Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment

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CME Activity

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Learning Objectives: On completion of this article, you should be able to: (1) distinguish key brain regions responsible for nociceptive processing; (2) identify highly prevalent comorbid mental health disorders as they occur in the context of chronic pain; and (3) formulate an evidence-based treatment plan for adults with chronic pain and mental health disorders.

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Abstract

Chronic pain and mental health disorders are common in the general population, and epidemiological studies suggest that a bidirectional relationship exists between these 2 conditions. The observations from functional imaging studies suggest that this bidirectional relationship is due in part to shared neural mechanisms. In addition to depression, anxiety, and substance use disorders, individuals with chronic pain are at risk of other mental health problems including suicide and cigarette smoking and many have sustained sexual violence. Within the broader biopsychosocial model of pain, the fear-avoidance model explains how behavioral factors affect the temporal course of chronic pain and provides the framework for an array of efficacious behavioral interventions including cognitive-behavioral therapy, acceptance-based therapies, and multidisciplinary pain rehabilitation. Concomitant pain and mental health disorders often complicate pharmacological management, but several drug classes, including serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and anticonvulsants, have efficacy for both conditions and should be considered first-line treatment agents.

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Chronic pain and mental health disorders are common in the general population; the prevalence of chronic pain ranges from 2% to 40%,[1] and the prevalence of mental health disorders range from 17% to 29%.[2,3] Concomitant with the high prevalence of both conditions, epidemiological and functional imaging studies suggest that a bidirectional relationship exists between chronic pain and mental health disorders. This is relevant to clinical practice because this bidirectional relationship may be partly mediated by shared neural mechanisms, which, in turn, may necessitate the use of targeted pharmacological and behavioral interventions aimed at treating both conditions. In addition, adults with chronic pain are at risk of other mental health problems including suicide and cigarette smoking and many have sustained sexual violence. Therefore, the objectives of this review were to (1) provide a working definition of the pain matrix, which is a proposed neural network responsible for the experience of chronic pain; (2) summarize the prevalence of commonly occurring mental health disorders in frequently encountered chronic pain conditions; and (3) identify behavioral and pharmacological treatments with efficacy for both chronic pain and mental health disorders.

METHODS

Similar to previously published strategies, databases of MEDLINE using the PubMed and Ovid platforms were searched using the keywords *pain matrix*, *neuromatrix*, *chronic pain*, *depression*, *anxiety*, *substance use*, and *suicide* with no date restrictions.[4] Keywords related to specific topics (eg, low back pain, fibromyalgia, migraine headache, behavioral treatment, and antidepressants) were cross-referenced with the initial search terms using the identified databases. Search terms were cross-referenced with review articles, and additional articles were identified by manually searching the reference lists.

Pain Matrix

The term *pain matrix* refers to a constellation of brain regions activated by nociceptive stimuli. The neurobiological tenets of the pain matrix stem from the conceptual framework of the neuromatrix that was espoused by Melzack[5] to describe a pattern of neural activation initially believed to represent the "neurosignature" of pain. However, numerous neuroimaging studies have since shown that brain regions activated by nociceptive stimuli can also be affected by various emotional and behavioral states.[6] This is relevant because the pain matrix provides the neural mechanistic basis for better understanding of how psychological factors affect pain.

The pain matrix was originally conceptualized as a constellation of interrelated brain regions functioning as a uniplanar circuit. However, a growing body of research suggests that the pain matrix may be more accurately construed as a hierarchical multilevel neural network progressing from the encoding of nociceptive stimuli to the conscious modulation and memory formation of the pain experience. Garcia-Larrea and Peyron[7] have proposed a pain matrix composed of 3 tiers, or levels, of interrelated neural activity (Figure 1). In this 3-tiered model, "first-order" processing refers to nociceptive activation of the spinothalamic tract, which comprises neurons in the dorsal horn of the spinal cord with axonal projections terminating in the posterior thalamus. Nociceptive stimuli are then posited to undergo "second-order" processing in the anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), and posterior parietal cortex. As a result, nociceptive stimuli are consciously perceived, subjected to attentional and cognitive modulation, and transformed into somatic, or "vegetative," responses. The perception and modulation of pain is further affected, or "reappraised," by the emotional context of the stimuli and further individualized by psychological factors that together coalesce in memory formation. Neural structures implicated in this final "third-order" process include the oribitofrontal, perigenual ACC, and anterolateral PFC regions. Brain regions comprising the second and third tiers interact with various descending tracts in the spinal cord, resulting in either inhibitory or facilitatory modulation of incoming nociceptive stimuli in a process termed *descending control*. In this 3-tiered model of the pain matrix, the experience of pain is the consequence of progressively complex and interrelated "orders" of neural activity aptly designated by Garcia-Larrea and Peyron[7] as the "nociceptive,"

