



AMERICAN COLLEGE OF
OCCUPATIONAL AND
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Depressive Disorders

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Summary of Recommendations

The following summary table contains recommendations for evaluating and managing Depressive Disorders from the Evidence-based Workplace Mental Health Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in [ACOEM's Methodology](#).¹ Recommendations are made under the following categories:

- Strongly Recommended, “A” Level
- Moderately Recommended, “B” Level
- Recommended, “C” Level
- Insufficient – Recommended (Consensus-based), “I” Level
- Insufficient – No Recommendation (Consensus-based), “I” Level
- Insufficient – Not Recommended (Consensus-based), “I” Level
- Not Recommended, “C” Level
- Moderately Not Recommended, “B” Level
- Strongly Not Recommended, “A” Level

Depressive Disorders Screening Tools	Strongly Recommended, Evidence (A)
Psychometric Testing	Moderately Recommended, Evidence (B)
Pharmacogenomics Testing	Recommended, Evidence (C)
Education	Recommended, Evidence (C)
Exercise	Recommended, Evidence (C)
Yoga	Recommended, Insufficient Evidence (I)
Tai Chi	Recommended, Insufficient Evidence (I)
Qi Gong	No Recommendation, Insufficient Evidence (I)
Weight Loss	Moderately Recommended, Evidence (B)
Dieting	No Recommendation, Insufficient Evidence (I)
Cognitive Behavioral Therapy	Moderately Recommended, Evidence (B)
Computer-Assisted Cognitive Therapy	Moderately Recommended, Evidence (B)
Acceptance and Commitment Therapy or Interpersonal Therapy	Moderately Recommended, Evidence (B)
Combined Use of CBT and an Antidepressant	Moderately Recommended, Evidence (B)
Bibliotherapy/Cognitive Bibliotherapy	Recommended, Insufficient Evidence (I)
Short-Term Psychosocial Psychotherapy	Moderately Recommended, Evidence (B)
Problem-Solving Therapy	No Recommendation, Insufficient Evidence (I)
Peer Support	No Recommendation, Insufficient Evidence (I)

¹ Guidance was developed with sufficient detail to facilitate assessment of compliance (Institute of Medicine [IOM]) and auditing/monitoring (Appraisal of Guidelines for Research and Evaluation [AGREE]) (1, 2). Alternative options to manage conditions are provided when comparative trials are available. (3-11) All AGREE (12), IOM (13), AMSTAR (14) and GRADE (2) criteria were adhered to (see [ACOEM's Methodology](#)). In accordance with the IOM's Trustworthy Guidelines, this guideline underwent external peer review and detailed records of the peer review processes are kept, including responses to external peer reviewers (2).

Psychosocial Adjunctive Methods	No Recommendation, Insufficient Evidence (I)
Suicide Prevention	Recommended, Insufficient Evidence (I)
Mind-Body Interventions	No Recommendation, Insufficient Evidence (I)
Mindfulness Therapy	Recommended, Insufficient Evidence (I)
Disease Management Programs	No Recommendation, Insufficient Evidence (I)
Emotional Freedom Therapy	No Recommendation, Insufficient Evidence (I)
Anti-Depressants	Moderately Recommended, Evidence (B)
Antipsychotics	Recommended, Evidence (C)
Symbyax (Olanzapine/Fluoxetine Combination)	Recommended, Evidence (C)
Nitrous Oxide	No Recommendation, Insufficient Evidence (I)
Ketamine	No Recommendation, Insufficient Evidence (I)
Esketamine	No Recommendation, Insufficient Evidence (I)
Anti-inflammatory Agents	Not Recommended, Insufficient Evidence (I)
Tumor Necrosis Factor Inhibitors	No Recommendation, Insufficient Evidence (I)
Cumin	No Recommendation, Insufficient Evidence (I)
St. John's Wort (Hypericum Perforatum)	No Recommendation, Insufficient Evidence (I)
Omega-3 Fatty Acids	No Recommendation, Insufficient Evidence (I)
Vitamin D	Not Recommended, Evidence (C)
B Vitamins	No Recommendation, Insufficient Evidence (I)
Cyanocobalamin (Vitamin B-12) Injections	No Recommendation, Insufficient Evidence (I)
Marijuana, Cannabis, Cannabinoids, and Cannabidiol	Not Recommended, Insufficient Evidence (I)
Transcranial Magnetic Stimulation and Repetitive Transcranial Magnetic Stimulation (rTMS)	Recommended, Evidence (C)
Deep Brain Stimulation	No Recommendation, Insufficient Evidence (I)
Vagal Nerve Stimulation	No Recommendation, Insufficient Evidence (I)
Electroconvulsive Therapy	Moderately Recommended, Evidence (B)
Low-Field Magnetic Stimulation	Moderately Recommended, Evidence (B)
Botulinum Toxin Injections	No Recommendation, Insufficient Evidence (I)
Acupuncture	No Recommendation, Insufficient Evidence (I)
Massage	No Recommendation, Insufficient Evidence (I)
Aromatherapy	No Recommendation, Insufficient Evidence (I)
Light Therapy	Recommended, Evidence (C)
Music Therapy	No Recommendation, Insufficient Evidence (I)
Acupuncture for Insomnia Treatment Related to Depressive Disorders	No Recommendation, Insufficient Evidence (I)
Cognitive Behavioral Therapy for Insomnia Treatment Related to Depressive Disorders	Moderately Recommended, Evidence (B)
Medications (other than benzodiazepines) for Insomnia Treatment Related to Depressive Disorders	Recommended, Evidence (C)

Related Terms

The language used in reporting studies related to the generic topic of “depression” can be vague, inconsistent, and confusing. The term *depression* is often used interchangeably with what would more precisely be termed *depressive disorder(s)*, *depressive symptoms*, or *depressed mood*. *Depression* is also used as a substitute for *major depressive disorder* or one of the other unipolar mood disorders with specific diagnostic criteria. Complicating matters further, there are terminology and criteria differences between the DSM, ICD-10, and ICD-11 nomenclatures. Frequently, studies are unclear about the definitions used, and the study selection criteria. In review articles, studies that define “depression” as a PHQ-9 score above a cutoff are sometimes combined with studies that use more specific criteria, such as a formal diagnostic interview and formal criteria.

- Depression
- Major Depressive Disorder
- Clinical Depression
- Depressive episode
- Dysthymia
- Psychotic Depression
- Seasonal Affective Disorder
- Situational Depression
- Adjustment Disorder
- Adjustment Disorder with Depression
- Depressed Mood
- Persistent Depressive Disorder
- Recurrent Depressive Disorder
- Depressive Episode

Introduction

Major depressive disorder (MDD) is the most common form of mental illness in developed countries. MDD affects approximately 11 million Americans per year [15]. The cumulative prevalence of major depressive disorder has been estimated at 16.6%, with a lifetime cumulative risk of 23.2% [17]. The median age of onset is reportedly 32 years for major depressive disorder [17]. The lifetime cumulative prevalence of persistent depressive disorder (formerly dysthymic disorder; dysthymia) has been estimated at 3.4% [17]. In 2010, the estimated prevalence of major depression among US workers was 7.6% [18]. The prevalence of depression varies somewhat between industries, with a 16.2% prevalence estimated among public transportation workers, 14.6% among social workers, and 13.3% among administration workers [19].

Depression has been associated with a 25% increased risk of occupational injury [20] and other injuries [21], and may be due to such factors as inattention and sleep deprivation. Work injuries have been associated with a subsequent risk of depression [22]. Depression and depressive

symptoms have also been shown to be risk factors for low back pain [23-29], neck pain [30-37], ischemic heart disease [38, 39], stroke [40], hip fracture [41], Alzheimer disease [42, 43], Parkinson disease [44], excessive daytime sleepiness [45], and carpal tunnel syndrome [46]. (See the [Introduction to the Workplace Mental Health guideline](#).) Depression has also been weakly associated with chemical dependency [47-49]. Depression and low occupational grade are synergistic risks for cardiac events among French workers [50]. High depressive symptoms reportedly increase the risk of pre-diabetic patients becoming diabetic [51]. Depression and depressive symptoms reportedly increase risk of mortality [39, 52-54], including among those with cardiac disease [55], stroke [56], and chronic obstructive pulmonary disease [57].

Numerous prospective cohort studies have found that depression and depressive symptoms develop among those with varying chronic diseases, including rheumatoid arthritis [58], multiple sclerosis [59], lung cancer [60], uterine cancer [61], sleep apnea [62], myocardial infarction [63], and insomnia [64]. Evidence also suggests low physical activity is associated with later risk of poor mental health, including depression [65, 66]. Perceptions of adverse workplace psychosocial factors [67] and social relationships [68] have been consistently found to predict an increased risk of depression.

Few occupational prospective cohort studies have analyzed the subsequent risk of depressive disorders and MDD. There are no studies with objective measures of exposure (e.g., numbers of coworkers, shift length). Other methodological challenges are common. One study reported 2.19-fold risk of MDD with repeated job strain, but did not assess MDD at baseline; the authors also reported a 1.61-fold risk of MDD with low work social support [69]. There are many retrospective studies with reported associated factors, including job strain or stress [16, 70-73]. Yet, some studies also show no increased risk from either job control or job strain [74]. There are numerous factors that have been associated with depressive disorders, MDD, and/or depressive symptoms, including: age [75], female sex [16, 75-77], short and/or long durations of sleep [64, 75, 77], alcohol [70, 75], passive and current smoking [78, 79], rheumatoid arthritis [58], hypertension [80], chronic disease [79], backaches, headaches, eye strain, respiratory difficulties, cardiovascular disease [81], poor health [82], number of offspring [83], low birth weight [84], professional work [75], unemployment or part-time work status [75, 81], technical-related careers [75], over 8 hours of work per day compared to working less than 8 hours [75], working 68 hours per week compared to the traditional 40 hours per week [85], sexual harassment [81], white collar jobs [81], blue collar jobs [82], perfectionism [86], low self-efficacy [86, 87], low job status [88], physically uncomfortable or dangerous occupations [88], low social support at work [81], dissatisfaction at work [71], and overtime [89]. Several of the above purported associated factors conflict.

The relationship between MDD, depressive symptoms and medical conditions is extraordinarily complex, as there are numerous studies showing depressive symptoms and depression causes diseases, injuries and disorders. Still, there are many other studies showing reverse relationships, sometimes for the same disorder.

Job strain has been reported to be a risk for subsequent depression in a meta-analysis with a combined risk estimate of 27% increased risk [90]. However, after excluding those with depressive symptoms at baseline, there was no statistically significant increased risk of depression among these 84,090 individuals. There was a lack of association between job strain and depression among those with low socioeconomic status, but elevated in those with moderate or high status.

Prospective cohort data conflict regarding whether effort-reward imbalance is a risk for depression as evidence includes an inability to predict antidepressant treatment [91], while other studies report this as a risk for depression [92-94]. Involuntary exit from work is a reported risk for depression [95]. Low satisfaction with work climate was a statistically negative risk for depressive disorders among Danish public service employees [96]. Economic and job instability was a risk for depressive symptoms in some studies [94, 97]. However, there was no increased risk of depression from business mergers and acquisitions [70] and depressive symptoms were reportedly related to mental disorders rather than work conditions in another study [98].

Multiple personality factors are reported risk for depressive symptoms in a meta-analysis [99], including low extraversion, high neuroticism, and low conscientiousness. Low self-efficacy is a risk for subsequent development of depression in Japanese workers [87]. The relationship between workplace social capital and subsequent risk of depression is U-shaped among a cohort of Japanese workers [100]. A study of Danish workers found elevated subsequent risks of depression from low procedural or relational justice [93].

Depression is associated with a 25% increased risk of occupational injury [20, 21]. Work injury has been associated with subsequent risk of depression [22]. Depression has been associated with disability [101-103] but not in another large cohort study [104].

Working over 60 hours per week was a risk for depressive disorder in a group of Japanese workers [89], working 11+ hours a day was a risk in another British cohort [105], and females working more than 55 hours a week was a risk in another [106].

The Nature of Depression

Although depression is among the most common of all mental health disorders, the nature of depression remains controversial and difficult to define. Depression is thought to occur in a number of subtypes, which includes major depressive disorder, persistent depressive disorder, adjustment disorder with depression, bipolar depression, seasonal affective disorder, premenstrual dysphoric disorder, bereavement, grieving, etc. Further complicating our understanding of depression is that studies related to the topic of “depression” may not define the manner in which this term is being used. The term *depression* is often used interchangeably with what would more precisely be termed *depressive disorder(s)*, *depressive symptoms*, or *depressed mood*. *Depression* is also used as a substitute for *major depressive disorder* or one of the other unipolar mood disorders with specific diagnostic criteria. Complicating matters further, there are terminology and criteria differences between the DSM-IV [107], DSM 5

[108], ICD-10, and ICD-11 nomenclatures. In review articles, studies that define “depression” as a PHQ-9 score above a cutoff are sometimes combined with studies that use more specific criteria, such as a formal diagnostic interview and formal criteria.

While the clinical presentations of these depressive subtypes are similar, their etiologies may differ. Similarly, the treatments for depression are highly divergent, and yet a number of these diverse treatments have been shown to be effective. Consequently, numerous subtypes of depression have been defined [108-110], and the etiology of depression has been attributed to a number of underlying mechanisms [111-119].

The Monoamine Hypothesis: Depression as Disease

Psychiatric/pharmaceutical treatment of depression, including major depressive disorder, is conceptually founded on the monoamine hypothesis (sometimes referred to as the “chemical imbalance” theory). The monoamine hypothesis states that depression is a disease state that is theorized to be caused by a deficiency of monoamine neurotransmitters (i.e., serotonin, norepinephrine and dopamine) in the synaptic clefts. The concentration of monoamine neurotransmitters in the synapse is theorized to regulate the transmission of signals [120-123]. A deficiency of these neurotransmitters is theorized to disrupt CNS functioning and cause depression.

The monoamine hypothesis has been quite productive with regard to the development of medications for depression, as most pharmaceutical treatments for depression are based on this hypothesis [124-128]. In order to correct these imbalances in neurotransmitter concentrations, most of these pharmaceuticals are theorized to block the reabsorption of neurotransmitters in the synapse, thus causing an increase in the synaptic concentration(s), which stimulates neurotransmission.

The major classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs and SNRIs block the synaptic reuptake of serotonin, norepinephrine, and other neurotransmitters [129-136]. TCAs and MAOIs are older antidepressants, but they are effective and continue to be prescribed. TCAs also block the reuptake of serotonin, as well as epinephrine [129, 131, 137, 138]. MAOIs block the metabolic activities of the monoamine oxidase enzyme that metabolizes serotonin, resulting in higher levels of serotonin, as well as epinephrine and dopamine [131, 139-141]. MAOIs have somewhat limited use due to adverse effects and the requirements for dietary restrictions to prevent high blood pressure and hypertensive crises.

Although the monoamine hypothesis has been successful in the development of effective treatments for depression, it also has considerable demonstrable inconsistencies. That is, while antidepressant medications rapidly increase the levels of neurotransmitters in the synaptic cleft, the therapeutic benefits of these medications typically take 2-4 weeks to appear. As this delay contradicts a central prediction of the theory, the mechanism of action of these medications remains unknown [142]. More recent versions of the monoamine theory have

hypothesized that depression is not due to synaptic concentrations of monoamines, but rather due to dysfunction of glial cells, which produce monoamines [143, 144]. Beyond monoamine theories, several alternative disease mechanisms have been hypothesized for major depression. These include theories that depression may also be caused by a brain injury or disease that results in atrophy of specific brain structures (e.g., dementia) or by toxicological syndromes [145]. There also is a growing body of research suggesting a genetic linkage to depression [146, 147], as well as nascent evidence associating inflammation with depression [148]. Several classes of anti-inflammatory medications have been trialed for the treatment of depression [149]. These medications include non-steroidal anti-inflammatory medications, omega-3 polyunsaturated fatty acids, N-acetylcysteine, pioglitazone, and tumor necrosis factor alpha inhibitors, such as infliximab [149, 150]. Overall, depression as a disease state may involve dysregulation of neurotransmitters, the sympathetic nervous system, inflammatory processes, genetic factors, and environmental stress [151].

Cognitive Theory: Depression and Dysfunctional Thinking

A second influential theory of depression is cognitive theory. Cognitive theory holds that emotional and behavioral problems are due to incorrect or maladaptive ways of thinking and distorted perceptions of oneself, others, and environmental circumstances [152]. In marked contrast to the monoamine hypothesis, which describes the origins of depression in biological terms, cognitive theory holds that depression has its origins in thought. Despite its differences from the monoamine hypothesis, cognitive theory has also been quite successful in generating effective treatments for depression.

Cognitive theory hypothesizes that behavior is guided by cognition, and that many cognitive processes, once learned, become habitual or “automatic.” In some cases, these cognitions are accurate and enable the individual to accurately perceive and effectively cope with the environment. In other cases, however, an individual’s cognitive processes may involve biased information processing, produce distorted perceptions, and lead to dysfunctional behavior and depression [112]. Studies have associated depression with helpless and pessimistic cognitions [153-155]. For example, one study found that patients who are prone to helpless thinking were far more likely to become depressed following a surgical intervention [156].

As cognitions often occur as in a rapid and automatic manner, the individual may not be explicitly aware of cognitions or the distorted perceptions created by these thoughts. Cognitive behavioral therapy (CBT) is the process of examining these cognitions and replacing those that are distorted or dysfunctional (e.g., catastrophizing [157-161] or kinesiophobia [162-164]) with cognitions that are accurate and more functional [111, 165]. Cognitive behavioral therapy could thus be said to involve something akin to the scientific method. In essence, the patient is taught to identify automatic cognitions, test the accuracy with which these hypothesized beliefs portray reality, and determine the degree to which they enable effective coping. The objective of cognitive therapy is to identify any faulty cognitions and replace them with more adaptive ones. A weakness of CBT is that, because it typically involves a process of journaling about thoughts and feelings, it is in essence “thinking about how you think.” Many such protocols require at least an average level of literacy. Recently, however, low-literacy versions of CBT have been developed [166].

Theories of CBT have attempted to reconcile it with biological models. The diathesis-stress model has been applied to depression, and it has been hypothesized that adverse childhood experiences may create a vulnerability to depression in adulthood. Later in life, if a vulnerable individual copes with environmental stressors using dysfunctional beliefs and maladaptive coping strategies, depression may result [167, 168]. Consistent with this hypothesis, studies have suggested that the effectiveness of cognitive therapy for depression could be associated with reduced activation of the amygdala and hippocampal regions of the brain [167], and that CBT treatment for depression may promote positive changes in brain functioning in the anterior cingulate cortex, the posterior cingulate, and the prefrontal cortex [169].

An emerging cognitive theory of depression is based on the effect of a specific cognitive deficit called “theory of mind” [170]. Theory of mind refers to a uniquely human ability to reason from someone else’s perspective (e.g., when John says, “I know what Mary is thinking,” he is theorizing about her mental processes). Theory of mind research originated in the study of persons with autism and schizophrenia, who appear to lack the capacity to reason from another person’s perspective. More recently, a meta-analysis examined theory of mind ability in nonautistic subjects who were either suffering from depression or were healthy controls. This study concluded that theory of mind impairment was significantly related to severity of depressive symptoms [171]. It is believed that this deficit profoundly degrades a person’s ability to function in the social environment. Some studies have found that cognitive therapies addressing theory of mind impairment may be effective for treating depression [172], and some studies have found that theory of mind impairment appeared reduced by transcranial magnetic stimulation [173-175].

Evolutionary Models of Depression

A weakness of research on psychological/psychiatric science is that there are no definitive biological tests for mental health disorders [176]. Instead, these conditions are defined by behavioral taxonomies in the DSM/ICD; from one version to the next, definitions of these disorders may be created, changed, or disappear altogether. It has been stated that in order for psychology/psychiatry to achieve the status of a “hard science,” it must establish a foundation in which the definitions of conditions originate in biology, genomics, and brain circuits, and which are then reconciled with behavior and self-reports [177]. A hard science approach may require embracing the standard theory of biology, which is evolutionary theory.

