchange of PDMP data between state PMPs.
- Now dormant and absent a funding source, the CURES program shuts down on July 1, 2013.

Controlled Substance Utilization Review and Evaluation System (CURES)

Building a Business Case: Estimating CURES ROI:

- Estimate number of claims by opioid use
- Determine potential savings via CURES access
- Adjust for CURES operating budget

Claims w/ Opioid Scripts	CA Claim Count (2011)	Pcnt of Claims
1 Scripts	47,434	41.1%
2-3 Scripts	28,508	24.7%
3-7 Scripts	15,745	13.6%
>7 Scripts	23,760	20.6%
Total:	115,447	100%

Controlled Substance Utilization Review and Evaluation System

CURES: ROI for California Workers' Compensation

Claims w/ Opioid Scripts	Avg Cost/ Claim (2010)	Total Payments	Est % Savings	Total Estimated Savings
1 Scripts	$8,260	$391,790,539	0%	-
2-3 Scripts	$11,102	$316,508,020	3%	$9,495,241
3-7 Scripts	$16,349	$257,412,625	5%	$12,870,631
>7 Scripts	$20,945	$497,653,698	7%	$34,835,759
Total:	$12,676	$1,463,364,882		$57,201,631

CURES Operating Budget: $3,700,000
ROI for CA WC: $15.5 : $1

Actual savings will depend upon several factors including:
- Access to CURES data
- Medical & Rx trends, Injury mix;
- Appropriate statutes, rules and regs.

Managing Pain Management in the California Workers' Comp System

Summary

- High rate of inappropriate opioid use;
- Limits in statutes/rules/regs make it difficult to regulate within traditional workers' comp controls
- Graduated use associated with adverse injured worker outcomes
- Small number of physicians associated with high prescribing patterns
- Rapid increase in drug testing associated to high opioid use with no national guidelines for testing
- CURES has significant potential to increase QOC and lower cost

Exhibit 23

Pharmaceuticals in the California Workers' Comp System

Agenda

- The California Workers' Compensation System
- Lessons from Washington and Texas

Texas Regulations

- Using clinical guidelines to address new and legacy claims
  - New claims with DOI after Sept 2011
  - Sept 2013 for all claims
- Closed formulary (ODG) is basis; no other formularies allowed
- Requirements placed on treating physician and payer (usually delegated to third party)
- Extensive regulations, reporting and administrative requirements

Exhibit 25

Texas: Formulary Process

- Formulary is diagnosis-specific
- Distinguishes between “Y” and “N” drugs
- “N” status require Prior Auth; blocked at retail pharmacy

Exhibit 26

Texas: Formulary Process

Results

- 5% of scripts were for N drugs after implementation; only 1 script approved
  - 11% were for N drugs before implementation
- 60% decrease in claimants receiving N drugs
- 57% decrease in opioids
- Biggest decreases in musculoskeletal therapy agents
  - 85% decrease in Soma
  - 99% decrease in Amrix

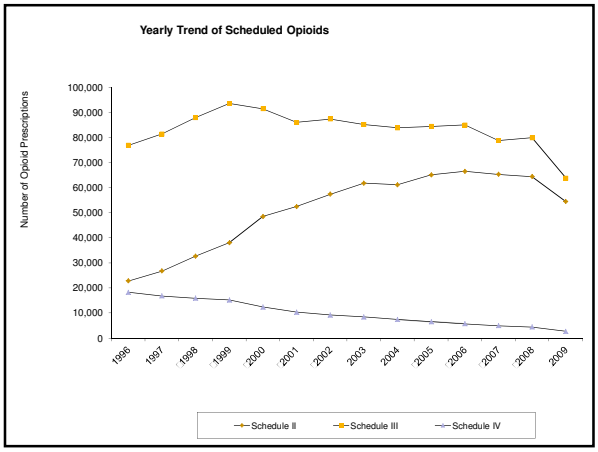
Washington State Opioid Treatment Regulations

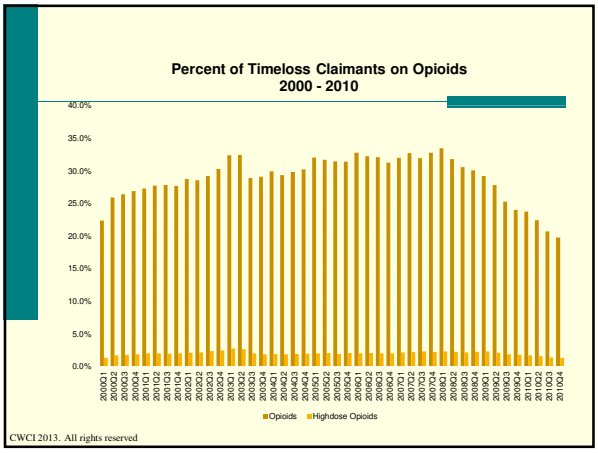
- Collaborative effort across all state health/medical programs
- Regulatory and legislative components
- Multi-year effort with strong education/outreach
- Emphasizes tracking patients for improved pain AND function
- Emphasizes widely agreed-upon best practices
  - Screening for substance abuse and other comorbidities
  - Prudent use of urine drug screens
  - Opioid treatment agreement
  - Single pharmacy and single prescriber
- Encourages use of Prescription Monitoring Program and Emergency Department Information Exchange, when available

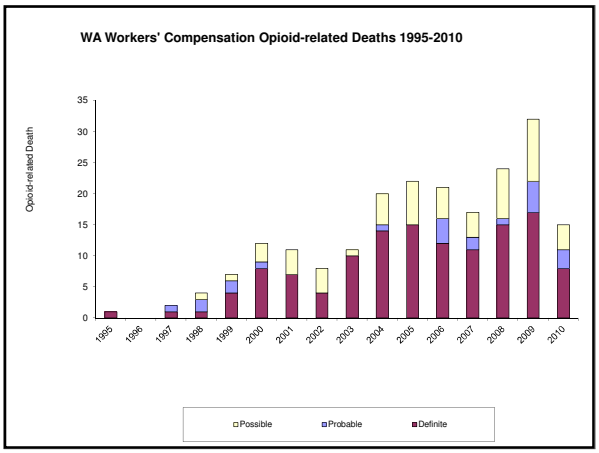
Guidance for Primary Care Providers on Safe and Effective Use of Opioids for Chronic Non-cancer Pain

- Establish an opioid treatment agreement
- Screen for
  - Prior or current substance abuse
  - Depression
- Use random urine drug screening judiciously
  - Shows patient is taking prescribed drugs
  - Identifies non-prescribed drugs
- Do not use concomitant sedative-hypnotics
- Track pain and function to recognize tolerance
- Seek help if dose reaches 120 mg MED, and pain and function have not substantially improved

http://www.agencymeddirectors.wa.gov/opioiddosing.asp
MED, Morphine equivalent dosec







Options from Other States

- Collaborate with insurers, state health agencies, medical societies, and policy makers to set dosing standards for chronic, non-cancer pain
- Review AMDG Opioid Dosing Guidelines (http://www.agencymeddirectors.wa.gov/opioiddosing.asp)
- Encourage/incent use of best practices (web-based MED calculator, use of state PMPs)
- Restrict /limit pay for office dispensed opioids
- ID high prescribers and offer assistance
- Incent community-based Rx alternatives (activity coaching and graded exercise early, opioid taper/multidisciplinary Rx later)