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"perceptive-attentional," and "reappraisal-emotional" matrices.

Epidemiology and Neurobiological Links Between Chronic Pain and Mental Health Disorders

Depression. The presence of depressive symptoms are often quantified using self-report questionnaires, and elevated levels suggest the presence of a mood disorder[8,9] (Table 1). However, in epidemiological studies, the presence of common mood disorders, including major depressive disorder, dysthymia, and bipolar disorder, are generally best identified using semi-structured interviews. The estimated current or 12-month prevalence of high levels of depressive symptoms or a mood disorder exceeds 50% in individuals with fibromyalgia,[17-23] temporomandibular joint disorder,[24,25] chronic spinal pain,[26-29] and chronic abdominal pain[30-32] (Table 2). The estimated prevalence of depression exceeds 20% in individuals with arthritis,[23,37,38,47-49] migraine headache,[37-41] and pelvic pain,[42-46] whereas the prevalence is lowest in individuals with neuropathic pain.[33-36] Across all chronic pain groups, the prevalence of major depressive disorder ranges from 2% to 61%,[19,21,23,26-29,37,38,40,42,43,47,49,57,58] the prevalence of dysthymia ranges from 1% to 9%,[21,26-29,37,40,49,57,58] and the prevalence of bipolar disorder ranges from 1% to 21%.[21,22,29,40,49]

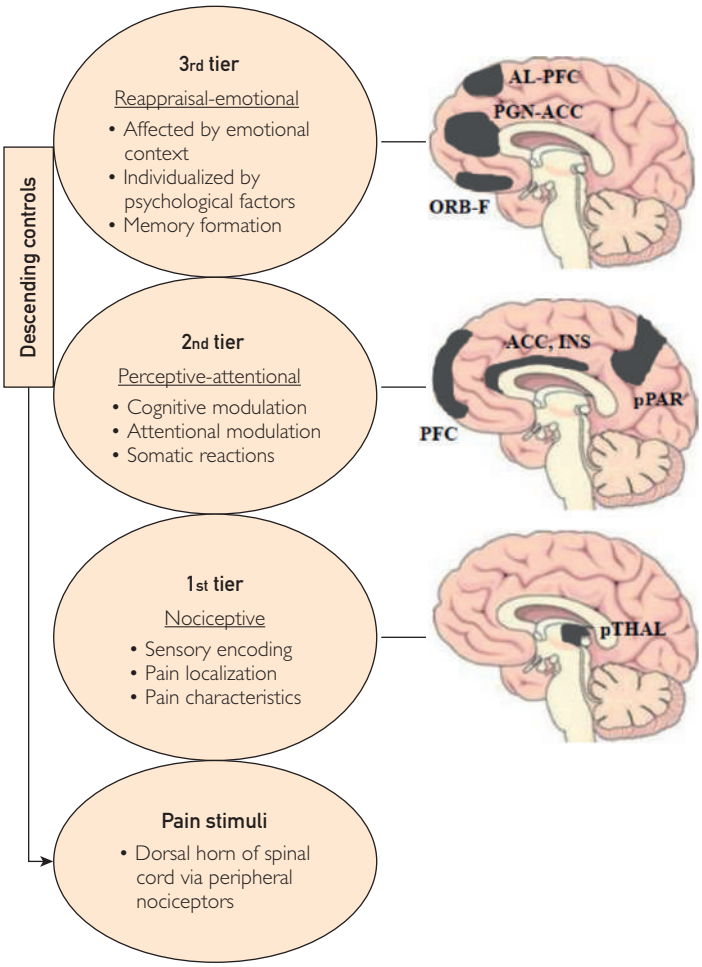

FIGURE 1. Schematic representation of the 3-tiered pain matrix. ACC = anterior cingulate cortex; AL-PFC = anteriolateral prefrontal cortex; INS = insula; ORB-F = orbitofrontal; PFC = prefrontal cortex; PGN-ACC = perigenual anterior cingulate cortex; pPAR = posterior parietal cortex; pTHAL = posterior thalamus.