From the evolutionary perspective, all traits or characteristics of a species exist because they have promoted survival [178-185]. In general, emotion can be defined as “a complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event” [152]. Emotions are believed to be superordinate mechanisms that regulate mental and bodily functions in a manner that helps the individual adapt to environmental stressors [180, 186]. For example, the emotions of anxiety and fear play an important role in the threat assessment system [187]; along with anger, they comprise the fight-or-flight response long known to play a crucial role in self-preservation [188]. Similarly, trauma may precipitate PTSD, a condition that is also believed to

have survival value [189]. In contrast to fear, anxiety, and anger, the value of depression is less certain from an evolutionary perspective.

Depression (also known as major depressive disorder, clinical depression, dysthymia, etc.) is traditionally thought of as a pathological state. From the evolutionary psychology perspective, depression may facilitate an individual's ability to relinquish an unreachable goal or promote feelings of helplessness to inhibit aggression against more powerful people [113]. One study observed that high mood predicted subsequent increased fertility rates, whereas low mood (suggestive of bad circumstances) predicted subsequent suppressed fertility [190]. Depression also has a noteworthy relationship to the immune system [115]. As vegetative symptoms of depression resemble symptoms of inflammation and illness [191], it has been theorized that inflammation plays a role in depression [192-198], while depression may improve an individual's ability to fend off pathogens [150, 199, 200].

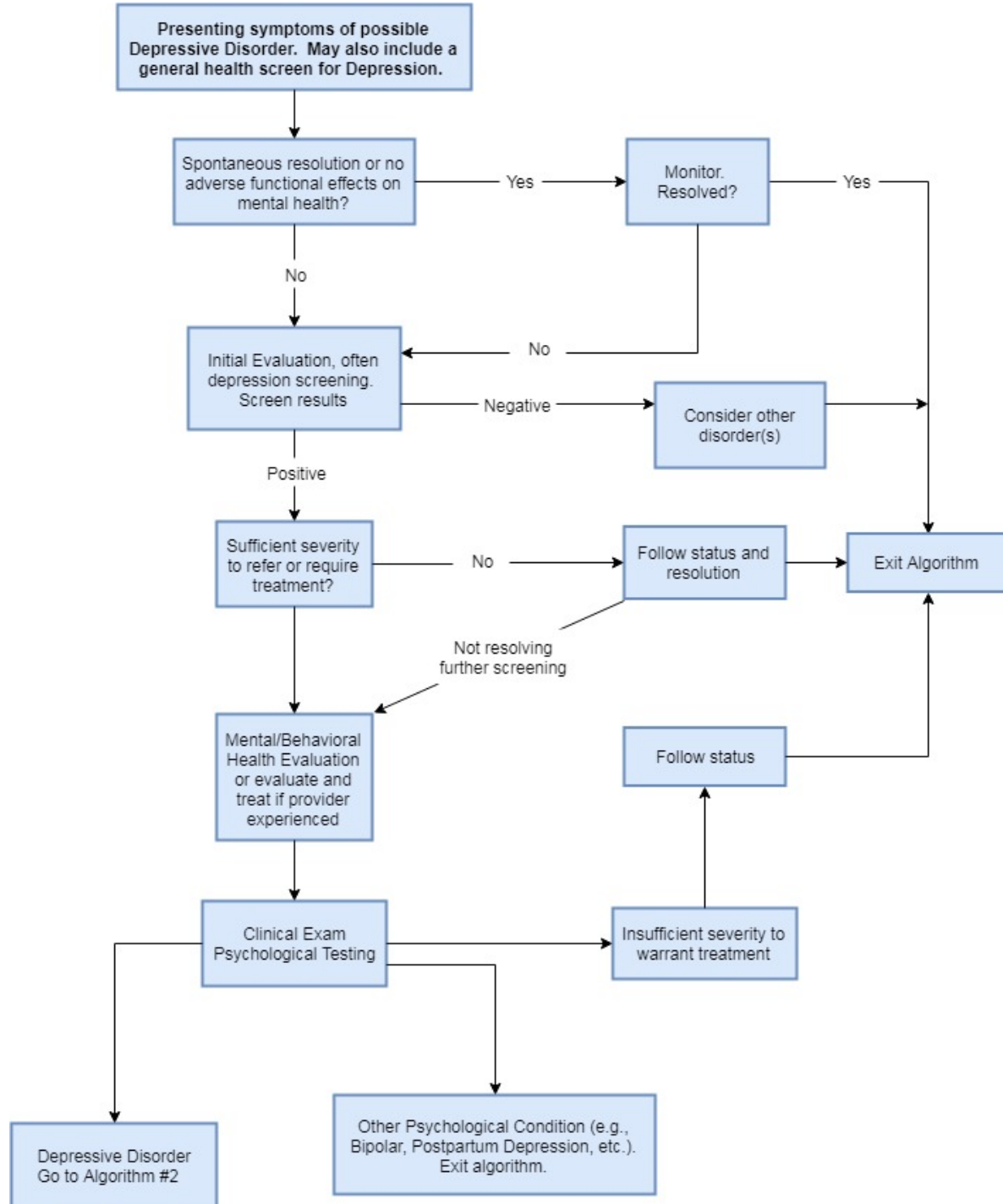
Evolutionary psychology has been called the "second wave" of cognitive theory [201, 202]. Although traditional cognitive theory focused on perception, categorization, reasoning, learning, and memory, evolutionary psychology views cognitive and emotional processes as being engineered by natural selection to adaptively regulate physiology and behavior [179, 180, 182, 200, 201]. One evolutionary theory hypothesizes that depression has similarities with pain related to noxious physical stimuli [178, 181, 183, 184]. Thus, just as noxious physical stimuli motivate the user to withdraw from actions that involve bodily felt pain, the noxious emotional experience of depression may motivate an individual to withdraw from circumstances that are emotionally harmful. Consider a person whose job involves performing heavy labor, but who sustains a serious back injury. While returning to work at the person's former job is the desired goal, it now may represent an objective threat to health, and the mental pain of depression may help motivate the individual to give up this desired but now harmful goal. This theory is consistent with the fact that physical pain and emotional pain share many of the same neural circuits in the brain. Although both may serve a self-protective function, excessive forms of both types of pain may give rise to dysfunction [200, 203-205].

For example, the emotion of depression tends to be associated with a loss of the ability to experience the pleasure associated with formerly enjoyable activities, a preoccupation with the loss, a perception of being powerless to change one's circumstances, a reduction of motivation, and disengagement from an activity, relationship, or goal. This process may be adaptive to the extent that it facilitates the individual's ability to "let go" of a goal that cannot be achieved or an activity or relationship that cannot be sustained. In some cases, the negative thoughts in depression are accurate appraisals of difficult life circumstances [206]. Preoccupation with these life challenges may promote the individual's ability to develop more realistic goals [206, 207]. Similarly, the emotion of fear tends to be associated with hypervigilance about environmental threat, enhanced memory of past threats, as well as motivation to engage in self-protective behavior such as categorizing objects in the environment as "friend or foe", initiating communications of danger to others and seeking their help, fearful mood, heightened level of arousal and energy, and exaggerated startle. To the extent that environmental threats are present, anxiety is adaptive [208, 209]. Thus, from the evolutionary standpoint, emotions

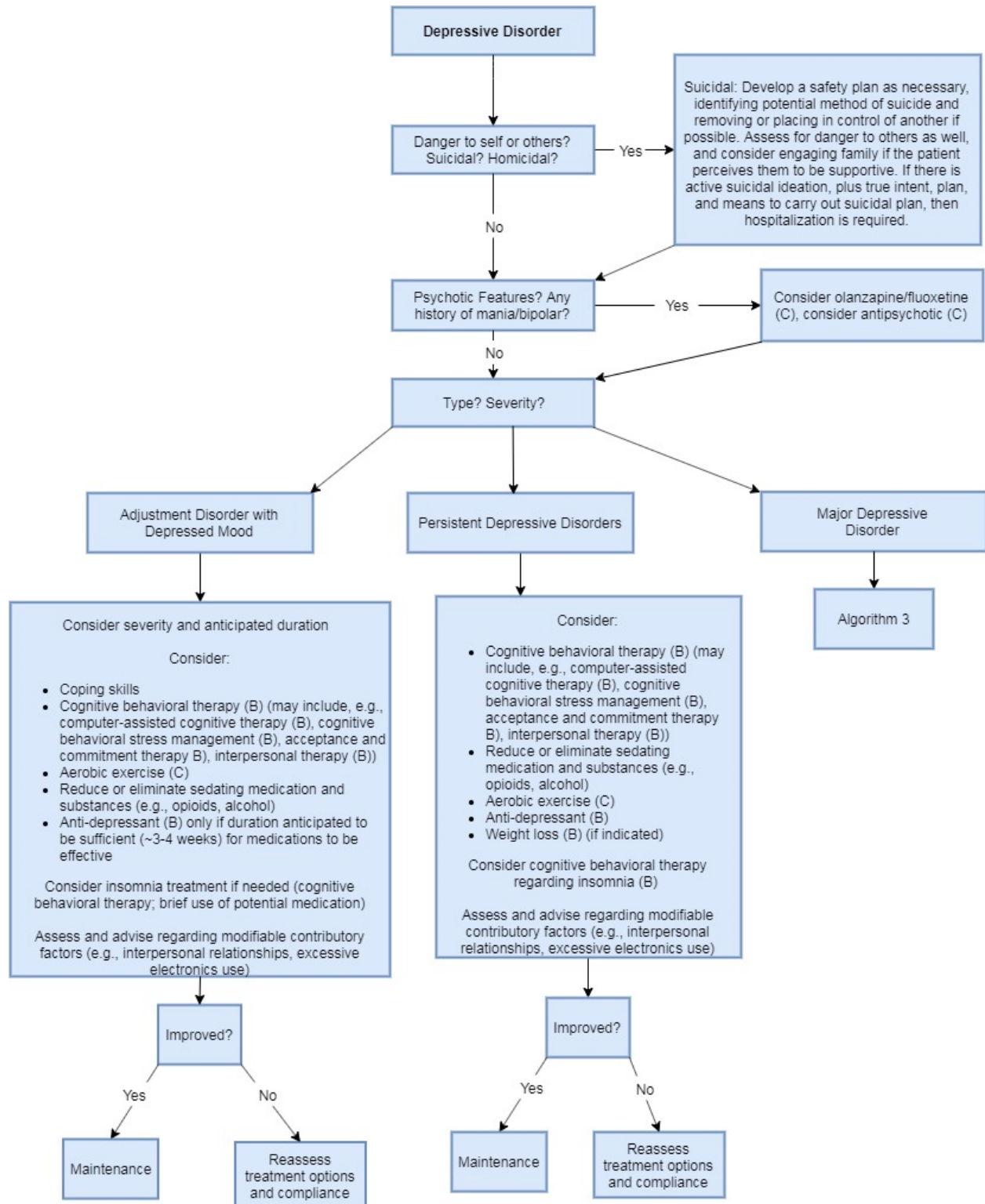
like depression are part of life; as such, the goal may not be to always relieve the emotion by treatment. Thus far, however, evolutionary theory has not produced a body of human research of a quality comparable to the monoamine or cognitive models of treatment.

Algorithms

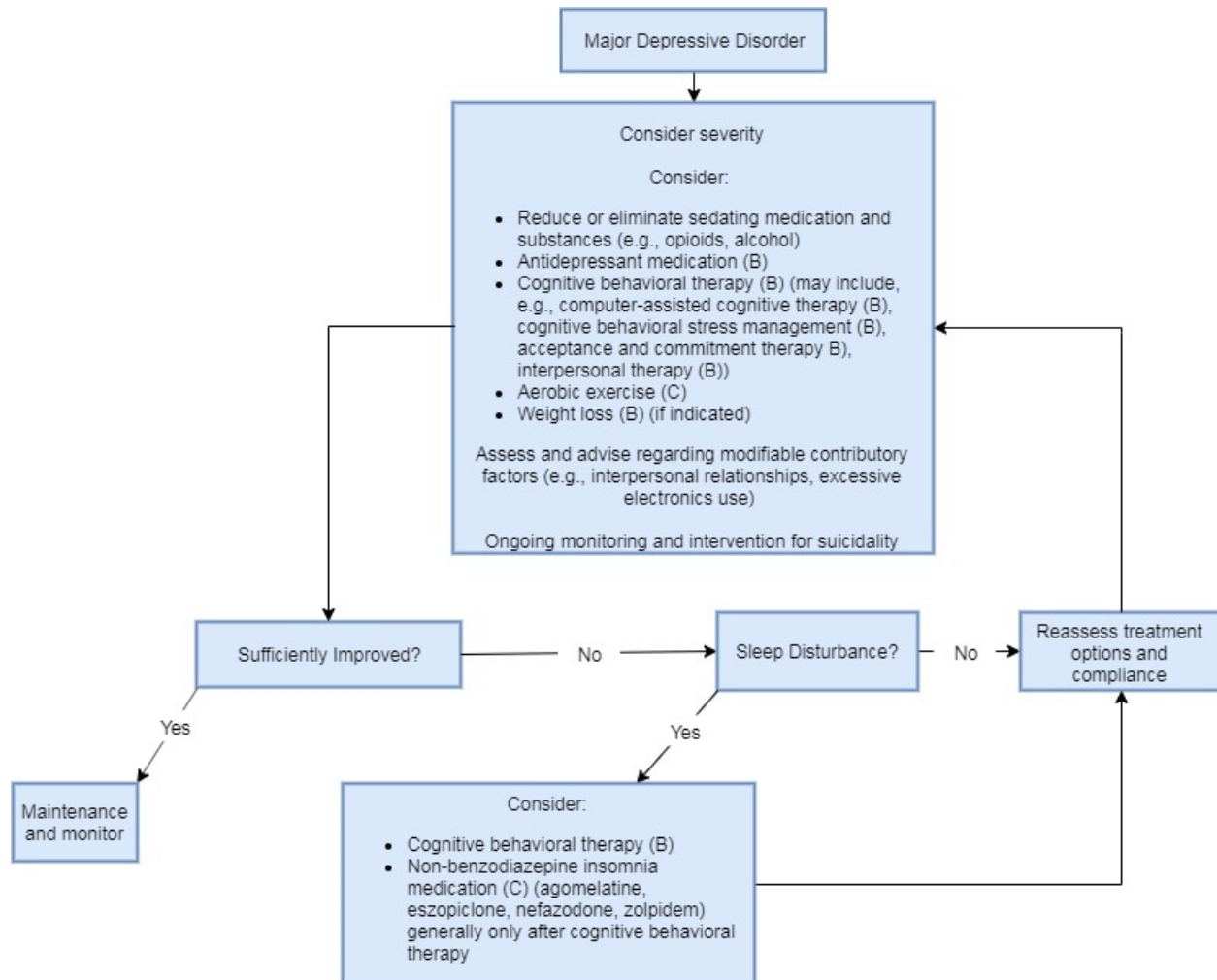
Algorithm 1. Presenting symptoms of possible depressive disorder



Algorithm 2. Management of depressive disorder by type



Algorithm 3. Management of major depressive disorder



Symptoms and Signs

There are many symptoms of depressive disorders, including the following:

- Persistent sadness, “blue”
- Depressed mood
- Hopelessness
- Pessimism
- Worthlessness
- Listlessness
- Irritability
- Difficulty remembering
- Recurrent crying
- Sleep disturbance(s), including falling asleep, awakening and being unable to regain sleep, early awakening and/or oversleeping

- Lack of energy
- Fatigue
- Weight gain or weight loss
- Lack of concentration
- Anhedonia (lack of pleasure in normally pleasurable activities)
- Withdrawal from interactions with family and/or friends

Depression may manifest or accompany systemic symptoms, including the following:

- Headaches
- Muscle aches
- Back pain
- Shoulder pain
- Cramps
- Digestive problems, which may include Irritable bowel syndrome

When depression is generally more severe, it may involve additional symptoms, including the following:

- Suicidal thoughts
- Delusions
- Hallucinations

Depressive Disorders is a symptom category of low mood disorders in the DSM-5. Within this category is Major Depressive Disorder (MDD): “The common feature of these disorders in the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function” [212]. It has some overlap with the DSM5 diagnosis of persistent depressive disorder which is characterized by chronic sadness, isolation, or despair.

Depression is not a psychiatric diagnosis but rather a symptom; it may become a disorder when symptoms become chronic and interfere with daily living and functions. Included in this group of psychiatric conditions are:

- Major Depressive Disorder,
- Persistent Depressive Disorder (Dysthymic Disorder), and
- Adjustment disorder with depression
- Bipolar disorder

Major Depressive Disorder:

Major depressive disorder (MDD) is a psychiatric condition classified as a depressive disorder in the DSM-5, and as a type of mood disorder in the ICD10/DSM-IV. “The diagnostic code for major depressive disorder is based on whether this is a single or recurrent episode, current severity, presence of psychotic features, and remission status” [212]. “The essential feature of a major depressive episode is a period of at least 2 weeks during which there is either depressed

mood or the loss of interest or pleasure in nearly all activities..." [212]. This is the most researched type of depression.

Additional criteria may include:

- changes in appetite,
- changes in sleep patterns,
- guilt, or
- suicidal ideation, among others.

Major depressive disorder involves multiple symptoms of depression that persist and significantly interfere with normal social and/or occupational functioning. Examples of symptoms include depressed mood, reduced interests or pleasure, weight changes, sleep disruption, fatigue, and reduced ability to think. Suicidal thoughts or attempts may occur. However, suicidal ideation tends to only occur with severe MDD and not with mild or moderate MDD.

*"Major depressive disorder represents the classic condition in this group of disorders. It is characterized by discrete episodes of at least 2 weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions and inter-episode remissions. A diagnosis based on a single episode is possible, although the disorder is generally recurrent. Careful consideration is given to the delineation of normal sadness and grief from a major depressive episode."*²

Major depressive disorder is a condition that often recurs. However, newer empirical research suggests that the sooner that MDD is treated, the less likely it is that relapses may occur. Because future episodes of depression may be precipitated over the years by discrete major events such as death in a family or divorce, treating the current episode of depression may have a prophylactic effect against future episodes.

The DSM5 definition of MDD differs from previous DSMs and ICDs in that it may be diagnosed when precipitated by a major loss, such as loss of a loved one, loss of health due to a serious medical condition, losses from a natural disaster, or financial ruin. In prior diagnostic formulations, a reaction to profound loss such as bereavement was not diagnosed as major depression. This was because the DSMs regard major depression as a disease state; thus, it was thought to be wrong to label an understandable reaction to loss as being a "disease".

² *Bereavement may induce great suffering, but it does not typically induce an episode of major depressive disorder. When they do occur together, the depressive symptoms and functional impairment tend to be more severe and the prognosis is worse compared with bereavement that is not accompanied by major depressive disorder. Bereavement-related depression tends to occur in persons with other vulnerabilities to depressive disorders, and recovery may be facilitated by antidepressant treatment"* [212].

MDD can appear cyclically. If these depressive episodes are seasonal, they may be called seasonal affective disorder. MDD should be distinguished from the following conditions:

Bipolar Disorder, Depressive Episode: A major depressive episode that occurs within the context of mood swings that cycle between depressed, normal, hypomanic, and manic states. Note that this is provided for definitional purposes, is treated differently, and is not in the scope of this guideline.

Adjustment Disorder with Depression: A depressive reaction to environmental stress or one that is out of proportion to the intensity of the stressor and resulted in a significant impairment of functioning. This can involve low mood, tearfulness, or hopelessness.

Persistent Depressive Disorder (Dysthymia): This condition is characterized by chronically depressed mood for at least two years. This is associated with weight change, appetite disturbance, sleep disturbance, low energy, low self-esteem, poor concentration, and feelings of hopelessness.

Disruptive Mood Dysregulation Disorder: A condition associated with severe and recurring outbursts of temper manifested either verbally or behaviorally that is grossly out of proportion to any provocation. These occur three or more times a week accompanied by persistently irritable mood. Note that this is provided for definitional purposes, is not considered a depressive disorder, is treated differently, and is not in the scope of this guideline.

Substance/Medication-induced Depression: This is a depressive condition that appears in reaction to use of a medication or substance. Substances known to precipitate depression include alcohol, inhalants, opioids, sedatives, amphetamines, and cocaine. Note that this is provided for definitional purposes, is treated differently, and is not in the scope of this guideline.

Depressive Disorder Due to Another Medical Condition: A persistent depressed mood that appears to be attributable to the direct pathophysiological effect of another medical condition.

History and Psychological/Psychiatric Examination

See the [Introduction to the Workplace Mental Health guideline](#).

Medical History Questionnaire

See the [Introduction to the Workplace Mental Health guideline](#).

Diagnostic Criteria

There are specific categories of depressive disorders that are widely recognized. Definitions of some of the more common types of depressive disorders follow.

DSM-5 depressive disorders categories include the following: Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (single or recurrent episodes), Persistent Depressive Disorder (dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-induced Depressive Disorder, Depressive Disorder due to another medical condition, Other Specified Depressive Disorder, and Unspecified Depressive Disorder.

The standard ICD-10 (without localized modifications) depressive disorders categories include: Depressive Episode (including mild, moderate, severe without psychotic symptoms, severe with psychotic symptoms), Other Depressive Episodes, Unspecified Depressive Episode, Recurrent Depressive Disorder (including with current mild or moderate episode or with severe episode without and with psychotic symptoms), Recurrent Depressive Disorder currently in remission, other Recurrent Depressive Disorders, Unspecified Recurrent Depressive, Persistent Mood disorders, Cyclothymia, Dysthymia, Other Persistent Mood/Affective Disorders, Unspecified Persistent Mood/Affective disorders.

The 2019 American ICD-10-CM depressive disorders categories include: Major depressive disorder (including mild, moderate, severe without psychotic symptoms, severe with psychotic symptoms, single episode, recurrent, in remission), persistent mood disorder, cyclothymic disorder, dysthymic disorder, monopolar depression NOS, disruptive mood dysregulation disorder, affective psychosis, other recurrent depressive disorder.

A complete listing of the diagnostic categories and criteria in use in the DSM-5 is available [108]. The ICD-10 criteria are also available and more commonly utilized outside of the US [213]. Succinct descriptions of some of the common DSM-5 depressive disorders are then followed by ICD-10 descriptions.

Major Depressive Disorder

DSM-5 criteria:

“A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition" [108].

Major Depressive Disorder may have the further additional specifications with: anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset and seasonal pattern.

Persistent Depressive Disorder (aka Dysthymia)

DSM-5 Criteria:

“This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder.

A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 year.

B. Presence, while depressed, of two (or more) of the following:

1. Poor appetite or overeating.
2. Insomnia or hypersomnia.
3. Low energy or fatigue.
4. Low self-esteem.
5. Poor concentration or difficulty making decisions.
6. Feelings of hopelessness.

C. During the 2-year period (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 years.

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g. hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 years but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted” [108].

Persistent Depressive Disorder may have further additional specifications with: anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, and peripartum onset.

Substance/Medication-induced Depressive Disorder

DMS-5 Criteria:

“A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities.

B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a depressive disorder that is not substance/medication-induced. Such evidence of an independent depressive disorder could include the following: The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced depressive disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.” [108]

Trials of treatment therapies often use non-standard definitions of depression compared with current diagnostic criteria. Whether these have material impacts on the treatment of depression is unknown. Regardless, where reported, the tables of evidence in this guideline

capture those details. Whether there are differences in treatments based on the types of depressive disorder is generally unclear in the quality evidence-based literature.

Diagnostic criteria per ICD-10 include:

Depressive Episode

Criteria include symptoms of at least 2 weeks duration with at least two of (depressed mood, loss of interest and enjoyment, and/or increased fatigability) and other symptoms with the numbers of symptoms conveying severity (e.g., reduced concentration and attention; reduced self-esteem and self-confidence; ideas of guilt and unworthiness; bleak and pessimistic views of the future; ideas or acts of self-harm or suicide; disturbed sleep; and/or diminished appetite). This may be further categorized as mild, moderate, and severe, with and without psychotic symptoms.

Recurrent Depressive Disorder

Recurrent Depressive Disorder involves repeated episodes of depression, but without meeting criteria for mania and without mood elevation unless there is brief mood elevation immediately after the depressive episode. This may be further categorized as mild, moderate, and severe, with and without psychotic symptoms.

Persistent Mood Disorders

This includes cyclothymia, dysthymia, and other persistent mood disorders. Generally, cyclothymia is a chronic and persistent instability of mood, while dysthymia is a chronic depression of mood that does not meet criteria for recurrent depressive disorder.

Recurrent Brief Depressive Disorder

A brief episode of depression that meets severity but not duration criteria for Depressive Episode.

Classification

The classification of Depressive Disorders generally follows the categories previously defined.

Treatment Overview

When analyzing the treatment of depressive disorders, it is important to note that there is variation.

Prevention

Data for primary prevention of depression are sparse. Considering that evidence suggests maintaining normal weight (or losing weight) and aerobic exercise are effective treatments for depressive disorders, it may be reasonable to infer that those same interventions would have a role in primary and secondary prevention.

Psychological Management

Evidence consistently supports cognitive behavioral therapy (CBT) for the treatment of depressive disorders. There are several types of CBT with evidence of efficacy, including computer-assisted cognitive therapy, acceptance and commitment therapy, and interpersonal

therapy. There is evidence suggesting a combined approach of CBT with anti-depressants is effective. In addition, there is evidence that CBT is effective in reducing future relapses. Modifiable contributory factors (e.g., excessive electronics usage, dysfunctional or inadequate interpersonal relationships, coping skills) should also be addressed. This will be discussed further in a later section within this module.

Assessment and treatment of suicidality is of utmost importance in the treatment of individuals with depressive disorders. Assessment of suicide risk can be done during management of depression or independently. Those with high suicide risk may need different or additional treatments directed towards suicide prevention. Suicidality management can involve both the patient and the provider(s) working together towards creating patient-specific treatments [210, 211]. Other exposures that can influence suicidality include modifying environmental risks, such as the removal of firearms or weapons, or hospitalizing a patient, either voluntarily or involuntarily.

Pharmacological Management

The management of depression should include a review of sedating medications, which may be contributing, such as opioids and cannabinoids. Pharmaceutical treatment of depression with multiple classes of anti-depressants has consistent evidence of efficacy. Selection of a particular anti-depressant is often based on a desire to treat accompanying symptoms, such as insomnia, and/or to avoid particular adverse effects. Because there is evidence of differing efficacy based on pharmacogenetic issues, a family history and information regarding what relatives have found most useful in the treatment of depression may assist. Treatment of psychotic features with olanzapine/fluoxetine has evidence of efficacy. If treatment of insomnia beyond CBT and anti-depressants is needed, selection of a non-benzodiazepine medication is advisable (e.g., agomelatine, eszopiclone, nefazodone, zolpidem). Severe and/or treatment-resistant major depressive disorder is treated with electroconvulsive therapy, which continues to be considered the gold standard.

Screening and Testing Recommendations

There are numerous screening and psychometric tests. Screening tests generally include few items, emphasize high sensitivity, and require less education to administer. In the case of depression, routine screening in the course of annual examinations of the general public is widely performed due to the combination of prevalence and severity of outcomes.

Psychometric tests generally have secure item pools, specific administration protocols that must be followed, have greater specificity, and require professionally trained mental health professionals to administer. While these instruments may suggest a diagnosis, neither screening nor psychometric tests are capable of making a diagnosis. The diagnosis should only be concluded after careful analysis of all available data, including from a thorough history and/or clinical interview.

Depressive Disorders Screening Tools

There are many depressive disorders screening tools. These include:

- PRIME-MD Patient Health Questionnaire (PHQ) [145, 214-231],
- Beck Depression Inventory (BDI) [225, 226, 232-266],
- Brief Symptom Inventory (BSI) [267-269],
- Quick Inventory of Depressive Symptomatology-Self-Report (QIDS; QIDS-SR) [270-280],
- Brief Battery for Health Improvement – 2nd Edition (BBHI 2) [281-284],
- Center for Epidemiological Studies Depression Scale (CESDS) [145, 235, 239, 240, 242, 285-332],
- Hamilton Depression Inventory (HDI) [224, 226, 237, 244, 271, 272, 275, 277, 279, 333-348],
- Zung Depression Scale [232, 243, 247, 335, 336, 349-357],
- Clinically Useful Depression Outcome Scale (CUDOS) [270, 358-360],
- Geriatric Depression Scale (GDS) [361-387],
- WHO-5 Wellbeing Index,
- Depression Anxiety Stress Scale (DASS) [388, 389] and
- PROMIS [390-398] and NIH Toolbox [399]

Depressive Disorders Screening Tools

Strongly Recommended.

The use of depressive disorders screening tools is strongly recommended.

Strength of Evidence – Strongly Recommended, Evidence (A)
Level of Confidence – High

<i>Indications:</i>	Patients at risk of depressive disorders. Evaluation should include focus on depressive disorders, anxiety disorder(s), bipolar, substance use disorder(s) and risk of suicide. There also is a general public health initiative to screen the entire population annually for depression regardless of symptoms or exposures.
<i>Benefits:</i>	Earlier identification of potential depressive disorders, assists with directing the patient to appropriate mental health services that include diagnostic confirmation. Suicide prevention.
<i>Harms:</i>	Negligible. Potential for false negative assurance of test results given, e.g., sensitivities range ~80-95% and specificities ~50-75%. False conclusions if a positive screen is inadvertently relied upon for diagnosis without additional testing/confirmation.
<i>Frequency/Dose/Duration:</i>	Generally only one administration for some occupational purposes, although annual screenings are performed for the general public and may also be appropriate among workers. Shorter version instruments (e.g., 2-question) are considered superior to longer instruments for purposes of screening primarily due to compliance and incrementally less gain with longer instruments [239, 337]; one trial with a 2-item tool reported sensitivity 96% and specificity 57% [239]. Data suggest electronic administrations also produce acceptable results [228, 275].
<i>Indications for Discontinuation:</i>	N/A
<i>Rationale:</i>	There are multiple high- and moderate-quality studies evaluating the efficacy and validity of screening tests for depressive disorders, most of which evaluated screening of MDD [273, 285, 347]. Two of the high-

quality studies assessed the tools against a structured clinical interview, one providing a comparison with the Hamilton Depression Rating Scale (HAMD) [347], while the other assessed the Quick Inventory of Depressive Symptomology (QIDS-SR) [273]; many other moderate-quality trials evaluated the clinical interview against other tools. There are no quality comparative trials identified that simultaneously assessed numerous screening tools to provide high-quality evidence of comparable utility. However, there are many sizable studies (e.g., [300]) and the largest study of highest-quality assessing the most tools compared B-PhQ, and WHO-5 [400]. One study reported consistencies among four tools of 0.83-0.88 [271]. Depressive Disorders screening tools are efficient, without adverse effects, are low cost and are strongly recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Brief symptom inventory, BSI; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 223 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 223 articles. We also found and reviewed 187 in Scopus, 260 in CINAHL, 141 in Cochrane Library, 13000 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: BBHI 2, Brief Battery for Health Improvement; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 2 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 1 article. We also found and reviewed 0 in Scopus, 252 in CINAHL, 1 in Cochrane Library, 8,240 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Beck depression inventory-2nd edition, BDI II; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory,

psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 2274 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 2407 articles. We also found and reviewed 969 in Scopus, 9 in CINAHL, 107 in Cochrane Library, 11000 in Google Scholar, and 8 from other sources†. We considered for inclusion 31 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 9 from Google Scholar, and 8 from other sources. Of the 48 articles considered for inclusion, 37 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Center of Epidemiological Studies Depression Scale, CES-D; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 2168 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 2392 articles. We also found and reviewed 3272 in Scopus, 4061 in CINAHL, 53 in Cochrane Library, 13600 in Google Scholar, and 6 from other sources†. We considered for inclusion 66 from PubMed, 13 from Scopus, 4 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 6 from other sources. Of the 90 articles considered for inclusion, 45 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Clinically Useful Depression Outcome Scale, CUDOS; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 23 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 29 articles. We also found and reviewed 133 in Scopus, 15 in CINAHL, 4 in Cochrane Library, 13300 in Google Scholar, and 1 from other sources†. We considered for inclusion 2 from PubMed, 0 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 6 articles considered for inclusion, 2 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Hamilton depression inventory, HAM-D, Hamilton depression rating scale; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological

inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1,292 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 1,303 articles. We also found and reviewed 221 in Scopus, 889 in CINAHL, 27 in Cochrane Library, 1,320 in Google Scholar, and 14 from other sources†. We considered for inclusion 11 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 14 from other sources. Of the 27 articles considered for inclusion, 24 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Patient Health Questionnaire, PHQ, PHQ-9; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 438 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 2988 articles. We also found and reviewed 699 in Scopus, 1787 in CINAHL, 38 in Cochrane Library, 1500 in Google Scholar, and 3 from other sources†. We considered for inclusion 18 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 3 from other sources. Of the 25 articles considered for inclusion, 12 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Psychological evaluation, psychological interview; depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1979 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 2066 articles. We also found and reviewed 20913 in Scopus, 16489 in CINAHL, 1456 in Cochrane Library, 88100 in Google Scholar, and 17 from other sources†. We considered for inclusion 24 from PubMed, 6 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 17 from other sources. Of the 48 articles considered for inclusion, 37 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Quick inventory of depressive symptomatology-self report, QIDS, QIDS-SR; depression, depressive

disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 34 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 53 articles. We also found and reviewed 38 in Scopus, 244 in CINAHL, 1209 in Cochrane Library, 46 in Google Scholar, and 2 from other sources†. We considered for inclusion 7 from PubMed, 1 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 12 articles considered for inclusion, 12 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Zung depression scale, depression, depressive disorder, major depressive disorder, MDD; psychological test, psychological inventory, psychological screening, psychology test, psychology inventory, psychology screening; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 907 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 1052 articles. We also found and reviewed 59 in Scopus, 77 in CINAHL, 5 in Cochrane Library, 3250 in Google Scholar, and 1 from other sources†. We considered for inclusion 17 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 1 from other sources. Of the 22 articles considered for inclusion, 9 diagnostic studies and 0 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Psychometric Testing: Depressive Disorders

There are several psychometric tests that are commonly used for evaluation of patients with potential Depressive Disorders. Examples include the Millon Clinical Multiaxial Inventory-IV (MCMI-IV), Personality Assessment Inventory (PAI), Battery for Health Improvement – 2nd Edition and the Minnesota Multiphase Personality Inventory-2 and MMPI-2-RF [232, 298, 340, 400-449]. Psychometric testing often follows a positive result from a screen. See the [Introduction to the Workplace Mental Health Guideline](#).

There are multiple studies evaluating the usage of psychometric testing and subscales for identifying elements of psychosis within mixed psychiatric patients including those with depressive disorders, anxiety disorders, PTSD, and/or substance abuse disorders [413, 417, 450-479]. Additional studies evaluated usage for community samples such as veterans, college students, etc. [439, 475, 480-487], fitness-for-duty evaluations [488], chronic pain patients [489, 490], injured workers and personal injury litigations [465, 491-499], within forensic evaluations or criminal settings [458, 500-507], and differentiating between true participants and simulators (malingering participants, either trained or untrained) [490, 496, 508-519].

Psychometric Testing: Depressive Disorders Moderately Recommended.

The use of psychometric testing is moderately recommended for depressive disorders.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **High**

<i>Indications:</i>	For individuals presenting with signs and symptoms consistent with a Depressive Disorder. May have tested positive with a prior depression screening test. Evaluation should especially include focus on various Depressive Disorders, anxiety disorder(s), bipolar, substance use disorder(s) and risk of suicide. Testing among chronic pain patients is also addressed in the Chronic Pain Guideline .
<i>Benefits:</i>	Provide psychometric evidence regarding potential for depressive disorders and especially for other mental health disorder(s).
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	One-time testing unless otherwise indicated (e.g., by subsequent recurrence of or significant changes in symptoms). Requires administration by a professionally trained mental health professional, usually a psychologist [520-522].
<i>Indications for Discontinuation:</i>	N/A
<i>Rationale:</i>	There are multiple moderate quality studies suggesting utility of psychometric testing for depressive disorders. The MMPI-2 has been suggested to be able to (1) distinguish depression [422], (2) differentiate between true depressives and simulators (malingering depressives) [426] and (3) differentiate MDD from dysthymia [423]. Data also suggest discriminatory ability of the Millon clinical Multiaxial Inventory II [415]. Psychometric testing has negligible adverse effects, is moderately costly and is recommended for assisting in the diagnosis of depressive disorders. Clinical correlation is required [417].

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Battery for Health Improvement, BHI 2; depression, depressive disorder, major depressive disorder, MDD; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency. We found and reviewed 24 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 28 articles. We also found and reviewed 256 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 6740 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: personality assessment inventory, PAI; depression, depressive disorder, major depressive disorder, MDD; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1102 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 1101 articles. We also found and reviewed 831 in Scopus, 170 in CINAHL, 197 in Cochrane Library, 19,500 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 5 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Minnesota Multiphasic Personality Inventory, MMPI; depression, depressive disorder, major depressive disorder, MDD; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 438 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 435 articles. We also found and reviewed 412 in Scopus, 846 in CINAHL, 36 in Cochrane Library, 4,520 in Google Scholar, and 7 from other sources†. We considered for inclusion 6 from PubMed, 0 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 18 articles considered for inclusion, 18 diagnostic studies and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Millon Clinical Multiaxial Inventory;

depression, depressive disorder, major depressive disorder, MDD; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 40 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 41 articles. We also found and reviewed 60 in Scopus, 124 in CINAHL, 2 in Cochrane Library, 713 in Google Scholar, and 2 from other sources†. We considered for inclusion 0 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 6 articles considered for inclusion, 5 diagnostic studies and 0 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Pharmacogenomics Testing

Pharmacogenomics testing has been used to guide psychiatric treatment based on the person's pharmacogenomics genotype to determine how they will respond to antidepressants and guide psychiatric treatment [523-525]. These tests are being used to attempt to aid in determining whether a person will have an adverse response to a medication, how well a medication will work particularly in treatment resistant patients and the likelihood of symptom relapse [526-530].

Pharmacogenomics Testing Recommended.

The use of pharmacogenomics testing is recommended for depressive disorders.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

<i>Indications:</i>	Select patients with moderate or severe MDD initiating treatment with anti-depressants who have had a prior treatment failure and/or patients needing to change treatments due to initial depression treatment failure [531].
<i>Benefits:</i>	Reduced adverse effects and potentially improved responses [530].
<i>Harms:</i>	Moderate cost, although declining.
<i>Frequency/Dose/Duration:</i>	One assessment, especially to assess CYP2D6 and CYP2C19.
<i>Rationale:</i>	There are multiple moderate quality studies [524, 527, 532, 533] and many low-quality studies [524-528, 532-538], which suggest benefits of pharmacogenomics testing for purposes of targeting anti-depressant treatment. However, there are methodological weaknesses [529, 530] and thus the magnitude of benefit is unclear. Pharmacogenomics testing is minimally invasive, has low adverse effects, but is high cost and thus is selectively indicated for those with moderate or severe depression and treatment failure. Another option is to query the family history and information regarding what relatives have found most useful in the treatment of depression.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Pharmacogenomic testing, pharmacokinetic testing; depression, depressive disorder, major depressive disorder, MDD; diagnosis, diagnostic, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, efficiency. We found and reviewed 21 articles in PubMed using the most recent sorting function. We conducted a secondary review in PubMed using the best match sorting function and found and reviewed 20 articles. We also found and reviewed 434 in Scopus, 8 in CINAHL, 36 in Cochrane Library, 16600 in Google Scholar, and 0 from other sources†. We considered for inclusion 6 from PubMed, 1 from Scopus, 2 from CINAHL, 3 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 17

articles considered for inclusion, 1 diagnostic study, 12 randomized trials and 2 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Treatment Recommendations

Education

Education training for depressive disorders typically involves teaching information and specific skills to assist in coping with depressive symptoms. Educational programs use various methods including online training, targeted training, to conduct motivational interviewing, teaching goal setting, and behavioral task assignments. It is often used in conjunction with treatments, such as CBT, antidepressants, or exercise [539-564].