The frequent co-occurrence of chronic pain and depression reflects the shared risks that exist between these 2 conditions as exemplified in the following 2 examples. First, in a population-based study[59] involving 845 adults, study participants with mild or disabling neck or low back pain were 2.0 to 2.5 times more likely to experience an episode of depression at 6- and 12-month follow-up than individuals without spinal pain. Conversely, pain-free individuals with severely elevated levels of depressive symptoms (n=790) were 4 times more likely to develop neck or low back pain at 6- and 12-months follow-up than individuals with low levels of depressive symptoms.[60] More specifically, the rate of neck or back pain increased by 4% for every 1-point increase in the severity of depressive symptoms.[60] Second, in a population-based study[61] involving 118,533 individuals, study participants with "chronic back pain" were 6 times more likely to be depressed than pain-free participants. Conversely, pain-free individuals subsequently diagnosed with depression were approximately 3 times more likely to develop chronic back pain than individuals without depression.[62] In addition, the rate of depression increased with greater pain severity.[61] Collectively, these 2 examples suggest that a bidirectional relationship exists between chronic spinal pain and depression, in which spinal pain is a risk factor for depression and depression is a risk factor for spinal pain. These studies also suggest that the bidirectional relationship is affected, in part, by

TABLE 1. Sensitivities and Specificities of Screening Questionnaire Cutoff Scores for Depression, Anxiety, and Substance Use Disorders

Variable	Cutoff score	Sensitivity (%)	Specificity (%)
Depression			
Beck Depression Inventory[8]	15	77	61
Hamilton Rating Scale for Depression[8]	17	81	65
Center for Epidemiologic Studies Depression Scale[9]	27	82	68
Patient Health Questionnaire Depression[8] (PHQ-9)	10	79	60
Anxiety			
Hospital Anxiety and Depression Scale—Anxiety[10,11]	8	88	81
Beck Anxiety Inventory[12]	5.5	76	77
Patient Health Questionnaire Anxiety[13] (Generalized Anxiety Disorder-7)	10	89	82
Substance use disorders			
Alcohol Use Disorders Identification Test[14]	8	88	77
CAGE questionnaire for alcohol misuse[15]	2	71	90
Drug Abuse Screening Test[16]	2	85	78
Current Opioid Misuse Measure[16]	10	84	82

a dose-response phenomenon between pain intensity and the severity of depressive symptoms.

Functional imaging studies support the bidirectional relationship between pain and depression. Various chronic pain conditions, including fibromyalgia, abdominal pain, and low back pain, have been associated with functional imaging alterations in brain regions responsible for processing emotional stimuli, including the ACC and PFC.[63-66] Conversely, in adults with depression, emotional processing in the insula has been reported to shift toward an insular region associated with processing pain stimuli in healthy individuals.[67,68]

Anxiety. *Anxiety* is a term used to describe excessive fear or worry, and individuals with high levels of anxiety can be identified using various screening questionnaires[10-13] (Table 1). Anxiety disorders are a group of conditions sharing features of excessive fear and anticipation of future threat; examples of commonly occurring anxiety disorders include generalized anxiety disorder (GAD), panic disorder, agoraphobia, and posttraumatic stress disorder (PTSD). The estimated current or 12-month prevalence of high levels of anxiety or the presence of an anxiety disorder exceeds 50% in individuals with temporomandibular joint disorder,[50-52] fibromyalgia,[18-21,23] and chronic abdominal pain,[30,32] whereas the prevalence exceeds 35% to 40% in individuals with migraine headache,[38,39,41] pelvic pain,[42,53] and arthritis[23,37,38,48,49] (Table 2). The prevalence of anxiety was lowest in individuals diagnosed with spinal pain[26-29,38] or neuropathic pain.[34-36] Across all chronic pain groups, the prevalence of GAD ranges from 1% to 10%[19,21,23,26,28,29,37,38,49,58] and the prevalence of panic disorder ranges from 1% to 28%.[19,23,26-29,37,38,49,58] Similarly, the prevalence of agoraphobia across all pain groups ranges from 1% to 8%[26,28,29,37,49,58] and the prevalence of PTSD ranges from 1% to 23%.[21,23,26,28,29,37,49]