Education Recommended.

Education is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Moderate

<i>Indications:</i>	Individuals with depression or depressive symptoms
<i>Benefits:</i>	Improved understanding and/or resolution and/or improvement of depressive symptoms
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Typically at least one formal teaching session, often in conjunction with the initiation of treatment, with subsequent education based on response to treatment, severity, patient’s knowledge, and retention.
<i>Indications for Discontinuation:</i>	Sufficient understanding of depression, resolution of symptoms, non-compliance.
<i>Rationale:</i>	There are many trials which have included an education component, however, most have co-interventions which preclude assessment of the efficacy of education. One trial of a psychoeducation program was ineffective compared with standard care. An education program has been used as the control group for CBT, and was inferior both times trialed the quality studies [542, 547]. However, one trial suggested prolonged remission [541] and another suggested higher recovery in patients with mild depression provided education [540]. One study suggests that education increased adherence to antidepressant medication for long-term success and prevention of relapse [552]. Education may be helpful for patient understanding; some evidence suggests the potential to improve recovery and prolong remission and thus education is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Education, Health Education, Education Program, Outcomes of Education, Patient Education; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 271 articles in PubMed, 8,208 in Scopus, 397 in CINAHL, 28 in Cochrane Library,

19,000 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 19 from PubMed, 1 from Scopus, 5 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 28 articles considered for inclusion, 26 randomized trials and 0 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Activity Modification and Exercise

Exercise has been used to treat depressive symptoms [565-638].

Exercise

Recommended.

Exercise is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

<i>Indications:</i>	Depressive symptoms sufficient to warrant treatment. Chronic pain patients with depressive symptoms (see the Chronic Pain guideline). Other first line treatments include CBT, anti-depressants.
<i>Benefits:</i>	Improvement in depressive symptoms, increased physical function and overall well-being. One trial reported reduced work lost time with aerobic exercise [631].
<i>Harms:</i>	Negligible, muscle soreness
<i>Frequency/Dose/Duration:</i>	At least three supervised exercise sessions per week for 16 weeks at 70%-85% heart rate maximum with a 10 min warm up, 30 minutes at proper intensity and 5 min cool down [575, 604]. While a self-directed aerobic exercise program may be attempted or even preferable, some evidence suggests lack of efficacy with that approach [604, 629]. Quality data suggest superiority of aerobic over strengthening exercise [571]. There are no quality data suggesting efficacy of flexibility or range of motion [615].
<i>Indications for Discontinuation:</i>	Resolution of depressive symptoms, non-compliance, or unanticipated adverse event.
<i>Rationale:</i>	There are many moderate quality studies with nearly all of the higher quality studies suggesting efficacy of aerobic exercise and some reporting efficacy of resistance training for treatment of depression including MDD [567-569, 571, 576-579, 627]. Lack of efficacy of aerobic exercise was shown in a trial that also had poor attendance with only 34-38% attendance rates [615], and in another with no supervised exercise [629]. Efficacy appears better in sustained exercise of higher frequency and intensity and shows improvement in mood, cognition and relapse rates [571-573, 575]. One trial suggested utility of exercise as an adjunct to medication [570]. One trial suggested superiority of exercise to medication [575], while another suggested equivalency to sertraline [574]. There is one moderate quality study suggesting lack of efficacy but it also reported low compliance yet superiority of aerobic exercise for reducing lost work time [631]. Exercise has been associated with improved symptoms of depression over education [567]. Exercise has low adverse effects, is of low to moderate cost depending upon whether self-directed, group sessions or via a personal trainer, nearly consistently shows efficacy and thus is recommended for treatment of depressive disorders.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Exercise; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial,

controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 625 articles in PubMed, 6924 in Scopus, 1869 in CINAHL, 329 in Cochrane Library, 17300 in Google Scholar, and 11 from other sources[†]. We considered for inclusion 58 from PubMed, 12 from Scopus, 16 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 11 from other sources. Of the 99 articles considered for inclusion, 51 randomized trials and 27 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Yoga Recommended.

Yoga is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

<i>Indications:</i>	Depressive symptoms sufficient to require therapy. Generally should have tried and adhered to aerobic exercise program first, as evidence of efficacy is stronger for aerobic and then for strengthening exercise.
<i>Benefits:</i>	Improvements in depression symptoms. Increased flexibility, posture, and overall well-being.
<i>Harms:</i>	Negligible, muscle soreness
<i>Frequency/Dose/Duration:</i>	Four one hour sessions of yoga for at least 6 weeks [640]
<i>Indications for Discontinuation:</i>	Lack of depressive symptom improvement or sufficient improvement to not warrant further sessions; non-compliance; intolerance.
<i>Rationale:</i>	There are some moderate quality studies, however the body of evidence has significant weaknesses and lack of clear evidence of efficacy. One trial suggested no differences between a high- and low-intensity yoga regimen [639]. Two studies suggest yoga improves depression scores and perceived stress [640, 642]. Some other studies show a lack of efficacy or equivalence to other treatment such as mindfulness [637, 641]. Yoga has negligible adverse effects, is low to moderate cost (depending on whether self-directed or supervised), is of questionable efficacy, and therefore there is a limited recommendation for use among those who trialed and adhered to aerobic exercise and/or had insufficient benefits and/or have particular motivation to comply with yoga.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Yoga; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 101 articles in PubMed, 78 in Scopus, 96 in CINAHL, 4 in Cochrane Library, 1,600 in Google Scholar, and 4 from other sources [†] . We considered for inclusion 15 from PubMed, 0 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 4 from other sources. Of the 25 articles considered for inclusion, 13 randomized trials and 3 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Tai Chi Recommended.

Tai Chi is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

<i>Indications:</i>	Depressive symptoms sufficient to require therapy. Generally should have tried and adhered to aerobic exercise program first, as evidence of efficacy is stronger for aerobic and then for strengthening exercise.
<i>Benefits:</i>	Improvements in depression symptoms. Increased flexibility, posture, and overall well-being.
<i>Harms:</i>	Negligible, muscle soreness
<i>Frequency/Dose/Duration:</i>	Two hours per week for 10 weeks [651].
<i>Indications for Discontinuation:</i>	Lack of depression symptom improvement or sufficient improvement to not warrant further sessions; non-compliance; intolerance.
<i>Rationale:</i>	There are few moderate quality studies and no clear evidence of an independent effect of Tai Chi for treatment of depression. Most studies were conducted in an older population, had wait-listed control biases, usual care biases, and In many of these studies there is either a small sample size, differences in contact time or Tai Chi was used in conjunction with another intervention such as a medication [564, 651-653]. Tai Chi has negligible adverse effects, is low to moderate cost (depending on whether self-directed or supervised), is of questionable efficacy, and therefore there is a limited recommendation for use among those who trialed and adhered to aerobic exercise and/or had insufficient benefits and/or have particular motivation to comply with Tai Chi.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: tai chi, tai ji, tai chi chih, tai chi chuan; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 43 articles in PubMed, 691 in Scopus, 38 in CINAHL, 2 in Cochrane Library, 946 in Google Scholar, and 1 from other sources [†] . We considered for inclusion 5 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 11 articles considered for inclusion, 5 randomized trials and 4 systematic reviews met the inclusion criteria. [†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Qi Gong No Recommendation.

There is no recommendation for or against the use of Qi Gong in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are no quality studies of Qi Gong for treatment of depressive symptoms. Qi Gong has few adverse effects, is of low to moderate cost and has no quality evidence of efficacy, thus, there is no recommendation for use of Qi Gong in the treatment of depression.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Qi Gong, Qigong; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 3 articles in PubMed, 174 in Scopus, 16 in CINAHL, 0 in Cochrane Library, 393 in Google Scholar, and 5 from other sources[†]. We considered for inclusion 2 from PubMed, 2 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 12 articles considered for inclusion, 2 randomized trials and 2 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

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Weight Loss Recommended.

Weight loss is moderately recommended for the treatment of patients with depressive disorders who are overweight/obese.

Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – Moderate

<i>Indications:</i>	Depressive symptoms sufficient to warrant treatment while also either overweight or obese. Other first line treatments include CBT, and SSRIs.
<i>Benefits:</i>	Improvement in depressive symptoms and overall wellbeing as well as improved physical function
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	10 weekly individual sessions focused on behavioral depression treatment including behavioral weight loss sessions and counseling [663]. Best outcomes are if combined with exercise [630]. Program may be internet-based [668].
<i>Indications for Discontinuation:</i>	Lack of depression symptom improvement or sufficient improvement to not warrant further sessions; non-compliance; intolerance.
<i>Rationale:</i>	A bi-directional relationship between obesity and depression has been observed; depression predicts development of obesity and obesity increases risk of depression [661]. There are multiple moderate quality studies showing efficacy for weight loss and improved depressive symptoms that correlate with weight loss [630, 663-665]. In [630], efficacy was achieved with a combination of exercise and weight loss. In one study, there was efficacy with an internet delivered approach to weight loss [668]. Weight loss that is not invasive has few adverse effects, is of low to moderate cost depending upon individual program and has quality evidence of efficacy, thus weight loss is recommended for the treatment of depression generally as an adjunctive treatment.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Weight Loss Programs, Weight Reduction Programs, Weight reduction, weight loss; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 16 articles in PubMed, 2379 in Scopus, 344 in CINAHL, 14 in Cochrane Library, 14 in Google Scholar, and 2 from other sources [†] . We considered for inclusion 6 from PubMed, 7 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 21 articles considered for inclusion, 10 randomized trials and 7 systematic reviews met the inclusion criteria.

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

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Dieting No Recommendation.

There is no recommendation for or against the use of dieting in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)
Level of Confidence – Low

Rationale:

There are no quality studies regarding dieting to treat depression. Dieting has few adverse effects, is typically low cost unless a commercial program is implemented, has no quality evidence of efficacy and thus there is no recommendation. Please see [Weight Loss](#) for discussion of that recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Diet, dieting, dietary program, nutrition, nutrition therapy, nutritional programs, food; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 828 articles in PubMed, 45,768 in Scopus, 164 in CINAHL, 489 in Cochrane Library, 8690 in Google Scholar, and 63 from other sources[†]. We considered for inclusion 6 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 8 articles considered for inclusion, 4 randomized trials and 4 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

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Behavioral and Psychological Interventions

Cognitive behavioral therapy (CBT) has been used extensively to treat depression [542, 544, 559, 561, 576, 679-745]. It includes a variety of component therapies, including cognitive therapy, relaxation therapy, and various types of exposure therapy. However, exposure to CBT for depressive disorders that impact the workplace allows for a gradual return to work. In other words, the individual gradually increases the hours spent in the workplace until the individual is working full-time. It is not the same as exposure treatment, which occurs with either PTSD or OCD. A gradual return-to-work (RTW) plan for individuals with psychological conditions who have been absent from the workplace was discussed in the Introduction.

CBT has been used to treat depressive disorders, to address the depressive triad of cognitive misperceptions about oneself, the world, and the future. These ruminations are called cognitive distortions, which frequently increase the severity of a current Major Depressive Disorder episode. Specific components of CBT address cognitive distortions to help the individual gain perspective and to identify strategies to address issues as they arise. As noted in the Introduction module, CBT is typically provided in a short-term manner from 6-12 weeks with weekly appointments. However, CBT is provided by many different types of professionals who may or may not have training on workplace issues or know how to set RTW goals as part of treatment. Frequently, while the depressive disorder symptoms are treated, the workplace issues are not. This lack of addressing stay at work (SAW) or RTW is problematic because the perceived workplace barriers are not addressed in treatment. This may lead to longer workplace absences.

More recently, CBT has been studied as a specific workplace intervention. There are key components for CBT that must occur in order to reduce problematic types of thinking and to identify more productive ways to respond to perceived negative people, events, and situations.

With traditional CBT, the focus of treatment is on the interaction between thoughts and emotions, and how this interaction impacts on the individual's behaviors. CBT teaches the individual to recognize problematic emotions and thoughts in order to distinguish them from unproductive, ruminative thoughts. The person learns how to distinguish between types of unproductive thinking (e.g., catastrophizing, all-or-none thinking, over-generalization) and recognize when ruminative thinking is counterproductive. More specifically, CBT teaches how to break the ruminative thought cycle and to devise more effective ways to respond to ruminative thoughts and problematic situations. Typically, cognitive restructuring involves keeping a thought record to track ruminative automatic thoughts, and to identify more adaptive alternative responses. By doing so, the individual's mood becomes more positive because the person can reduce or stop unproductive worrying.

In addition to cognitive restructuring, behavioral activation is an additional active component of CBT. Behavioral activation requires the individual to schedule activities, such as exercise and social engagements, to help the individual to decrease the social withdrawal associated with

depressive disorders. In addition, these scheduled tasks are gradually increased to increase the individual's rewarding experiences. This type of intervention is associated with a gradual improvement in mood. Over time, the individual may experience increased motivation from improved mood.

As the individual improves, the individual is taught successive approximation. In this CBT technique, the individual learns how to break difficult or perceived overwhelming tasks into smaller steps so that the person is able to master these smaller steps by utilizing the skills needed to achieve the larger task.

More recently, empirical research has examined the impact of CBT for workplace interventions. This type of CBT is called work-focused CBT (w-CBT or CBT-w). There are common barriers that individuals with Depressive disorders perceive that impede the individual's return to work. These barriers can be divided into distinct categories: *individual issues* (e.g., personality or coping issues, individual perception of the workplace, severe Major Depressive Disorder with comorbid health conditions); *work* (e.g., workplace conflict, lack of support at work, and lack of guidance or training at work); and *healthcare* (e.g., insufficient mental health care and insufficient care from occupational physician).

With w-CBT, the individual's problematic thoughts and feelings are identified. The individual is taught cognitive restructuring regarding identified, perceived negative workplace situations, such as workplace conflict, as well as the individual's perceptions of inability to continue to work. Cognitive restructuring is helpful in assisting individual's stay at work or in returning to work.

As the individual masters behavioral activation in one's personal life, the focus then switches to address the issue of the individual's negative perception of work capacity. Once again, the individual schedules activities that relate to the workplace, such as learning about workplace resources or such as keeping track of the successful completion of daily workplace tasks. These tasks are gradually increased so that the individual begins to experience positive experiences within the workplace. This change may positively impact on the individual's perception of the workplace and increases motivation at work.

Frequently, employees struggle with large workplace projects or, if the organization has experienced downsizing, increased work responsibilities. If the individual struggles with specific workplace duties, then the task is broken into smaller steps so that the person identifies what actions to take to successfully complete the task.

When a w-CBT component is added to traditional CBT treatment, it is found to be more effective in reducing workplace absences, increasing worker workplace positivity, and addressing real or perceived workplace problems to help the individual better cope and problem-solve at work. Most importantly, these changes remained at 6 months, 1 year, and 2 years of follow-up. W-CBT specifically engages the individual to identify perceived barriers to SAW or RTW. W-CBT does not increase the length that CBT treatment is provided. The

treatment timeframe of 6-12 weeks remains the same. Instead, workplace issues are identified as part of the initial evaluation. Then, those issues are addressed as treatment goals. In addition, the individual is taught effective coping and problem-solving skills to increase resiliency in the workplace so that problems are addressed as they occur. Thus, when a work-focused component is added to CBT, it has been found that the individual returns to work sooner than with other types of treatment. The individual learns to utilize workplace resources to address workplace conflict to increase workplace positivity.

w-CBT utilizes the same graduated RTW plan for individuals who have been off of work with a depressive disorder for more than 3 months. However, there are no permanent restrictions or limitations associated with w-CBT. For individuals with a depressive disorder who remain working but struggle with various aspects of work, including reduced productivity, w-CBT can be provided while the individual continues to work.

Regarding other stakeholders' perceptions of factors that impede the individual's ability to stay at work or return to work after a workplace leave due to Major Depressive Disorder, there is agreement from all stakeholders that personality and coping issues as well as severity of the Major Depressive Disorder play a role in negatively impacting on workplace functioning. However, workplace supervisors tend to emphasize the need for the employee to obtain mental health treatment, but that treating professionals must address the issues that arise in the workplace due to the employee's perception of the workplace as well as improving problem-solving at work in setting RTW goals. Occupational physicians report that safety issues and the lack of support in the workplace are the most important treatment issues to address.

Consequently, it is essential for all stakeholders to understand the primary issues that relate to presenteeism as well as workplace absences. In this way, the goals of SAW and RTW are better supported.

There are identified issues that relate to the individual taking repeated workplace absences related to mental health conditions. However, many of those issues are psychosocial issues that are subjective in nature. The most common issues that either impede RTW with a Depressive disorder or are involved in subsequent workplace leave are: supervisor conflict, negative treatment outcome expectation, negative RTW expectation, and negative perception of self-efficacy regarding workplace functioning. Psychosocial issues have been discussed in the Introduction module previously. It is important to identify the presence of psychosocial issues since they are the primary factors that impact on SAW and RTW. These are the issues to address within w-CBT. While psychosocial issues are not psychological conditions, they are the concerns that are consistently found to interfere with treatment outcome and returning to work.

Some individuals who have been diagnosed with a Depressive disorder and may also have a comorbid physical condition. Comorbid Depressive disorders and physical condition can, at times, result in more frequent workplace absences, particularly if the physical condition causes significant impairment in physical functioning. When an individual with a Depressive disorder

has a serious comorbid physical condition, the individual can be taught CBT strategies to cope with working and having a serious physical condition. However, there may be instances, where significant physical impairment in functioning exists, such as when a person is receiving chemotherapy or has a terminal illness. The Depressive disorder can still be addressed, but the individual may need to take workplace leave to address the lack of physical tolerance and capacity.

Computer-assisted cognitive behavioral therapy has been studied [557, 559, 731, 735, 737, 746-796].

Cognitive Behavioral Therapy Moderately Recommended.

The use of cognitive behavioral therapy is moderately recommended for the treatment of patients with depressive disorders.

*Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – High*

CBT: Computer-Assisted Cognitive Therapy

The use of computer-assisted cognitive therapy is moderately recommended for the treatment of patients with depressive disorders.

*Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – Moderate*

CBT: Acceptance and Commitment Therapy or Interpersonal Therapy

The use of acceptance and commitment therapy or interpersonal therapy is moderately recommended for the treatment of patients with depressive disorders.

*Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – Moderate*

CBT: Combined Use with an Antidepressant

The combined use of CBT and an anti-depressant is moderately recommended for the treatment of patients with depressive disorders.

*Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – Moderate*

Indications:

Depressive disorder sufficient to require treatment. CBT may be first line treatment and is often used in addition to antidepressants. For severe depressive disorders, is generally used as adjunctive, rather than as a stand-alone treatment. There is moderate quality evidence supporting the efficacy of a combination of CBT and an anti-depressant [696, 727].