Similar to depression, a bidirectional relationship exists between chronic pain and anxiety. This is particularly evident in individuals with migraine headache. In population-based studies, individuals with migraine are 2 to 3 times more likely to be diagnosed with GAD, panic disorder, agoraphobia, or PTSD than individuals without migraine.[40] Conversely, individuals with anxiety disorders are twice as likely to develop migraine headache than individuals without anxiety disorders.[69] The observations from functional neuroimaging studies support this bidirectional relationship, suggesting that overlapping brain areas (thalamus, PFC, and ACC) are activated by both chronic pain and anxiety.[70-72]

Substance Abuse. Opioid use disorder (OUD) is a major threat to US public health.[73,74] In adults with chronic pain receiving long-term opioid therapy, the estimated current prevalence of OUD in 2 systematic reviews[75,76] ranges from 1% to 43%. In these 2 reviews,[75,76] the current prevalence of OUD in studies assessed to be of high methodological quality ranges from 1% to 23%. Important substance use—related risk factors for current and lifetime OUD in adults with chronic pain receiving long-term opioid therapy include a history of opioid abuse, history of substance abuse treatment, and history of illicit drug use including cannabis.[77-80] Despite the importance of OUD, individuals with chronic pain are at risk of other substance use disorders (SUDs), which can be identified using various screening questionnaires[14-16] (Table 1). The estimated current or 12-month prevalence of alcohol and other nonopioid SUDs is highest in adults with fibromyalgia,[19,20,23] chronic spinal pain,[26-29] or

arthritis[23,49] and lowest in individuals with neuropathic pain[54-56] or migraine headache[40] (Table 2). Across all pain groups, the prevalence of alcohol abuse or dependence ranges from 2% to 22%[19,23,26-29,40,49,55] and the combined prevalence of drug abuse, drug dependence, or any SUD (OUD not specified) ranges from 1% to 25%.[19,20,27-29,40,49,54,56]

Akin to depression and anxiety, a bidirectional relationship exists between chronic pain and SUD. The estimated prevalence of chronic pain in individuals with SUD ranges from 27% to 87%.[81-83] In population-based studies, individuals with chronic pain are approximately 2 to 3 times more likely to develop an SUD than individuals without chronic pain,[84] and individuals with SUD are approximately 1.5 times more likely to develop chronic pain.[85]

Functional imaging and preclinical studies support the bidirectional relationship between chronic pain and SUD. For example, the medial PFC is involved in processing pain stimuli. In addition, the medial PFC and the nucleus accumbens are key components of the mesocorticolimbic circuitry, which is the principal reward system of the brain and plays a key role in the neurobiology of SUD.[86,87] In response to nociceptive stimuli, connectivity between the medial PFC and the nucleus accumbens may potentiate the development of chronic pain.[88,89] In addition to shared neural circuits, preclinical studies suggest that the transition from acute to chronic pain and opioid tolerance share common cellular mechanisms.[90]

TABLE 2. Estimated Prevalence of Depression, Anxiety, and Substance Use Disorders in Commonly Occurring Chronic Pain Conditions

Variable	Prevalence (%)
Depression	
Spinal pain (lumbar, thoracic, or neck)[26-29]	2-56
Neuropathic pain[33-36]	4-12
Fibromyalgia[17-23]	21-83
Migraine headache[37-41]	17-28
Temporomandibular joint disorder[24,25]	16-65
Pelvic pain[42-46]	19-22
Abdominal pain[30-32]	9-54
Arthritis[23,37,38,47-49]	3-39
Anxiety	
Spinal pain (lumbar, thoracic, or neck)[26-29,38]	1-26
Neuropathic pain[34-36]	5-27
Fibromyalgia[18-21,23]	18-60
Migraine headache[38,39,41]	2-45
Temporomandibular joint disorder[50-52]	15-65
Pelvic pain[42,53]	12-41
Abdominal pain[30,32]	21-51
Arthritis[23,37,38,48,49]	1-35
Substance use disorder	
Spinal pain (lumbar, thoracic, or neck)[26-29]	4-14
Neuropathic pain[54-56]	1-9
Fibromyalgia[19,20,23]	1-25
Migraine headache[40]	1-6
Arthritis[23,49]	1-12

Current and 12-mo prevalence rates grouped together.

Other Mental Health Conditions

Suicide. In 2013, the rate of suicide in the United States was 12.6 per 100,000 person-years, which is equivalent to 113 suicides daily.[91] For the same time point, suicide was the 10th leading cause of death overall (n=41,419) and the 2nd leading cause of death among all people 15 to 34 years of age (n=11,226).[91] In a large study involving approximately 260,00 veterans, the rate of suicide among veterans with mild to severe pain ranged from 45 to 81 per 100,00 person-years.[92,93] Suicidal ideation is a frequently occurring symptom in 28% to 48% of treatment-seeking adults with chronic pain.[94-96] In addition to suicide risk factors found in the general population, important pain-related risk factors include high levels of comorbid mental health problems, high pain intensity, analgesic medication use, and pain-related psychological factors[92,97] (Figure 2). Diagnostic groups that may be at increased risk include individuals with chronic back pain, migraine headache, and fibromyalgia.[92] Because of high rates of suicidality, clinicians should regularly ask patients with chronic pain about suicidal thoughts and behaviors and be prepared to implement the appropriate level of clinical care[92] (Figure 2).

Sexual Violence and Abuse. Approximately 1 in 5 women (18%) and 1 in 71 men (1%) in the United States have been raped.[98] In addition, an estimated 13% of women and 6% of men have experienced sexual coercion and 27% of women and 12% of men have experienced unwanted sexual contact.[98] Survivors of sexual violence and abuse are at risk for developing chronic pain and other health problems (eg, irritable bowel syndrome and

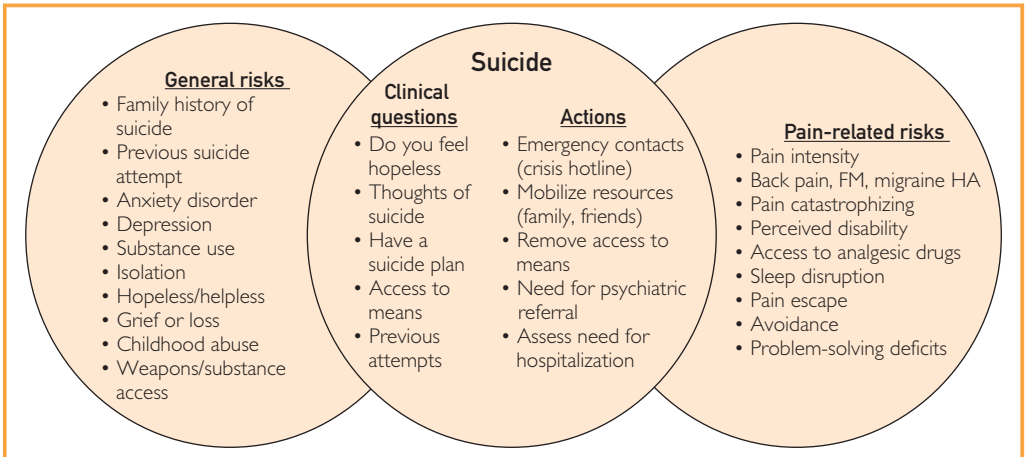

FIGURE 2. Schematic representation of the risks factors, clinical questions, and actions related to the assessment and management of suicide in adults with chronic pain. FM = fibromyalgia; HA = headache. Adapted from *Curr Pain Headache Rep*[92] with permission.

psychogenic seizures).[99,100] More specifically, individuals with a history of rape or sexual abuse are approximately 2.5 to 3.5 times more likely to develop fibromyalgia, chronic musculoskeletal pain, or chronic pelvic pain.[100] Although the neural mechanisms linking the associations between sexual violence and chronic pain have not been fully elucidated, targets of ongoing research include genetic and epigenetic factors, stress-related disruption of the hypothalamic-pituitary axis, and immune dysfunction.[101] In clinical practice, screening patients for a history of sexual violence and abuse is critically important because most survivors do not volunteer this information to health care professionals.[102]