<i>Benefits:</i>	Improvement in depressive symptoms, and one study suggests possible suicide prevention when combined with imipramine [687].
<i>Harms:</i>	Infrequent and negligible.
<i>Frequency/Dose/Duration:</i>	Variable regimens have been used. One 45-50 min psychotherapy session and one 1.5-hour mindfulness-skills training group every week for 16- 18 weeks [685, 708], but studies show continuation with CBT yields best results suggesting ongoing intervention is required to maintain gains [766].
<i>Indications for Discontinuation:</i>	Symptom resolution, non-compliance, lack of efficacy or adverse effects.
<i>Rationale:</i>	There are many types of CBT and many moderate quality studies suggesting efficacy of CBT for depressive disorders. However, quality evidence for any specific CBT type is variable, ranging from good to insufficient. CBT components with quality evidence allowing evidence-based guidance include Computer-Assisted Cognitive Therapy, Interpersonal Therapy & Acceptance and Commitment Therapy. Multiple moderate quality studies show efficacy of CBT compared to usual care [544, 699, 703, 708]. However, patient commitment to various CBT programs is necessary for success when treating depression and often the studies have high attrition rates. Some studies suggest that CBT reduces or prevents depressive relapse [542, 692]. There is a suggestion that individuals with high coping and self-efficacy skills respond better to CBT than others [707]. In one study, the combination of IPT and imipramine were associated with less suicidal ideation [687]. CBT has low adverse effects, is of moderate cost depending upon treatment type and duration, has evidence of efficacy for the treatment of mild to moderate depression, and thus, CBT is recommended, suggesting ongoing intervention is required to maintain gains.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: acceptance and commitment therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 31 articles in PubMed, 210 in Scopus, 37 in CINAHL, 2 in Cochrane Library, 15,900 in Google Scholar, and 6 from other sources. We considered for inclusion 8 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 6 from other sources. Of the 14 articles considered for inclusion, 11 randomized trials and 2 systematic reviews met the inclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Interpersonal Therapy, interpersonal psychotherapy, IPT; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed</p>

688 articles in PubMed, 8577 in Scopus, 247 in CINAHL, 438 in Cochrane Library, 2770 in Google Scholar, and 82 from other sources†. We considered for inclusion 29 from PubMed, 9 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 7 from other sources. Of the 48 articles considered for inclusion, 24 randomized trials and 24 systematic reviews met the inclusion criteria. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Cognitive Therapy, Cognitive Behavioral Therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 2565 articles in PubMed, 13,469 in Scopus, 933 in CINAHL, 1440 in Cochrane Library, 14,100 in Google Scholar, and 35 from other sources†. We considered for inclusion 31 from PubMed, 6 from Scopus, 6 from CINAHL, 7 from Cochrane Library, 0 from Google Scholar, and 35 from other sources. Of the 85 articles considered for inclusion, 57 randomized trials and 18 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: computer cognitive therapy, internet cognitive therapy, computer cognitive behavior therapy, internet cognitive behavior therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 267 articles in PubMed, 384 in Scopus, 325 in CINAHL, 16 in Cochrane Library, 4,270 in Google Scholar, and 10 from other sources†. We considered for inclusion 58 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 10 from other sources. Of the 68 articles considered for inclusion, 56 randomized trials and 11 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Bibliotherapy/Cognitive Bibliotherapy Recommended.

The use of bibliotherapy/cognitive bibliotherapy is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

<i>Indications:</i>	Depressive disorder sufficient to require treatment. CBT may be first line treatment and is often used in addition to antidepressants. For severe depressive disorders, is generally used as adjunctive, rather than as a stand-alone treatment. There is moderate quality evidence supporting the efficacy of a combination of CBT and an anti-depressant [696, 727].
<i>Benefits:</i>	Improvement in depressive symptoms, and one study suggests possible suicide prevention when combined with imipramine [687].
<i>Harms:</i>	Infrequent and negligible.
<i>Frequency/Dose/Duration:</i>	Variable regimens have been used. One 45-50 min psychotherapy session and one 1.5-hour mindfulness-skills training group every week for 16-18 weeks [685, 708], but studies show continuation with CBT yields best results suggesting ongoing intervention is required to maintain gains [766].
<i>Indications for Discontinuation:</i>	Symptom resolution, non-compliance, lack of efficacy or adverse effects.
<i>Rationale:</i>	There are many types of CBT and many moderate quality studies suggesting efficacy of CBT for depressive disorders. However, quality evidence for any specific CBT type is variable, ranging from good to insufficient. CBT components with quality evidence allowing evidence-based guidance include Computer-Assisted Cognitive Therapy, Cognitive Bibliotherapy, Interpersonal Therapy, and Acceptance and Commitment Therapy. Multiple moderate quality studies show efficacy of CBT compared to usual care [544, 699, 703, 708]. However, patient commitment to various CBT programs is necessary for success when treating depression and often the studies have high attrition rates. Some studies suggest that CBT reduces or prevents depressive relapse [542, 692]. There is a suggestion that individuals with high coping and self-efficacy skills respond better to CBT than others [707]. In one study, the combination of IPT and imipramine were associated with less suicidal ideation [687]. CBT has low adverse effects, is of moderate cost depending upon treatment type and duration, has evidence of efficacy for the treatment of mild to moderate depression, and thus, CBT is recommended, suggesting ongoing intervention is required to maintain gains.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: bibliotherapy, therapeutic storytelling; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic,

systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 47 articles in PubMed, 508 in Scopus, 22 in CINAHL, 40 in Cochrane Library, 3,500 in Google Scholar, and 137 from other sources†. We considered for inclusion 6 from PubMed, 2 from Scopus, 4 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 17 articles considered for inclusion, 10 randomized trials and 5 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Short-term Psychodynamic Psychotherapy Moderately Recommended.

The use of short-term psychodynamic psychotherapy is moderately recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Moderately Recommended, Evidence (B)

Level of Confidence – Moderate

<i>Indications:</i>	Depressive disorder sufficient to require treatment. Short-term psychodynamic psychotherapy may be first line treatment and is often used in addition to antidepressants. For severe depressive disorders, is generally used as adjunctive to medications [862] rather than as a stand-alone treatment.
<i>Benefits:</i>	Improvement in depressive symptoms, and one study suggested reduced depression recurrence over 4 years [860].
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	May be in-person sessions or internet based [861]. Begin at 8 sessions. May need additional prescriptions of additional blocks of 8 sessions based on incremental functional gain. Among the quality trials, there are highly variable numbers of sessions used, e.g., the highest quality trial used 20 sessions, once per week over 5-6 months (confrontation, clarification, and interpretation) as did a few other trials [846, 847]. Other quality studies also used 8 sessions [851, 854]. Yet others used 15-30 [856], 16 [852, 854], 40 [855], and the highest being 2-3/wk for up to 3 years [848]. Evidence of increase efficacy with increased numbers of appointments is poor with some evidence suggesting better efficacy with 8 appointments [854, 863], suggesting a need to treat for short term and determine whether additional treatments is warranted.
<i>Indications for Discontinuation:</i>	Symptom resolution, non-compliance, lack of efficacy or adverse effects.
<i>Rationale:</i>	There are multiple moderate quality trials suggesting efficacy that include various durations of short-term psychodynamic psychotherapy [690, 705, 846, 848, 852-856, 860-864]. Equivalency to fluoxetine has been suggested [864]. Short-term psychodynamic psychotherapy has low adverse effects, is low to moderate to high cost depending upon numbers of treatments and treatment duration, has quality evidence of efficacy, and thus is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Insight Oriented Therapies, Psychodynamic Psychotherapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 38 articles in PubMed, 478 in Scopus, 59 in CINAHL, 24 in Cochrane Library, 856 in Google Scholar, and 17 from other sources [†] . We considered for inclusion 10 from PubMed, 16 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 0 from Google

Scholar, and 17 from other sources. Of the 48 articles considered for inclusion, 33 randomized trials and 8 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Problem-Solving Therapy No Recommendation.

There is no recommendation for or against the use of problem-solving therapy in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are a few quality trials. The highest quality trial suggested equivalency to medication and no synergistic effect [884]. Another suggested a 32% reduced incidence of MDD among those with subclinical depressive symptoms [563]. Yet, how to actualize this type of finding is unclear. Other trials are negative [885, 886, 888]. Thus, there is a significant conflict in the literature regarding potential efficacy and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Problem solving therapy, problem solving; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 354 articles in PubMed, 1387 in Scopus, 316 in CINAHL, 169 in Cochrane Library, 15200 in Google Scholar, and 5 from other sources.† We considered for inclusion 26 from PubMed, 3 from Scopus, 8 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 42 articles considered for inclusion, 15 randomized trials and 27 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

**Peer Support
No Recommendation.**

There is no recommendation for or against the use of peer support in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are few moderate-quality studies and all have significant weaknesses. All are affected by either wait-listed control bias [550, 898, 900] or usual care bias [902]. Outcomes despite these biases in favor of finding differences are modest. Thus, there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Peer Support, Social Support, Peer Counseling; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 66 articles in PubMed, 1154 in Scopus, 93 in CINAHL, 1 in Cochrane Library, 4970 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 16 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 6 randomized trials and 12 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Psychosocial Adjunctive Methods No Recommendation.

There is no recommendation for or against the use of psychosocial adjunctive methods in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)
Level of Confidence – Low

Rationale:

There are no quality studies of psychosocial adjunctive methods for treatment of depressive disorders and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Psychosocial Adjunctive Methods, Psychosocial Support Systems; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 9 articles in PubMed, 20 in Scopus, 0 in CINAHL, 8533 in Cochrane Library, 1400 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 0 from PubMed, 2 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 0 randomized trials and 4 systematic reviews met the inclusion criteria.

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

Suicide prevention encompasses many modes. Treatments for suicide prevention can include cognitive therapy [903], suicide prevention training programs [904, 905], electroconvulsive therapy [906, 907], antidepressants such as lithium [908-910], vitamins [911], intervention programs such as visiting therapists and discussing suicide prevention strategies [912, 913], medical and educational care from home health organizations [914-917], etc. Multiple randomized controlled trials have attempted to evaluate suicidal behaviors and prevention among those with depressive disorders [903, 911, 913, 916, 918].

Suicide Prevention Recommended.

Suicide prevention is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

<i>Indications:</i>	MDD, particularly if there has been suicidal ideation, suicide attempt(s) and/or past suicidality. Threshold for implementation among those with mild depressive symptoms should be low, particularly if suicidal ideation discovered.
<i>Benefits:</i>	Reduction in suicidality, suicide attempts and potentially suicides.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Three 60- to 90-min sessions on a weekly basis and a 4 th session if necessary of Attempted Suicide Short Intervention Program (ASSIP) [912].
<i>Indications for Discontinuation:</i>	Sufficient resolution of depressive symptoms and/or suicide risk, completion of course, non-compliance.
<i>Rationale:</i>	Most quality trials have multiple co-interventions, precluding assessment of what is effective for suicide prevention [916, 918, 919]. However, some evidence suggests the ability to prevent suicide attempts [903, 912]. The cognitive therapy employed by Brown et al. [903] reduced suicide attempts 42%. Suicide prevention is an important public health goal. It has negligible cost, some evidence of efficacy and is thus recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Suicide prevention; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 384 articles in PubMed, 3702 in Scopus, 251 in CINAHL, 8 in Cochrane Library, 7690 in Google Scholar, and 1 from other sources. † We considered for inclusion 13 from PubMed, 11 from Scopus, 11 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 36 articles considered for inclusion, 14 randomized trials and 11 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Mind-Body Interventions No Recommendation.

There is no recommendation for or against the use of mind-body interventions in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are few quality studies of mind/body interventions, with all quality studies having significant weaknesses (e.g., usual care biases and small sample sizes), the larger study suggested a lack of benefit and thus, the literature shows no clear evidence of efficacy [924, 925]. Therefore, there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Mind-body therapies, mind body therapy, mind body techniques, mind body intervention, mind body interventions, mind-body intervention; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 522 articles in PubMed, 220 in Scopus, 56 in CINAHL, 461 in Cochrane Library, 70 in Google Scholar, and 0 from other sources. We considered for inclusion 9 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 8 randomized trials and 1 systematic review met the inclusion criteria.

Comments:

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

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Mindfulness Therapy Recommended.

Mindfulness therapy is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – Low

<i>Indications:</i>	Individuals with depressive symptoms
<i>Benefits:</i>	Improvement in depression symptoms.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Weekly 2.5-hour sessions of Mindfulness therapy
<i>Indications for Discontinuation:</i>	Symptom resolution or lack of efficacy
<i>Rationale:</i>	There are multiple moderate quality studies of mind/body interventions that suggest efficacy, although many trials had numerous co-interventions. One study showed improvement in PTSD symptoms in combat veterans using Mind/Body Interventions over Present Centered Group Therapy [965]. Another study suggested improvement in PTSD symptoms and sleep quality but no improvement in depressive symptoms or overall quality of life [966], and in Oman 2013, self-efficacy improved. However, one study found lack of efficacy [967] but the other quality studies show improvement in PTSD symptoms. Mind/Body Interventions have low adverse effects, are moderately costly depending upon treatment duration, have some evidence of efficacy and thus are recommended for PTSD. There is no recommendation for art therapy, music therapy, spiritual based interventions, as there is no quality evidence of efficacy.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Mindfulness, mindfulness therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 149 articles in PubMed, 2196 in Scopus, 219 in CINAHL, 8 in Cochrane Library, 2340 in Google Scholar, and 7 from other sources. † We considered for inclusion 11 from PubMed, 14 from Scopus, 15 from CINAHL, 1 from Cochrane Library, 3 from Google Scholar, and 7 from other sources. Of the 51 articles considered for inclusion, 26 randomized trials and 25 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Disease Management Programs No Recommendation.

There is no recommendation for or against the use of disease management programs for the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

Nearly all trials have either usual care biases [539, 545, 972, 973, 975-980, 982, 983, 985, 986, 988, 1004] or wait-listed control biases [981, 984]. The only exception was one trial which reported no significant efficacy [974]. Specific disease management programs thus carry no recommendation; however, the principles of providing the best care for the patient do naturally apply.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: disease management, disease management program; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1,123 articles in PubMed, 9,878 in Scopus, 126 in CINAHL, 364 in Cochrane Library, 786 in Google Scholar, and 5 from other sources[†]. We considered for inclusion 38 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 43 articles considered for inclusion, 38 randomized trials and 5 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Emotional Freedom Therapy No Recommendation.

There is no recommendation for or against the use of emotional freedom therapy in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There is only one small trial [689] of 17 subjects; thus, there is no recommendation for emotional freedom techniques.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Emotional Freedom Techniques; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 17 articles in PubMed, 38 in Scopus, 12 in CINAHL, 2 in Cochrane Library, 4410 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 2 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic review met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

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Social Media and Computer Use

Excessive social media use has been associated with depressive symptoms [1007]. Excessive computer use has also been associated with obesity and physical inactivity, both of which have been associated with depressive symptoms [1007-1011]. In a study of 442 young adults, overuse or “pathological” use of social networking sites was associated with negative outcomes as mediated by self-regulation, jealousy, social comparison, aggression and depression [1007]. Another study of 1,787 young adults (ages 19-32 years) found an approximately 3-fold risk of depression among the highest quartile of social media users [1008]. Another study of 1,749 young adults found problematic social media use was associated with a 9% increased risk of depression [1011]. In a one-year longitudinal study of the effects of social networking sites (SNS), “social capital” was associated such that low social capital groups had worse outcomes, including increased depression [1009]. In a systematic review, online social networking was noted to be complex and may have both positive and negative impacts on well-being [1010].

There are no quality randomized controlled trials involving reductions or alterations in social media use and measures of depression. Addressing excessive or problematic social media use may be warranted for patients with depressive symptoms.

Medications

There are many classes of anti-depressant medications used to treat depressive disorders. These include atypical anti-depressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs).

Antidepressants

Moderately Recommended.

Antidepressants are moderately recommended for the treatment of patients with depressive disorders.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **High**

Indications:

Depressive disorder sufficient to require medication. May be prescribed in conjunction with other treatments, especially CBT which in many trials has comparable efficacy [728, 732, 733], psychotherapy [850, 864] and exercise. Selection of an anti-depressant is typically dependent on several factors, including concomitant symptoms to potentially address simultaneously (e.g., sleep disturbance), anticipated potential for adverse effects, prior adverse effects, co-morbid psychiatric morbidity (e.g., anxiety), other medical disorders, and cost [1012, 1013]. Another option is to query the family history and information regarding what medication relatives have found most useful in the treatment of depression.

Benefits:

Improvements in depressive symptoms, improved function, potential to reduce suicide risk, and improvements in other symptoms accompanying depression.

Harms:

SSRIs (including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, etc.): Common adverse effects observed for the use of selective serotonin reuptake inhibitors can include sleep disturbances, nausea, diarrhea, headache, dizziness, fatigue, sexual dysfunction. Some patients experience weight gain, increased risk of non-vertebral fractures or bleeding. Abrupt discontinuation of SSRIs can cause anxiety, mood destabilization, insomnia, dizziness, nausea, vomiting, or even electric-shock sensations [1014].

Citalopram: Restlessness and sleep disturbances, vivid dreams, diarrhea, headache, dizziness, fatigue, sexual dysfunction, weight gain, hyponatremia, possible increased risk of nonvertebral fractures, bleeding. Symptoms of abrupt discontinuation include: nervousness, anxiety, irritability, electric-shock sensations, bouts of tearfulness or crying, dizziness, lightheadedness, insomnia, confusion, trouble concentrating, nausea, vomiting, pregnancy risk class C [1014].

Escitalopram: Restlessness and sleep disturbances, vivid dreams, diarrhea, headache, dizziness, fatigue, sexual dysfunction, weight gain, hyponatremia, possible increased risk of nonvertebral fractures, bleeding. Symptoms of abrupt discontinuation include: nervousness, anxiety, irritability, electric-shock sensations, bouts of tearfulness or crying, dizziness, lightheadedness, insomnia, confusion, trouble concentrating, nausea, vomiting, pregnancy risk class C [1014].

Fluoxetine: More serious adverse effects include: worsening of depression, serious allergic reactions, irregular heartbeats, hyponatremia, bleeding, suicidal ideation as well as mania in patients with bipolar disorder. Common minor adverse effects include: sleepiness, nervousness, insomnia, dizziness, nausea, tremor, skin rash, constipation, upset stomach, loss of appetite, headache, dry mouth, diaphoresis and weight loss. Abrupt termination of Fluoxetine may cause adverse gastrointestinal effects including cramping, nausea, vomiting, diarrhea as well as flu-like symptoms, loss of appetite, lightheadedness, fatigue, headache, dizziness, insomnia, sexual dysfunction and weight gain. Pregnancy risk class C.

Fluvoxamine: Nausea, vomiting, drowsiness, dizziness, loss of appetite, trouble sleeping, weakness, and sweating may occur. The least common or rare side effects include: easily bruising, shaking, sexual problems, fainting, black stool, seizures, eye or vision problems, serotonin syndrome, increased heartrate, hallucinations, prolonged erections, or allergic reactions [1015].

Paroxetine: More serious adverse effects include: worsening of depression, serious allergic reactions, irregular heartbeats, hyponatremia, bleeding, suicidal ideation as well as mania in bipolar patients. Common minor adverse effects include: sleepiness, nervousness, insomnia, dizziness, nausea, tremor, skin rash, constipation, upset stomach, loss of appetite, headache, dry mouth,

diaphoresis and weight loss. Abrupt termination of Paroxetine may cause adverse gastrointestinal effects including cramping, nausea, vomiting, diarrhea as well as flu-like symptoms, loss of appetite, lightheadedness, fatigue, headache, dizziness, insomnia, sexual dysfunction and weight gain. Compared to other SSRIs, Paroxetine has a higher incidence of severe withdrawal symptoms due to a shorter relative half-life. Pregnancy risk class D.

Sertraline: Worsening depression, allergic reactions, irregular heartbeat, hyponatremia, bleeding, suicidal ideation as well as mania in bipolar patients. Common minor adverse effects include: sleepiness, nervousness, insomnia, dizziness, nausea, tremor, skin rash, constipation, upset stomach, loss of appetite, headache, dry mouth, diaphoresis and weight loss. Abrupt termination of Sertraline may cause adverse gastrointestinal effects including cramping, nausea, vomiting, diarrhea as well as flu-like symptoms, loss of appetite, lightheadedness, fatigue, headache, dizziness, insomnia and memory loss.