Personality Characteristics and Disorders. The area of personality characteristics and personality disorders (PDs) is a broad field of study. Consequently, the ensuing discussion will be limited to the personality characteristic of neuroticism and commonly occurring PDs. *Neuroticism* can generally be defined as the propensity to experience negative emotions (eg, fear, worry, frustration, jealousy, and anger). Higher levels of neuroticism in individuals with chronic pain have been associated with increased reactivity to pain,[103] greater disability and lower quality of life,[104] use of passive coping strategies,[105] greater pain-related suffering,[106] and greater pain-related anxiety.[107]

Personality disorder is generally used to describe a "pervasive disturbance in how an individual experiences and thinks about the self, others, and the world, manifested in maladaptive [and inflexible] patterns of cognition…emotional expression, and behavior."[108,p722] In the general population, the prevalence of PD ranges from 4% to 6%, but the prevalence in individuals in the health care setting ranges from 25% to 50%.[108] In individuals with chronic pain, the prevalence of borderline PD (impulsivity and instability in relationships, self-image, affect) ranges from 1% to 28%; that of narcissistic PD (grandiosity, need for admiration, and lack of empathy) ranges from 2% to 23%; that of histrionic PD (excessive emotionality and attention seeking) ranges from 6% to 23%; that of dependent PD (submissive and excessive care needs) ranges from 2% to 17%; and that of obsessive-compulsive PD (excessive orderliness, perfectionism, and control) ranges from 7% to 16%.[21,27,109]

When a patient with a difficult personality characteristic or PD is encountered in clinical practice, referral to a mental health professional should be considered for a diagnostic assessment and development of a treatment plan. In general, the mainstay of treatment is psychotherapy including cognitive-behavioral therapy (CBT) (eg, for the treatment of

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obsessive-compulsive PD) and dialectical behavioral therapy (eg, for the treatment of borderline PD).[110]

Cigarette Smoking. The prevalence of smoking in the general population has declined to 19.3% over the past decade.[111] However, the prevalence of smoking in patients seeking treatment for chronic pain was 24.2% in 2000 and 28.3% in 2010.[112] This is important because smoking remains the single greatest preventable cause of death in the United States[113] The increased prevalence of smoking may be due in part to clinical characteristics unique to adults with chronic pain. For example, smokers with chronic pain report greater pain severity partly due to greater levels of depression and greater levels of functional impairment.[114,115] In addition, smokers with chronic pain are more likely to use opioids and consume higher doses of opioids because of the use of greater quantities by men.[116,117] These clinical observations related to opioid use are supported by preclinical studies suggesting that the antinociceptive effects of nicotine and morphine are linked, and morphine-related antinociception is affected by activation of centrally located nicotinic acetylcholine receptors.[118] Smokers with chronic pain also report that smoking is an important coping strategy for pain and distress, which could partly explain why it is difficult for these individuals to quit smoking.[115,119] Thus, this patient group may require specifically tailored smoking cessation interventions that incorporate behavioral treatments of chronic pain.[120]

Behavioral Treatment

Although pain is an individualized and internal experience, clinically observable signs and symptoms of pain are complex and multifaceted forms of behavior. When viewed from the biopsychosocial perspective, the clinical manifestations of pain can be conceptualized as the interrelationship between biological factors, psychological processes, and social influences. Within the broader biopsychosocial model, several behavioral models, particularly the fear-avoidance model, have been developed to explain how psychological factors affect the temporal course of pain and provide the framework for a range of behavioral treatments.