SNRIs (including duloxetine, desvenlafaxine, milnacipran, reboxetine, venlafaxine, etc.): Common adverse effect is a dose-dependent increase in blood pressure [1014].

Duloxetine: SNRIs can cause a dose-dependent increase in blood pressure [1014].

Venlafaxine: Increased sweating, tachycardia, and urinary retention, nausea, vomiting, increased blood pressure. Symptoms of abrupt discontinuation are common especially due to short half-life and include: withdrawal symptoms increase in blood pressure, False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine, prolonged QT interval. Pregnancy risk category C [1016].

TCAs (including amoxapine, amineptine, amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, maprotiline, mianserin, nortriptyline, protriptyline, etc.): Tricyclic antidepressants most commonly cause anticholinergic effects, orthostatic hypotension, weight gain, sedation, and sexual dysfunction. Less common adverse effects include problems with cardiac conduction [1014, 1017]. Tricyclic antidepressants during pregnancy have reported jitteriness and convulsions in newborns [1014]. Some TCAs have been associated with somnolence [1018].

Amitriptyline: sedation, dry mouth, and weight gain [1017, 1019]. In addition, it can cause orthostatic hypotension, sexual dysfunction, and anticholinergic effects such as urinary retention, constipation, blurred vision, and confusion [1017].

Clomipramine: Dizziness, drowsiness, dry mouth, constipation, stomach upset, nausea, vomiting, changes in appetite/weight, flushing, sweating, tiredness and blurred vision may occur. Less common or rare side effects include allergic reaction, serotonin

syndrome/toxicity, increased heartrate, changes in vision, muscle twitching, mental/mood changes, fever, sexual problems, numbness/tingling, shakiness, trouble urinating or dark urine, easy bruising, stomach pain, painful breasts or menstrual periods, or muscle stiffness [1020].

Desipramine: Headache, nausea, dizziness, drowsiness, nervousness, trouble sleeping, blurred vision, increased appetite, weight gain, constipation and dry mouth may occur. Less common or rare side effects include: mental/mood changes, painful breasts, or menstrual periods, ringing in the ears, sexual problems, shakiness (tremors) numbness/tingling, trouble urinating, easily bruising, signs of infections, stomach pain, dark urine, chest pain, seizures, fainting, slurred speech, weakness on one side, or changes in vision [1021].

Dothiepin: Drowsiness, dizziness, blurred vision, constipation, nausea, vomiting, sweating, dry mouth, problems with urination, tremors, speech problems, sensitivity of skin to sunlight, sexual problems, increased appetite or weight gain, changes in blood sugar, mental changes, irregular heartrate, or convulsions [1022].

Imipramine: Serious adverse effects include: severe allergic reaction, worsening of depression, irregular heartbeat, difficulties breathing or swallowing, sever rash, fever, sore throat or other signs of infections, muscle spasms, uncontrollable shaking, difficulties in walking, speech disturbances and jaundice, Other less severe adverse effects include: dry mouth, blurred vision, headache, drowsiness, dizziness, constipation, nausea and vomiting, loss of appetite, diarrhea, stomach cramps, weight gain or weight loss and increased sweating

Maprotiline: Drowsiness, dizziness, dry mouth, blurred vision, constipation, or trouble urinating may occur. Less common or rare side effects include: heartburn, mental changes, shaking, stomach pain, severe dizziness, irregular heartbeat, fainting, seizures, eye or vision problems, or allergic reaction [1023].

Mianserin: Drowsiness [1024-1026]. Rare side effects include peripheral anticholinergic effects, blood dyscrasias, or decrease in white cell production [1024]. A few randomized controlled trials reported rare cases of mental changes, tremors, increased sweating, or skin rashes. Most common adverse effects in the trials include: drowsiness, dry mouth, constipation, dizziness, or headache [1027].

Mirtazapine: More severe adverse effects include: risky behavior, suicidal ideation, increased depression, rash, blisters, racing or uneven heartbeat, hyponatremia, sudden rigidity, high fever, hallucinations, tremors, profuse sweating and confusion. More common adverse effects include; drowsiness, dizziness, vision changes, (including blurred vision), constipation, weight gain, and dry mouth

Nortriptyline: Sedation, dry mouth, and weight gain [1017, 1019]. In addition, it can cause orthostatic hypotension, sexual dysfunction, and

anticholinergic effects such as urinary retention, constipation, blurred vision, and confusion [1017]

Protriptyline: Drowsiness, dizziness, dry mouth, blurred vision, constipation, weight gain, or trouble urinating may occur. Less common or rare side effects include: heartburn, mental changes, shaking, mask-like facial expressions, muscle spasms, severe stomach pain, decreased sexual desire, enlarged painful breasts, irregular heart rate, seizures, eye or vision problems, or allergic reaction [1028]

Minaprine: Mental/mood changes, increased motor activity, sleeplessness, sweating, nausea, vomiting, dry mouth, or tachycardia. Less common or rare side effects include: dizziness, dystonia, nausea, decreased motor activity, or hair loss [1029]

MAOIs (including isocarboxazid, moclobemide, minaprine, phenelzine, pirlindole, selegiline, tranylcypromine, etc.): Sleep disturbances, orthostatic hypotension, sexual dysfunction, and weight gain [1014]. MAOI medications can have interactions with food high in tyramine; therefore, dietary restrictions should reduce/avoid foods with tyramine such as caffeine, chocolate, aged cheeses, aged/dried/fermented/salted/smoke/pickled/processed meats and fish, banana peels, beef/chicken liver, bouillon cubes, commercial gravies, concentrated yeast extracts, fava beans, Italian green beans, broad beans, fermented bean curd, homemade yeast-leavened bread, kim chee, orange pulp, overripe or spoiled fruits, packaged soups, red wine, sauerkraut, sherry, snow pea pods, sourdough bread, soy sauce, soybeans, soybean paste/miso, tofu, tap beer and ale, vermouth, avocados, various types of beer, eggplant, canned figs, fish roe, peanuts, port wine, raisins, raspberries, red plums, spinach, tomatoes, white wine, etc. [1023, 1030].

Moclobemide: Increased or irregular heartbeat, muscle stiffness, severe throbbing headache, slow heartbeat, or pressure in the head. Less common side effects include: anxiety, vision changes, dizziness, irregular heart rate, high blood pressure, irritability, nervousness, restlessness, unusual tiredness or weakness. Rare side effects include: aggressive behavior, bleeding gums, burning or tingling sensation, chest pain, confusion, mental changes, difficulty speaking, irregular heartbeat, feeling of something in the eye, headache, increase in urination, irregular periods, irritation or soreness of the mouth, inflammation, loss of balance, loss of interest in self, memory problems, painful urination or trouble passing stool, ringing in the ears, skin rash, stomach pain, or uncontrolled movements [1031]

Phenelzine: Dizziness, drowsiness, tiredness, weakness, problems sleeping, constipation, and dry mouth may occur. Less common or rare side effects include: fainting, mental changes, muscle stiffness, sexual problems, shaking, swollen legs, unusual weight gain, eye or vision problems, stomach pain, seizures, dark urine, yellowing eyes/skin, high blood pressure, chest pain, serotonin syndrome, or allergic reaction (WebMD 2019). Phenelzine can have interactions with food high in tyramine; therefore, dietary restrictions should

reduce/avoid foods with tyramine such as caffeine, chocolate, aged cheeses, aged/dried/fermented/salted/smoke/pickled/processed meats and fish, banana peels, beef/chicken liver, bouillon cubes, commercial gravies, concentrated yeast extracts, fava beans, Italian green beans, broad beans, fermented bean curd, homemade yeast-leavened bread, kim chee, orange pulp, overripe or spoiled fruits, packaged soups, red wine, sauerkraut, sherry, snow pea pods, sourdough bread, soy sauce, soybeans, soybean paste/miso, tofu, tap beer and ale, vermouth, avocados, various types of beer, eggplant, canned figs, fish roe, peanuts, port wine, raisins, raspberries, red plums, spinach, tomatoes, white wine, etc. [1032]

Amineptine: Insomnia, nervousness, headache, anxiety, vertigo, drowsiness, palpitations, weight gain, nausea, or abdominal pain [1033]

Agomelatine: A study suggested that adverse effects such as anxiety, headache, abdominal pain, and diarrhea were similar in patients taking agomelatine compared to placebo, but were not common [1034, 1035]. Another study suggested more common adverse effects of dizziness, nasopharyngitis, and influenza were reported in patients taking agomelatine [1035, 1036]

Amineptine: Insomnia, nervousness, headache, anxiety, vertigo, drowsiness, palpitations, weight gain, nausea, or abdominal pain [1033]

Bupropion: Agitation and suicidal thoughts or mania [1037, 1038]. Most common adverse effects were insomnia, anxiety, nausea, headaches, and dry mouth [1014, 1037, 1038]. Seizures can occur with the use of bupropion, but are rare; thus bupropion is relatively contraindicated in those with a history of seizures [1014, 1038]. Rare cases show anorexia and hypersensitivity reactions [1014]

Trazodone: Nausea, vomiting, diarrhea, drowsiness, dizziness, tiredness, blurred vision, changes in weight, headache, muscle ache/pain, dry mouth, bad taste in the mouth, stuffy nose, constipation, or change in sexual interest/ability may occur. The less common or rare side effects include: shaking, nightmares, ringing in the ears, problems urinating, blood in urine, signs of infection, shortness of breath, stomach pain, chest/jaw/left arm pain, fainting, irregular heartbeat, seizures, eye pain, vision changes, serotonin syndrome, hallucinations, loss of coordination, unexplained fever, unusual agitation/restlessness, painful or prolonged erection in males, or allergic reaction [1039]

Vortioxetine: Adverse effects are similar to that of SSRIs [1014]

Nefazodone: Structurally similar to trazodone and has been withdrawn from the market in some countries because of rare severe hepatotoxicity [1014].

<i>Frequency/Dose/Duration:</i>	Per manufacturer's recommendations.
<i>Indications for Discontinuation:</i>	Lack of efficacy, adverse effects, non-compliance, resolution of depression sufficiently to not require medication
<i>Rationale:</i>	There are many dozens of placebo-controlled RCTs showing efficacy of the anti-depressants (see Tables of evidence: [1013]), nearly all of which are moderate-quality. There is no clear quality evidence of superiority of one anti-depressant over another. If there is a lack of efficacy of an anti-depressant, the three main pharmacological options are to increase dose, switch to another medication or add a second medication. There is no clear consensus on which option to select. There is some literature support indicating it would be reasonable first to switch to an alternate medication rather than increase dose, as there tends to be little incremental treatment gain while adverse effects commensurately increase [1040, 1041]. Anti-depressants have moderate adverse effects, are low to moderately costly especially depending on duration, have quality evidence of efficacy and are thus recommended. There are many factors affecting selection of anti-depressants.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: citalopram, celaxa; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 628 articles in PubMed, 5845 in Scopus, 903 in CINAHL, 80 in Cochrane Library, 2240 in Google Scholar, and 3 from other sources†. We considered for inclusion 20 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 28 from other sources. Of the 52 articles considered for inclusion, 25 randomized trials and 1 systematic review met the inclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Escitalopram; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 742 articles in PubMed, 2605 in Scopus, 255 in CINAHL, 28 in Cochrane Library, 1120 in Google Scholar, and 10 from other sources†. We considered for inclusion 55 from PubMed, 4 from Scopus, 5 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 10 from other sources. Of the 74 articles considered for inclusion, 44 randomized trials and 26 systematic reviews met the inclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date</p>

limits using the following terms: Fluoxetine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 749 articles in PubMed, 9748 in Scopus, 740 in CINAHL, 588 in Cochrane Library, 4620 in Google Scholar, and 79 from other sources†. We considered for inclusion 41 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 79 from other sources. Of the 120 articles considered for inclusion, 106 randomized trials and 14 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: fluvoxamine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 159 articles in PubMed, 1,593 in Scopus, 132 in CINAHL, 200 in Cochrane Library, 1,240 in Google Scholar, and 11 from other sources†. We considered for inclusion 0 from PubMed, 9 from Scopus, 9 from CINAHL, 6 from Cochrane Library, 2 from Google Scholar, and 11 from other sources. Of the 37 articles considered for inclusion, 32 randomized trials and 5 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Paroxetine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 462 articles in PubMed, 1905 in Scopus, 315 in CINAHL, 9 in Cochrane Library, 3000 in Google Scholar, and 12 from other sources†. We considered for inclusion 71 from PubMed, 14 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 12 from other sources. Of the 100 articles considered for inclusion, 82 randomized trials and 12 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Sertraline, Zoloft, Depression, depressive disorder, major depressive disorder, MDD; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized,

randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 670 articles in PubMed, 9221 in Scopus, 983 in CINAHL, 372 in Cochrane Library, 2710 in Google Scholar, and 94 from other sources[†]. We considered for inclusion 38 from PubMed, 6 from Scopus, 4 from CINAHL, 7 from Cochrane Library, 0 from Google Scholar, and 41 from other sources. Of the 96 articles considered for inclusion, 88 randomized trials and 4 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Desvenlafaxine, Desvenlafaxine succinate, pristin; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 59 articles in PubMed, 516 in Scopus, 129 in CINAHL, 30 in Cochrane Library, 144 in Google Scholar, and 135 from other sources[†]. We considered for inclusion 17 from PubMed, 10 from Scopus, 4 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 32 articles considered for inclusion, 17 randomized trials and 15 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Duloxetine Hydrochloride, Duloxetine, Cymbalta, Irenka, Depression, depressive disorder, major depressive disorder, MDD; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 285 articles in PubMed, 3999 in Scopus, 419 in CINAHL, 133 in Cochrane Library, 999 in Google Scholar, and 179 from other sources[†]. We considered for inclusion 33 from PubMed, 22 from Scopus, 4 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 9 from other sources. Of the 71 articles considered for inclusion, 37 randomized trials and 26 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Milnacipran, Milnacipran Hydrochloride; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed

63 articles in PubMed, 123 in Scopus, 1 in CINAHL, 58 in Cochrane Library, 303 in Google Scholar, and 5 from other sources†. We considered for inclusion 10 from PubMed, 1 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 19 articles considered for inclusion, 13 randomized trials and 6 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Reboxetine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 67 articles in PubMed, 1109 in Scopus, 171 in CINAHL, 11 in Cochrane Library, 425 in Google Scholar, and 0 from other sources†. We considered for inclusion 19 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 21 articles considered for inclusion, 13 randomized trials and 3 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Venlafaxine, Effexor XR; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 385 articles in PubMed, 3615 in Scopus, 29 in CINAHL, 215 in Cochrane Library, 2210 in Google Scholar, and 36 from other sources†. We considered for inclusion 34 from PubMed, 14 from Scopus, 2 from CINAHL, 2 from Cochrane Library, 3 from Google Scholar, and 36 from other sources. Of the 91 articles considered for inclusion, 51 randomized trials and 19 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Amitriptyline; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 448 articles in PubMed, 1821 in Scopus, 234 in CINAHL, 8906 in Cochrane Library, 2530 in Google Scholar, and 39 from other sources†. We considered for inclusion 34 from PubMed, 8 from Scopus, 8 from CINAHL, 3 from Cochrane Library, 3 from Google Scholar, and 39 from other sources. Of the 96 articles considered for inclusion, 87 randomized trials and 9 systematic reviews met the

inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Amoxapine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 21 articles in PubMed, 219 in Scopus, 8 in CINAHL, 21 in Cochrane Library, 211 in Google Scholar, and 1 from other sources†. We considered for inclusion 11 from PubMed, 3 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 16 articles considered for inclusion, 14 randomized trials and 2 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Clomipramine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 27 articles in PubMed, 502 in Scopus, 15 in CINAHL, 50 in Cochrane Library, 1290 in Google Scholar, and 25 from other sources†. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 25 from other sources. Of the 27 articles considered for inclusion, 27 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Desipramine, Norpramin; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 247 articles in PubMed, 4141 in Scopus, 244 in CINAHL, 152 in Cochrane Library, 1280 in Google Scholar, and 0 from other sources†. We considered for inclusion 18 from PubMed, 3 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 22 articles considered for inclusion, 16 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Dothiepin Hydrochloride; depression,

depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 38 articles in PubMed, 34 in Scopus, 0 in CINAHL, 32 in Cochrane Library, 105 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 1 from Scopus, 0 from CINAHL, 3 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 11 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: doxepin; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 109 articles in PubMed, 596 in Scopus, 2 in CINAHL, 131 in Cochrane Library, 640 in Google Scholar, and 0 from other sources†. We considered for inclusion 13 from PubMed, 6 from Scopus, 0 from CINAHL, 3 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 24 articles considered for inclusion, 7 randomized trials and 5 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Imipramine, Tofranil; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 587 articles in PubMed, 4309 in Scopus, 540 in CINAHL, 497 in Cochrane Library, 218 in Google Scholar, and 72 from other sources†. We considered for inclusion 24 from PubMed, 15 from Scopus, 7 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 72 from other sources. Of the 121 articles considered for inclusion, 112 randomized trials and 2 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Maprotiline; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol.

We found and reviewed 94 articles in PubMed, 852 in Scopus, 1 in CINAHL, 2 in Cochrane Library, 532 in Google Scholar, and 11 from other sources[†]. We considered for inclusion 11 from PubMed, 15 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 11 from other sources. Of the 41 articles considered for inclusion, 40 randomized trials and 1 systematic review met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: mianserin; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 228 articles in PubMed, 923 in Scopus, 161 in CINAHL, 297 in Cochrane Library, 583 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 12 from PubMed, 5 from Scopus, 10 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 29 articles considered for inclusion, 27 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Mirtazapine, Remeron, Remeronsoftab; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 144 articles in PubMed, 2169 in Scopus, 262 in CINAHL, 133 in Cochrane Library, 3 in Google Scholar, and 25 from other sources[†]. We considered for inclusion 18 from PubMed, 9 from Scopus, 5 from CINAHL, 3 from Cochrane Library, 0 from Google Scholar, and 10 from other sources. Of the 45 articles considered for inclusion, 31 randomized trials and 10 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: nortriptyline; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 344 articles in PubMed, 1984 in Scopus, 379 in CINAHL, 0 in Cochrane Library, 1180 in Google Scholar, and 11 from other sources[†]. We considered for inclusion 8 from PubMed, 0 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 11 from other sources. Of the 22 articles considered for

inclusion, 20 randomized trials and 2 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Protriptyline; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 2 articles in PubMed, 166 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 229 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 1 systematic review met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Trimipramine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 27 articles in PubMed, 280 in Scopus, 22 in CINAHL, 1 in Cochrane Library, 277 in Google Scholar, and 0 from other sources†. We considered for inclusion 5 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 4 randomized trials and 1 systematic review met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Monoamine oxidase inhibitors, MAOI, isocarboxazid, marplan, phenelzine, nardil, selegiline, emsam, tranylcypromine, parnate; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 404 articles in PubMed, 5362 in Scopus, 29 in CINAHL, 228 in Cochrane Library, 30800 in Google Scholar, and 187 from other sources†. We considered for inclusion 55 from PubMed, 6 from Scopus, 0 from CINAHL, 8 from Cochrane Library, 8 from Google Scholar, and 34 from other sources. Of the 111 articles considered for inclusion, 38 randomized trials and 8 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Moclobemide; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 96 articles in PubMed, 5409 in Scopus, 4 in CINAHL, 88 in Cochrane Library, 553 in Google Scholar, and 41 from other sources†. We considered for inclusion 13 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 41 from other sources. Of the 56 articles considered for inclusion, 55 randomized trials and 1 systematic review met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: agomelatine, agomelatin, toxil, ago-178, s 20098 ; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 54 articles in PubMed, 740 in Scopus, 22 in CINAHL, 10 in Cochrane Library, 288 in Google Scholar, and 3 from other sources†. We considered for inclusion 8 from PubMed, 1 from Scopus, 2 from CINAHL, 2 from Cochrane Library, 4 from Google Scholar, and 3 from other sources. Of the 20 articles considered for inclusion, 13 randomized trials and 7 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: amineptine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 11 articles in PubMed, 129 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 57 in Google Scholar, and 8 from other sources†. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 8 from other sources. Of the 11 articles considered for inclusion, 7 randomized trials and 0 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Bupropion, busiprone, wellbutrin, buspar, zyban, aplenzin, budeprion; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials,

random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 284 articles in PubMed, 5300 in Scopus, 337 in CINAHL, 149 in Cochrane Library, 2120 in Google Scholar, and 30 from other sources†. We considered for inclusion 26 from PubMed, 10 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 10 from other sources. Of the 49 articles considered for inclusion, 23 randomized trials and 16 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Nefazodone; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 91 articles in PubMed, 1225 in Scopus, 4 in CINAHL, 74 in Cochrane Library, 558 in Google Scholar, and 2 from other sources†. We considered for inclusion 12 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 18 articles considered for inclusion, 15 randomized trials and 3 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Trazodone; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 78 articles in PubMed, 832 in Scopus, 42 in CINAHL, 80 in Cochrane Library, 933 in Google Scholar, and 3 from other sources†. We considered for inclusion 20 from PubMed, 18 from Scopus, 2 from CINAHL, 9 from Cochrane Library, 2 from Google Scholar, and 3 from other sources. Of the 55 articles considered for inclusion, 34 randomized trials and 8 systematic reviews met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: vortioxetine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 57 articles in PubMed, 182 in Scopus, 57 in CINAHL, 45 in Cochrane Library, 111,000 in Google Scholar, and 0 from

other sources[†]. We considered for inclusion 11 from PubMed, 0 from Scopus, 15 from CINAHL, 2 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 28 articles considered for inclusion, 18 randomized trials and 10 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Antipsychotics Recommended.

Antipsychotics are recommended for the treatment of patients with depressive disorders.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

<i>Indications:</i>	Major Depressive Disorder with psychotic features or treatment-resistant depression.
<i>Benefits:</i>	Improvements in both MDD and psychotic features. Also indicated for treatment-resistant depression [1060], and bipolar disorder.
<i>Harms:</i>	Dizziness, drowsiness, fatigue, diarrhea, constipation, blurred vision, dry mouth, increased appetite, weight gain, increase suicidal thoughts. Monitoring for metabolic syndrome is needed. First generation anti-psychotics cause dystonic effects and tardive dyskinesia.
<i>Frequency/Dose/Duration:</i>	There are multiple dosing regimens in the quality literature; doses used in the higher quality trials are below. For Treatment-Resistant Depression: Amisulpride 50 mg/d [1086] Aripiprazole 2-5 mg/d, increased by 2-5 mg/day per visit to a maximum of 15 mg/day [1050] Brexipiprazole 3 mg/d [1091] Dixyrazine 50 mg/d [1070] Flupenthixol (0.5-2.5 mg/day) [1081] Olanzapine 6mg/Fluoxetine 25mg [1061] Quetiapine XR 150-300 mg/d [1064] Risperidone – Graduated dosing starting at 0.25 mg/d to 1 mg/d increased to max 2 mg/d [1071] Sulpiride 100 mg/Paroxetine 10-40 mg/d [1082] Ziprasidone 20-mg/ twice per day increased to a maximum dose of 20-80 mg/twice per day (40-160 mg total)/ plus Escitalopram 10mg/d [1075] For MDD with Psychotic Features: Lurasidone 20-60 mg/d [1044] Pherphenazine 1-3 (16 mg tablets/d) [1043]
<i>Indications for Discontinuation:</i>	Intolerability, adverse effects, non-compliance, lack of efficacy.
<i>Rationale:</i>	Multiple moderate-quality trials suggest efficacy for treatment of depressive disorders with psychotic features, as well as for treatment-resistant depression [1046, 1050-1052, 1060]. Some trials suggested the time to remission was longer with olanzapine/fluoxetine [1062] or Quetiapine [1084]. Many antipsychotics are used to potentiate antidepressant effects for a faster onset of action [1064, 1085]. They are also used for their sedation effects for patients with insomnia related to depression and anxiety. Risperidone has been used to treat MDD with suicidal ideation with efficacy [1090]. Antipsychotics have low to moderate adverse effects, are of moderate cost depending on duration of need, and are selectively recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: antipsychotics; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized

controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 742 articles in PubMed, 2355 in Scopus, 653 in CINAHL, 272 in Cochrane Library, 4920 in Google Scholar, and 26 from other sources[†]. We considered for inclusion 41 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 26 from other sources. Of the 68 articles considered for inclusion, 64 randomized trials and 4 systematic studies met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Aripiprazole, Abilify; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 75 articles in PubMed, 1280 in Scopus, 81 in CINAHL, 28 in Cochrane Library, 885 in Google Scholar, and 200 from other sources[†]. We considered for inclusion 12 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 6 from other sources. Of the 20 articles considered for inclusion, 12 randomized trials and 4 systematic studies met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Symbyax (Olanzapine/Fluoxetine Combination)

Recommended.

Symbyax (olanzapine/fluoxetine combination) is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

<i>Indications:</i>	Major Depressive Disorder with psychotic features
<i>Benefits:</i>	improvements in both MDD and psychotic features. Also indicated for treatment-resistant depression [1060]. It is also used to treat bipolar disorder.
<i>Harms:</i>	Dizziness, drowsiness, fatigue, diarrhea, constipation, blurred vision, dry mouth, increased appetite, weight gain, increase suicidal thoughts.
<i>Frequency/Dose/Duration:</i>	Per manufacturer’s recommendation. Usual dose is olanzapine 6mg/fluoxetine 25mg.
<i>Indications for Discontinuation:</i>	Intolerability, adverse effects, non-compliance, lack of efficacy.
<i>Rationale:</i>	Multiple moderate-quality trials suggest efficacy of including for treatment-resistant depression [1060]. One trial suggested the time to remission was longer with olanzapine/fluoxetine [1062]. Olanzapine/fluoxetine has low to moderate adverse effects, is moderate cost depending on duration of need, and is selectively recommended.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: olanzapine, fluoxetine, olanzapine-fluoxetine, Symbyax; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 858 articles in PubMed, 1513 in Scopus, 2 in CINAHL, 12 in Cochrane Library, 676 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 4 articles considered for inclusion, 4 randomized trials and 0 systematic studies met the inclusion criteria.</p> <p>[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.</p>

Nitrous Oxide No Recommendation.

There is no recommendation for or against the use of nitrous oxide in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are few studies which have used nitrous oxide for treatment-resistant depression. In one experimental study of 24 hours, nitrous oxide resulted in improvements at both 2- and 24-hours after inhalation in 20 subjects [1092]. Nitrous oxide is either not invasive or is minimally invasive if an IV is also used, has some adverse effects, is moderate cost, but as it lacks evidence of short- or longer-term durable efficacy, there is no recommendation for treatment-resistant depression.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Nitrous oxide, nitrogen oxide, nitric Oxide, n20, Depression, depressive disorder, major depressive disorder; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 43 articles in PubMed, 8701 in, 279 in CINAHL, 12 in Cochrane Library, 967 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

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

Ketamine has been used in a number of studies to treat depression [1093-1104].

Ketamine

No Recommendation.

There is no recommendation for the treatment of patients with depressive disorders with ketamine.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

Several high-and moderate-quality studies of ketamine for treatment-resistant major depression have suggested very short-term benefits. However, population sizes assessed are small and durability of the effect is not well established and one study suggested waning benefits at seven days [1101]. Repeated administrations have been attempted. Oral ketamine has also been used and suggested improved depression scores up to 6 weeks [1104]. Ketamine may be invasive (or non-invasive if oral/intranasal route is used), has moderate to severe adverse effects, is of moderate to high cost, and has some evidence of short-term efficacy for treatment-resistant depression, but no quality evidence of sustained benefits and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Ketamine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 90 articles in PubMed, 1735 in Scopus, 97 in CINAHL, 60 in Cochrane Library, 1890 in Google Scholar, and 2 from other sources†. We considered for inclusion 21 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 29 articles considered for inclusion, 8 randomized trials and 18 systematic studies met the inclusion criteria.

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

Esketamine No Recommendation.

There is no recommendation for the treatment of patients with depressive disorders with esketamine.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

Two modest-sized, moderate-quality studies of esketamine for treatment-resistant major depression suggest potential short-term benefits. However, population sizes assessed are small and durability of the effect is not well established. Esketamine is not invasive, has moderate adverse effects, is of moderate to high cost, and has some evidence of short-term efficacy for treatment-resistant depression, but no quality evidence of sustained benefits and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: esketamine; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 1 articles in PubMed, 40 in Scopus, 2 in CINAHL, 16 in Cochrane Library, 102 in Google Scholar, and 0 from other sources.† We considered for inclusion 1 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 0 systematic reviews met the inclusion criteria.

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

Anti-inflammatory Agents Not Recommended.

Anti-inflammatories (e.g., celecoxib), and other drugs with possible anti-inflammatory properties (e.g., minocycline, pioglitazone, simvastatin, mifepristone, pentoxifylline), are not recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

Some limited evidence suggests there may be a relationship between inflammatory markers and depression; however, there is no clear evidence of efficacy for treatment of depression with anti-inflammatories and no quality evidence of a durable effect. The only longer-term study was prematurely terminated due to the improbability of meeting the study's goals [1119]. Anti-inflammatories are non-invasive, have low to moderate adverse effects depending on the type/class, are low to moderate cost in aggregate depending on the agent, but have no evidence of durable efficacy; thus, they are not recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Anti-Inflammatory; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 680 articles in PubMed, 2075 in Scopus, 82 in CINAHL, 30 in Cochrane Library, 5800 in Google Scholar, and 8 from other sources. We considered for inclusion 10 from PubMed, 0 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 8 from other sources. Of the 29 articles considered for inclusion, 10 randomized trials and 6 systematic studies met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Tumor Necrosis Factor Inhibitors No Recommendation.

There is no recommendation for or against the use of tumor necrosis factor inhibitors in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

Some limited evidence suggests there may be a relationship between inflammatory markers and depression. There are several trials of TNF-inhibitors especially involving patients with moderate to severe psoriasis [1127, 1130, 1131]. There are sparse trials among those with depression and without a known systemic inflammatory disorder, showing no clear evidence of efficacy with durable effect [1126]. Post hoc analyses have suggested possible efficacy among those with high inflammatory markers [1126], but this theory has not been rigorously tested. TNF inhibitors are invasive, have moderate to high adverse effects, are high cost, have no evidence of durable efficacy and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Tumor Necrosis Factor Inhibitors, Etanercept, Infliximab, Adalimumab, Certolizumab Pegol; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 34 articles in PubMed, 181 in Scopus, 32 in CINAHL, 19 in Cochrane Library, 5220 in Google Scholar, and 6 from other sources.† We considered for inclusion 4 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 9 articles considered for inclusion, 3 randomized trials and 4 systematic reviews met the inclusion criteria.

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

Alternative Therapies

Cumin has been used to treat depression [1132-1137].

Cumin

No Recommendation.

There is no recommendation for or against the use of cumin in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are only a few moderate quality studies and no clear evidence of efficacy as the data conflict. Cumin is non-invasive, has low adverse effects, is generally low cost, has no control over quality and dosing, has no clear evidence of efficacy and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: cumin, cuminum; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 0 articles in PubMed, 19 in Scopus, 0 in CINAHL, 30 in Cochrane Library, 163 in Google Scholar, and 6 from other sources.† We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 6 from other sources. Of the 6 articles considered for inclusion, 3 randomized trials and 1 systematic review met the inclusion criteria.

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

St. John's Wort (*Hypericum Perforatum*) No Recommendation.

There is no recommendation for or against the use of St. John's Wort (*Hypericum Perforatum*) in the treatment of patients with depressive disorders.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale:

There are several moderate quality trials with St. John's Wort. Three moderate quality placebo-controlled studies suggest some efficacy [1147-1149], and three moderate quality studies show lack of efficacy [1150-1152]. In several other moderate-quality studies there is evidence of comparable efficacy to an antidepressant of known efficacy [1138, 1153-1159]. St. John's Wort is non-invasive, of moderate cost, has some adverse effects, has some efficacy, but dosing is not controlled and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: St. John's Wort, Saint John's Wort, hypericum; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 119 articles in PubMed, 1623 in Scopus, 56 in CINAHL, 0 in Cochrane Library, 4210 in Google Scholar, and 9 from other sources[†]. We considered for inclusion 24 from PubMed, 4 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 9 from other sources. Of the 39 articles considered for inclusion, 18 randomized trials and 21 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

:

Omega-3 Fatty Acids No Recommendation.

There is no recommendation for or against the use of omega-3 fatty acids in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are several moderate quality studies using omega-3 fatty acids to improve symptoms of depression with mixed efficacy. There is modest efficacy in some studies [617, 1161] but there is lack of efficacy in others [1160, 1162, 1165, 1166]. There may be some benefit for omega-3 fatty acids potentiating the effects of certain antidepressants [1164, 1167]. Omega-3 fatty acids have low adverse effects, are low to moderate cost depending upon treatment duration, but have no clear evidence of efficacy. Thus, there is no recommendation for omega-3 fatty acids for use in the treatment of depression.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Omega 3 Fatty Acids; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 151 articles in PubMed, 879 in Scopus, 113 in CINAHL, 87 in Cochrane Library, 900 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 30 from PubMed, 8 from Scopus, 4 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 44 articles considered for inclusion, 10 randomized trials and 33 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Vitamin D Not Recommended.

Vitamin D is not recommended for the treatment of patients with depressive disorders. There are other indications for its use.

Strength of Evidence – Not Recommended, Evidence (C)
Level of Confidence – Low

Rationale:

The two high-quality studies suggest lack of efficacy [1188, 1191] and include the largest sample size to date in an RCT of vitamin D. In contrast, two moderate quality studies suggest benefits [1190, 1192] including additive benefit with fluoxetine [1192]. An unblinded study of injections also reported some benefits [1189]. Vitamin D is not invasive unless provided by injection, has generally low adverse effects, is low cost, but with the strongest evidence showing lack of efficacy, it is not recommended for treatment of depression. There are other indications for its use.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vitamin D; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 55 articles in PubMed, 593 in Scopus, 46 in CINAHL, 3 in Cochrane Library, 7270 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 11 from PubMed, 2 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 16 articles considered for inclusion, 5 randomized trials and 5 systematic reviews met the inclusion criteria.

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

B Vitamins

No Recommendation.

There is no recommendation for or against the routine use of B-vitamins (folate, thiamine, riboflavin) for adjunctive use with anti-depressants. There is a low threshold for use in those with questions of dietary deficiencies.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

One high-quality trial suggested lack of efficacy of vB12 [1201, 1202] in a population of elderly vitamin B deficient individuals. However, efficacy has been reported for adjunctive use in select patients with folate, riboflavin, vB12 [1193]; thiamine [1197]; and folate [1196]. The B-vitamins thiamine, folate and riboflavin are not invasive, have negligible adverse effects, are low cost, have some evidence of efficacy in some populations and thus may be selectively recommended. However, there is not evidence of utility in a general population of healthy working age adults.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: B Vitamins; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 26 articles in PubMed, 221 in Scopus, 17 in CINAHL, 16 in Cochrane Library, 17,300 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 2 from PubMed, 4 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 15 articles considered for inclusion, 5 randomized trials and 3 systematic reviews met the inclusion criteria.

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

Marijuana, Cannabis, Cannabinoids, and Cannabidiol Not Recommended.

The use of marijuana, cannabis, cannabinoids, and cannabidiol is not recommended for the treatment of patients with depressive disorders.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are no quality trials of cannabinoids for treatment of depressive disorders. Cannabinoids have significant adverse effects, and in the absence of evidence of efficacy, they are not recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Marijuana, medical marijuana, cannabis, cannabinoids, cannabidiol; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 22 articles in PubMed, 1362 in Scopus, 40 in CINAHL, 15 in Cochrane Library, 1,920 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 5 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 0 randomized trials and 2 systematic reviews met the inclusion criteria.

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

Neuromodulation Therapies

Transcranial magnetic stimulation, a non-invasive brain stimulation treatment, has been suggested for treatment of numerous neuropsychiatric conditions such as anxiety, suicidal ideation and used extensively for depression [1213-1251].

Transcranial Magnetic Stimulation and Repetitive Transcranial Magnetic Stimulation (rTMS) Recommended.

Transcranial magnetic stimulation and repetitive transcranial magnetic stimulation (rTMS) are recommended for patients with treatment-resistant major depressive disorder.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

<i>Indications:</i>	Major Depressive Disorder resistant to treatment with at least 3 anti-depressant medications, CBT and psychotherapy; generally should include declining ECT; or, MDD with suicidality and resistant to at least one trial of anti-depressant. Some data suggest synergistic responses with anti-depressants [1221].
<i>Benefits:</i>	Improvement in symptoms of depression, however, the durability is unclear.
<i>Harms:</i>	Seizure, intolerance, thermal injury, headache, hearing loss, dizziness, nausea, exacerbation of symptoms, electrical shock. FDA Class II [1252]
<i>Frequency/Dose/Duration:</i>	Daily M-F for 4 weeks [1213]. 1Hz rTMS (Magstim Super Rapid stimulator), every weekday at 100% of MT with 600 pulses/session, sessions being 600 s. Coil placed 45° from midline of scalp.
<i>Indications for Discontinuation:</i>	Resolution of depression symptoms, intolerance, non-compliance.
<i>Rationale:</i>	There are multiple moderate quality trials using TMS for the treatment of depression with many of the available studies have small sample sizes, unequal contact time, issues of blinding both subjects and assessors, high dropout rates, making interpretation of results challenging. Importantly, durability is somewhat unclear. However, most sham-controlled studies suggest modest efficacy compared to sham [1213, 1215, 1218, 1222, 1223, 1253], although two RCTs suggest a lack of efficacy compared to sham [1220, 1233]. One trial suggested ECT was more cost-effective and had higher efficacy over 6 months [1249]. A few studies suggest TMS may be appropriate for drug resistant depression patients [1221]. TMS has been compared to ECT with conflicting results of efficacy [1232, 1236, 1241]. There are conflicting studies as to which side of the brain the TMS should be applied or if it is better applied unilaterally or bilaterally [1213, 1216, 1253], or what is the optimum Hz and/or frequency [1214, 1216, 1233]. In some studies, outcomes were best in younger subjects [1227, 1229], and some studies suggest TMS may potentiate the antidepressant response [1226, 1230]. TMS is not invasive, has moderate to high adverse effects, is moderate to high cost depending upon duration of treatment, and has some evidence for efficacy and is therefore selectively recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Transcranial Magnetic Stimulation; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 288 articles in PubMed, 91277 in Scopus, 185 in CINAHL, 173 in Cochrane Library, 1220 in Google Scholar, and 24 from other sources[†]. We considered for inclusion 72 from PubMed, 3 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 24 from other sources. Of the 97 articles considered for inclusion, 39 randomized trials and 57 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Deep Brain Stimulation No Recommendation.

There is no recommendation for or against the use of deep brain stimulation in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

<i>Harms:</i>	Intracranial hemorrhage (7.3%), infection (10.9%), cerebrospinal fluid leakage, cognitive impairment. A total of 64.5% of patients had one or more adverse events by year 7. FDA Class III [1252]
<i>Rationale:</i>	There are conflicting studies regarding whether deep brain stimulation is effective for depressive disorders [1264, 1265], potential harms are extensive (intracranial hemorrhage (7.3%), infection (10.9%), cerebrospinal fluid leakage, cognitive impairment; a total of 64.5% of patients had one or more adverse events by year 7. FDA Class III [1252]) and thus there is no recommendation.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Deep Brain Stimulation; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 65 articles in PubMed, 524 in Scopus, 48 in CINAHL, 17 in Cochrane Library, 5440 in Google Scholar, and 0 from other sources [†] . We considered for inclusion 12 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 16 articles considered for inclusion, 2 randomized trials and 7 systematic reviews met the inclusion criteria.