Fear-Avoidance Model of Pain. The fear-avoidance model is one of the most widely recognized theoretical constructs used to explain how psychological processes mediate the transition of episodic acute pain to chronic pain with associated disability[121] (Figure 3). The underpinnings of this model are key psychological processes, including emotions, cognitions, attention, and behaviors, that coalesce to form fear-avoidance beliefs and behaviors, which, in turn, become the key drivers of pain-related disability.[122] In the fear-avoidance model, the primary factor is the emotion of fear, which develops in response to negative cognitions exaggerating the potential threat of pain, including an exaggerated negative interpretation of pain-related health information. This exaggerated set of pain-related cognitions is termed *pain catastrophizing*, which is often manifested clinically as the anticipation of the worst possible outcome in association with a negative affect (eg, depressive symptoms and anxiety). Fear serves to focus attention on pain and associated symptoms, leading to a state of hypervigilance and subsequent avoidance of activities (occupational and social) and body

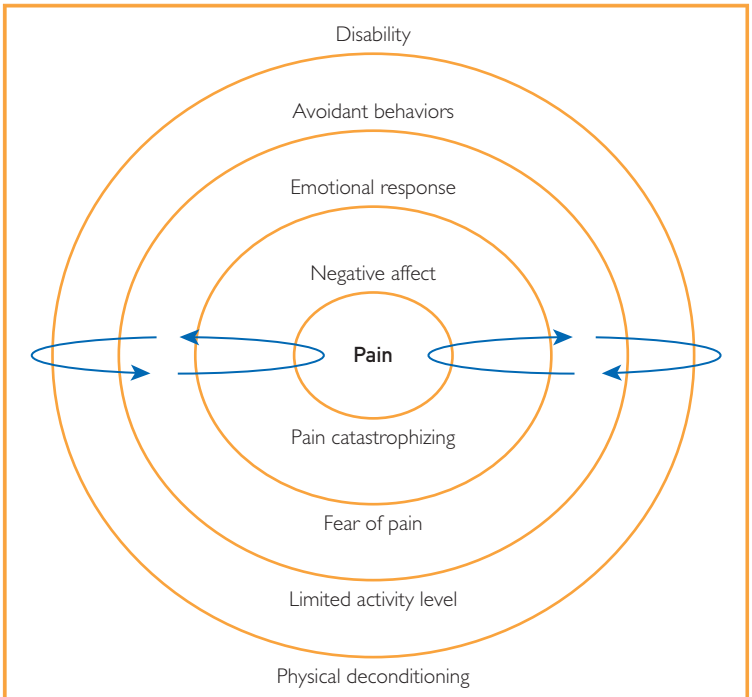

FIGURE 3. Schematic representation of the fear-avoidance model of chronic pain.

movements (walking and physical therapy modalities) perceived to potentially worsen pain.[122] These psychological processes and resultant avoidant beliefs and behaviors do not necessarily evolve in a sequential pattern; rather, these interrelated phenomena occur simultaneously and set into play a self-perpetuating and deleterious cycle culminating in a state of physical disuse and disability.

In accordance with the 3-tiered model of the pain matrix, functional imaging research supports the theoretical constructs of the fear-avoidance model.[7] For instance, the anticipation of pain has been associated with activation of brain regions comprising the "perceptive-attentional" and "reappraisal-emotional" tiers in individuals with chronic pain with high levels of pain catastrophizing, fear-avoidance beliefs, and negative affect.[123]

Cognitive-Behavioral Therapy. Cognitive-behavioral therapy is widely used to treat pain-related functional disabilities. In general, CBT is a skills-based intervention that emphasizes identifying and changing maladaptive cognitions, emotions, and behaviors. Brief (eg, 1-2 sessions) or longer-term (eg, successive sessions during a 2- to 4-month time period) treatment can be delivered in either individual or group-based sessions. When applied within the fear-avoidance model, CBT targets the deleterious effects of pain catastrophizing and avoidant beliefs (eg, examples of maladaptive cognitions), fear (eg, example of a maladaptive emotion), and avoidant behaviors (eg, a set of maladaptive behaviors) with the goal of developing and adopting coping strategies aimed at enhancing an active problem-solving approach to successfully confront and self-manage health-related threats posed by pain. Although CBT therapists use various techniques, several components are considered "core elements" of this approach, including (1) graded homework assignments (eg, typically using a workbook style manual); (2) cognitive restructuring (eg, teaching how to challenge maladaptive cognitions); (3) relaxation training (eg, diaphragmatic breathing, progressive muscle relaxation, and imagery); (4) time-based activity pacing (eg, activity pace based on time rather than task accomplishment); and (5) extinguishing *pain behaviors* (defined as verbal and nonverbal expressions of pain).[124] Other techniques include distraction (eg, actively diverting attention away from pain), reinterpretation (eg, changing thoughts about pain), dissociation (eg, separating feelings of pain from other sensations), coping self-statements (eg, affirming self-statements), and emotional disclosure (eg, expressive writing).[125]