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

Vagal Nerve Stimulation No Recommendation.

There is no recommendation for vagal nerve stimulation for the treatment of depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are two moderate-quality RCTs, one with multiple reports. The highest quality trial showed no differences between low-, medium- and high-dose raising questions of efficacy [1268]. The other suggests modest efficacy with a 50% higher response rate compared with sham [1267]. Vagal nerve stimulation is invasive, has adverse effects (e.g., paralysis, fatality, medicalization), is high cost, has no clear evidence of efficacy and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vagus nerve stimulation, vagal nerve stimulation; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 18 articles in PubMed, 559 in Scopus, 35 in CINAHL, 7 in Cochrane Library, 1,390 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 6 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 4 randomized trials and 3 systematic reviews met the inclusion criteria.

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

Electroconvulsive Therapy Moderately Recommended.

Electroconvulsive therapy is moderately recommended for patients with treatment-resistant major depressive disorder.

Strength of Evidence – Moderately Recommended, Evidence (B)
Level of Confidence – High

<i>Indications:</i>	Treatment-resistant depression, generally having failed at least 3 medications, CBT, and psychotherapy. Generally also may be reasonable to have tried and failed Transcranial Magnetic Stimulation.
<i>Benefits:</i>	Prompt improvement in depressive symptoms and/or psychosis
<i>Harms:</i>	Complications of anesthesia, tooth damage, cognitive impairment, amnesia.
<i>Frequency/Dose/Duration:</i>	One administration. Generally not repeated unless severe MDD recurs and is again treatment resistant. Some data suggest improved efficacy when combined with an aerobic exercise program [635].
<i>Indications for Discontinuation:</i>	N/A
<i>Rationale:</i>	There are many trials of ECT and its history of use is long for treatment of severe MDD. There are sham-controlled trials showing efficacy [1294]. As this is a long-established treatment, most of the recent literature evaluates details of techniques, anesthesia, requirement for post-procedure anti-depressants, etc. ECT is minimally invasive, has adverse effects, is costly, has evidence of efficacy and thus is indicated for treatment-resistant MDD.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Electroconvulsive Therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 683 articles in PubMed, 3380 in Scopus, 678 in CINAHL, 314 in Cochrane Library, 1940 in Google Scholar, and 14 from other sources [†] . We considered for inclusion 40 from PubMed, 1 from Scopus, 4 from CINAHL, 9 from Cochrane Library, 0 from Google Scholar, and 14 from other sources. Of the 68 articles considered for inclusion, 31 randomized trials and 37 systematic reviews met the inclusion criteria.
<i>Comments:</i>	Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

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

Low-Field Magnetic Stimulation Moderately Recommended.

Low-field magnetic stimulation is moderately recommended for patients with treatment-resistant major depressive disorder.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

<i>Indications:</i>	Treatment-resistant depression, generally having failed at least 3 medications, CBT, and psychotherapy. Typically used as adjunctive to an anti-depressant [1320, 1323, 1325].
<i>Benefits:</i>	Relatively rapid improvement in depressive symptoms
<i>Harms:</i>	Moderate. May have increased risk of seizures. Tolerance of wearing a helmet 1-2 times/day [1326-1328].
<i>Frequency/Dose/Duration:</i>	Daily or BID sessions. 220V; alternating +50 and -50V pulses, 3msec; 12msec pauses [1323].
<i>Indications for Discontinuation:</i>	Intolerance, non-compliance, resolution of depression.
<i>Rationale:</i>	There are several trials of low voltage pulsed electromagnetic fields for the treatment of treatment-resistant depression. Sham-controlled trials suggesting considerable efficacy [1320, 1323, 1329]. Durability of the effects are unclear and the trials are up to 15 days [1320] to 8 weeks [1325]; thus, there is no intermediate or long-term moderately or higher quality study. Low voltage pulsed electromagnetic fields are not invasive, have low to moderate adverse effects, are costly over time, have some evidence of efficacy and thus is indicated for treatment-resistant MDD.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Low-Field Magnetic Stimulation, LFMS; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 16 articles in PubMed, 61 in Scopus, 3 in CINAHL, 12 in Cochrane Library, 7 in Google Scholar, and 3 from other sources [†] . We considered for inclusion 4 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 3 from other sources. Of the 11 articles considered for inclusion, 3 randomized trials and 4 systematic reviews met the inclusion criteria.

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

Injection Therapies

Botulinum toxin injections have been used to treat depression [1330-1335].

Botulinum Toxin Injections

No Recommendation.

There is no recommendation for or against the use of botulinum toxin injections in the treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There are few studies trialing botulinum injections for the treatment of depression. One study used dissimilar doses of the drug in males cf. females and there were considerable baseline group differences in baseline depression duration, suggesting randomization failure [1330]. The remaining two small studies would show changes in the glabellar facial region after injection, which changes the appearance of frown lines, thus potentially unblinding the studies. Botulinum toxin injections are invasive, have significant adverse effects, are high cost, and require high quality trials in large populations to support a recommendation in favor of these injections.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: botulinum toxin, botox; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 14 articles in PubMed, 602 in Scopus, 8 in CINAHL, 6 in Cochrane Library, 594 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 6 articles considered for inclusion, 4 randomized trials and 2 systematic reviews met the inclusion criteria.

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

Cyanocobalamin (Vitamin B-12) Injections Not Recommended.

Cyanocobalamin (vB12) injections are not recommended for the treatment of patients with depressive disorders [1201, 1202]. Cyanocobalamin is recommended for those with elevated Methylmalonic acid or known vB12 deficiency and/or pernicious anemia.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

One high quality trial suggested lack of efficacy of vB12 [1201, 1202] in a population of elderly vitamin B deficient individuals. However, efficacy has been reported for adjunctive use in select patients with folate, riboflavin, vB12 [1193]; thiamine [1197]; and folate [1196]. The B-vitamins thiamine, folate and riboflavin are not invasive, have negligible adverse effects, are low cost, have some evidence of efficacy in some populations and thus may be selectively recommended. However, there is not evidence of utility in a general population of healthy working age adults.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: B Vitamins; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 26 articles in PubMed, 221 in Scopus, 17 in CINAHL, 16 in Cochrane Library, 17,300 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 2 from PubMed, 4 from Scopus, 5 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 15 articles considered for inclusion, 5 randomized trials and 3 systematic reviews met the inclusion criteria.

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

Allied Health Interventions

Acupuncture has been used to treat depression [1336-1345].

Acupuncture

No Recommendation.

There is no recommendation for or against the use of acupuncture in the treatment of depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There is a lack of sham-controlled trials of acupuncture to treat depressive disorders. The available trials are subject to contact time and/or wait list control biases [1339, 1340, 1342]. Acupuncture is minimally invasive, has low adverse effects is cumulatively moderate to high cost, but in the absence of quality evidence of efficacy, there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: acupuncture; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 9 articles in PubMed, 221 in Scopus, 58 in CINAHL, 5 in Cochrane Library, 2082 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 8 from PubMed, 0 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 4 randomized trials and 5 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

**Massage
No Recommendation.**

There is no recommendation for or against massage for the treatment of depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)
Level of Confidence – Low

Rationale:

There are no quality studies of the use of massage for depressive symptoms and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Massage; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 83 articles in PubMed, 560 in Scopus, 561 in CINAHL, 65 in Cochrane Library, 1890 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials and 2 systematic reviews met the inclusion criteria.

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

Aromatherapy has been used to treat depression [681, 1353-1357].

Aromatherapy No Recommendation.

There is no recommendation for or against aromatherapy for the treatment of depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

There is one small moderate-quality trial regarding aromatherapy for treatment of depression and the trial suggested a lack of benefit although there was a trend towards better sleep [1356].

Aromatherapy is not invasive, has low adverse effects, is low cost although cumulatively could result in at least moderate costs, has no quality evidence of efficacy and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Aromatherapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 17 articles in PubMed, 183 in Scopus, 16 in CINAHL, 0 in Cochrane Library, 435 in Google Scholar, and 1 from other sources[†]. We considered for inclusion 3 from PubMed, 3 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 10 articles considered for inclusion, 2 randomized trials and 6 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Light Therapy Recommended.

Light therapy is recommended for the treatment of patients with depressive disorders.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

<i>Indications:</i>	MDD with or without a seasonal (winter) pattern (seasonal affective disorder) [1364].
<i>Benefits:</i>	Improvement in depressive symptoms.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Exposure to white fluorescent light box (Model Daylight 10000, ultraviolet filter, rated at 10,000 lux at distance of 14 in from screen to cornea) ASAP after awakening between 07:00 and 08:00 hours [1364]
<i>Benefits:</i>	Improvement in depressive symptoms.
<i>Harms:</i>	Negligible.
<i>Rationale:</i>	There are multiple moderate- and high-quality trials. Most of the higher-quality trials were positive [722, 1367-1369, 1371], but one high quality trial was negative [1364-1366]. Studies showing efficacy included both MDD without a seasonal component and seasonal affective disorder. Light therapy has negligible effects, is low cost, has evidence of efficacy and thus is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: phototherapy, light therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 383 articles in PubMed, 757 in Scopus, 127 in CINAHL, 195 in Cochrane Library, 659 in Google Scholar, and 0 from other sources [†] . We considered for inclusion 42 from PubMed, 0 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 45 articles considered for inclusion, 37 randomized trials and 8 systematic reviews met the inclusion criteria.
	[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.
<i>Comments:</i>	Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Music Therapy No Recommendation.

There is no recommendation for or against music therapy for treatment of patients with depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

All of the few moderate quality studies were subject to usual care biases and all had short follow-up intervals [1403-1405], resulting in an inability to interpret modest short-term improvements. Music therapy has no adverse effects, is low to cumulatively moderate cost, but without quality evidence of efficacy, there is no recommendation. Yet, engagement in joyful activities should naturally result in recommendations from providers for patients to pursue areas of interest including music.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: music therapy; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 86 articles in PubMed, 395 in Scopus, 133 in CINAHL, 2 in Cochrane Library, 4660 in Google Scholar, and 6 from other sources[†]. We considered for inclusion 18 from PubMed, 11 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 32 articles considered for inclusion, 5 randomized trials and 15 systematic reviews met the inclusion criteria.

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Insomnia Treatment Related to Depressive Disorders

Insomnia treatment has been used to help treat depression, and has typically included CBT and/or medications [311, 926, 1408-1443].

Acupuncture for Insomnia Treatment Related to Depressive Disorders No Recommendation.

There is no recommendation for or against the use of acupuncture for insomnia treatment related to depressive disorders.

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

Level of Confidence – Low

Cognitive Behavioral Therapy for Insomnia Treatment Related to Depressive Disorders Moderately Recommended.

Cognitive behavioral therapy is moderately recommended for insomnia treatment related to depressive disorders.

Strength of Evidence – Moderately Recommended, Evidence (B)

Level of Confidence – Moderate

Medications (Other than Benzodiazepines) for Insomnia Treatment Related to Depressive Disorders Recommended.

Medications (other than benzodiazepines) are recommended for insomnia treatment related to depressive disorders.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

Indications:

Depressive disorder patients with sleep disruption. CBT is considered first-line treatment [1409, 1410, 1413, 1415, 1419, 1444]. Medications are generally reserved for those who have inadequate results with CBT for sleep regulation, and there is some evidence that CBT and medication are synergistic [1414, 1428]. Anti-depressant medication selection and timing of administration is also often used for purposes of sleep regulation.

Benefits:

Improved sleep regulation, which may improve depression

Harms:

Negligible for CBT alone. Medicalize insomnia with medication rather than non-medical management; dependence on medication to induce sleep

Frequency/Dose/Duration:

Numbers of appointments and content of CBT is variable, although an initial set of 4-6 appointments is generally recommended.

Medications in the moderate quality trials used:

Agomelatine 25-50mg/day [1431, 1442],

Eszopiclone 3mg/day [1423, 1425, 1426, 1443],

Nefazodone 100mg BID-200mg BID [1427, 1428],
Zolpidem 5-10mg QHS [1408, 1445]

Antidepressants have also been used to treat insomnia symptoms due to sedative effects. These drugs include: Amitriptyline [1081, 1446-1449], Mirtazapine [1429, 1450], and Trazodone [1451-1456].

Benzodiazepines are not recommended for this indication due to dependency and general potential to worsen depression.

Medications are often combined with CBT.

Indications for Discontinuation:

Resolution of depression, improvement in depression and sleep disruption sufficient to wean off medication, non-compliance, intolerance.

Rationale:

Many quality trials document efficacy of CBT for insomnia associated with depressive disorders [1409, 1410, 1413, 1415, 1419, 1444], and there is evidence of synergistic efficacy with medications [1414, 1428]. CBT is low to moderate cost, has evidence of efficacy, and thus is recommended.

There are many moderate quality trials of medications suggesting efficacy of sleep-regulating medication for sleep induction in depressed patients. Sleep medications have moderate risks including development of dependency, are low to moderate cost over time, but in select cases are recommended when other means including CBT and potential use of anti-depressants that assist with sleep regulation prove inadequate.

There are two trials of acupuncture and they conflict [1435, 1438]; thus, there is no recommendation for acupuncture or electroacupuncture.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: insomnia treatment, sleep initiation and maintenance disorders, sleep disorder treatment, insomnia, sleep disorders, circadian rhythm; depression, depressive disorder, major depressive disorder, MDD; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; not pediatric, not review, not adolescents, and not protocol. We found and reviewed 290 articles in PubMed, 3,102 in Scopus, 509 in CINAHL, 9 in Cochrane Library, 5,840 in Google Scholar, and 50 from other sources[†]. We considered for inclusion 33 from PubMed, 4 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 3 from other sources. Of the 41 articles considered for inclusion, 26 randomized trials and 4 systematic reviews met the inclusion criteria.

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

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

Comments:

Per ACOEM Methodology, articles which are scored as low quality are not fully abstracted into a table as they do not result in material changes to evidence-based guidance.

Appendix: PICO Questions

Screening and Testing:

P - Workers and/or patients with suspected Depression
I - Depressive Disorders Screening Tools
C - What is the quality evidence supporting the use of Depressive Disorders Screening tools?
O - Identification of Depression and/or associated symptoms

P - Workers and/or patients with suspected Depression
I - Psychometric Testing
C - What is the quality evidence supporting the use of Psychometric Testing?
O - Identification of Depression and/or associated symptoms

P - Workers and/or patients with suspected Depression
I - Pharmacogenomic Testing
C - Is there quality evidence supporting the use of Pharmacogenomic Testing?
O - Identification of Depression and/or associated symptoms

Education:

P - Workers and/or patients with Depression
I - Education
C - What is the quality evidence supporting the use of Education?
O - Improved Depression and/or associated symptoms

Exercise/Weight Loss/Dieting:

P - Workers and/or patients with Depression
I - Exercise
C - Is Exercise superior to sham or equivalent to other treatments?
O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression
I - Yoga
C - Is Yoga superior to sham or equivalent to other effective treatments?
O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression
I - Tai Chi
C - Is there quality evidence for the use of Tai Chi for Depression treatment?
O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression
I - Qi Gong
C - Is there quality evidence regarding Qi Gong for Depression treatment?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Weight Loss

C - Is Weight Loss an effective treatment strategy for Depression?

O - Improved Depression and/or associated symptoms.

P - Workers and/or patients with Depression

I - Dieting

C - Is Dieting an effective treatment strategy for Depression?

O - Improved Depression and/or associated symptoms.

Behavioral and Psychological Interventions:

P - Workers and/or patients with Depression

I - Cognitive Behavioral Therapy (CBT)

C - Is CBT superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Computer-assisted Cognitive Therapy

C - Is Computer-assisted Cognitive Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Acceptance and Commitment Therapy

C - Is Acceptance and Commitment Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Interpersonal Therapy

C - Is Interpersonal Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Bibliotherapy/Cognitive Bibliotherapy

C - Is Bibliotherapy/Cognitive Bibliotherapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Insight-oriented Therapies inclusive of Short-Term Psychosocial Psychotherapy

C - Are Insight-Oriented Therapies superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Problem Solving Therapy

C - Is Problem Solving Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Peer Support

C - Is Peer Support superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Psychological Adjunctive Methods

C - Are Psychological Adjunctive Methods superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Suicide Prevention

C - Is Suicide Prevention an effective treatment for Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Mind/Body Interventions for Stress Relief

C - Are Mind/Body Interventions superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Mindfulness Therapy

C - Is Mindfulness Therapy an effective treatment for Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Disease Management Programs

C - Are Disease Management Programs effective in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Emotional Freedom Therapy

C - Is Emotional Freedom Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

Medications:

P - Workers and/or patients with Depression

I - Antidepressants

C - Are Antidepressants superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Antidepressants in combination with Cognitive Behavioral Therapy (CBT)

C - Is Combination Antidepressant with CBT superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Antipsychotics

C - Are Antipsychotics superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Combination Olanzapine/Fluoxetine (Symbyax)

C - Is Symbyax superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

Miscellaneous Medical Therapies including Vitamins and Allied Therapies:

P - Workers and/or patients with Depression

I - Nitrous Oxide

C - Is there quality evidence supporting the use of Nitrous Oxide in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Ketamine

C - Is Ketamine superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Hypericum Perforatum (St. John's Wort)

C - Is there quality evidence for Hypericum Perforatum as an effective treatment for Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Omega-3-Fatty Acids

C - Is there quality evidence for the use of Omega-3 Fatty Acids in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Vitamin D

C - Is Vitamin D an effective treatment for Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - B Vitamins (not including B-12 injections)

C - Are B Vitamins effective in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - B-12 Vitamin Injections (Cyanocobalamins)

C - Are B-12 Vitamin Injections in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Botulinum Toxin Injections

C - Is there quality evidence to support the use of Botulinum Toxin Injections in the treatment of Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Marijuana, Cannabis, Cannabinoids

C - Is there quality evidence for the use of Marijuana/Cannabis/Cannabinoids for treating Depression?

O - Improved Depression and/or associated symptoms

Non-invasive Magnetic Therapies and Acupuncture:

P - Workers and/or patients with Depression

I - Acupuncture

C - Is Acupuncture superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Transcranial Magnetic Stimulation (TMS and rTMS)

C - Is TMS superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Low Field Magnetic Stimulation

C - Is Low Field Magnetic Stimulation superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

Electroconvulsive Therapy:

P - Workers and/or patients with Depression

I - Electroconvulsive Therapy (ECT)

C - Is ECT superior to placebo, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

Invasive Therapies:

P - Workers and/or patients with Depression

I - Deep Brain Stimulation

C - Is there quality evidence to support the use of Deep Brain Stimulation is effective in treating Depression?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Vagal Nerve Stimulation

C - Is there quality evidence to support the use of Vagal Nerve Stimulation in Depression treatment?
O - Improved Depression and/or associated symptoms

Relaxation Therapies:

P - Workers and/or patients with depression

I - Massage

C - Is Massage superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Aromatherapy

C - Is Aromatherapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

P - Workers and/or patients with Depression

I - Light Therapy

C - Is Light Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and associated symptoms

P - Workers and/or patients with Depression

I - Music Therapy

C - Is Music Therapy superior to sham, or equivalent to other effective treatments?

O - Improved Depression and/or associated symptoms

Insomnia Related to Depression Therapies:

P - Workers and/or patients with Insomnia related to Depression

I - Acupuncture

C - Is Acupuncture for Depression related Insomnia superior to sham, or equivalent to other effective treatments?

O - Improved Depression related Insomnia and associated symptoms

P - Workers and/or patients with Insomnia related to Depression

I - Cognitive Behavioral Therapy (CBT)

C - Is CBT superior to sham, or equivalent to other effective treatments?

O - Improved Depression related Insomnia and associated symptoms

P - Workers and/or patients with Insomnia related to Depression

I - Non-Benzodiazepine Medications

C - Are Non-Benzodiazepine Medications superior to sham, or equivalent to other effective treatments?

O - Improved Depression related Insomnia and associated symptoms and associated symptoms

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