Cognitive-behavioral therapy yields long-term improvements in pain intensity, disability, quality of life, pain-related coping, depressed mood, and health care–seeking behaviors.[126-128] The favorable effects of CBT on clinical pain outcomes is supported by functional imaging research. In a cohort of adults with fibromyalgia, functional imaging after CBT exhibited increased activation of brain regions associated with executive cognitive control, suggesting that CBT enhances access to cognitive regions involved in the reappraisal of pain.[129]

Acceptance-Based Therapies. Acceptance-based therapies emphasize that inflexible beliefs about chronic pain (eg, chronic pain is curable and expectation for total pain relief) halt the pursuit of highly regarded life values, resulting in a state of despondency and disability.[130] Two widely used acceptance-based approaches for chronic pain include acceptance and commitment therapy and mindfulness-based stress reduction. Acceptance and commitment therapy promotes awareness and nonjudgmental acceptance of chronic pain while identifying and committing to pursue goals supporting highly regarded life values. An important outcome of therapy is enhanced functioning through the contextual acceptance of pain. Acceptance and commitment therapy differs from CBT, which focuses on recognizing, evaluating, and making changes to unhelpful pain-related thoughts, emotions, and behaviors. Mindfulness-based stress reduction uses mindfulness meditation to develop intentional and nonjudgmental awareness of the present moment. After 6 to 8 weeks of mentored training, individuals develop the ability to sustain an open and accepting state of consciousness in which self-regulated attention is maintained on momentary experience.

The effects of acceptance-based therapies on clinical outcomes of chronic pain have

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been mixed. For example, in 2 systematic reviews[131,132] that included trials of acceptance and commitment therapy and mindfulness-based stress reduction, small to moderate effects were observed for pain, depression, anxiety, quality of life, and physical well-being. However, in 2 systematic reviews that included only mindfulness-based interventions, small effects on pain, depression, and anxiety were found at 2- to 6-months follow-up,[133] but no significant effects were observed when the meta-analyses were restricted to studies incorporating active control groups.[134] Functional imaging studies suggest that mindfulness meditation reduces activation of the primary somatosensory cortex and increases activity in brain regions implicated in the cognitive regulation and reappraisal of pain.[135]

Multidisciplinary Pain Rehabilitation. *Multidisciplinary pain rehabilitation* (MPR), otherwise termed *interdisciplinary pain rehabilitation*, refers to an integrated approach to treat chronic pain by a team of health care professionals who share common treatment objectives. Typically, treatment is delivered within the broader context of the biopsychosocial model, and group-based CBT is used to target pain-related impairments in physical and emotional functioning. The goals of treatment include improvements in functioning, which are achieved through the integrated delivery of group-based treatments (eg, group-based CBT, physical therapy, and occupational therapy) provided by psychologists, physicians, physical and occupational therapists, nurses, vocational specialists, and pharmacists.[136] The clinical milieu of an MPR program also provides an optimal environment to initiate and complete medically directed opioid tapering, which is being increasingly recognized as an unmet need for many patients.[137] Most MPR programs are delivered in the outpatient setting, and in highly intensive programs, treatment is provided 6 to 8 hours daily for 15 consecutive working days. In less intensive programs, treatment is provided 2 to 4 hours daily, 2 to 3 times weekly for a 4- to 6-week period.

Multidisciplinary pain rehabilitation has been associated with significant improvements in pain intensity, functional disability, and sustained employment[138] and reductions in a broad range of medical costs.[139] Aerobic and strengthening exercises during the course of MPR have been associated with significant improvements in several key physiological measures of strength, aerobic fitness, and pain perception.[140-142] Opioid tapering during MPR has been associated with significant reductions in medication costs[143,144] without adversely affecting immediate or long-term treatment outcomes.[145-147]

Psychopharmacological Treatment

Pain often complicates the pharmacological treatment of mental health disorders; conversely, mental health disorders can complicate the pharmacological treatment of pain. The ensuing content will be limited to medications with dual analgesic and psychotropic properties including serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and anticonvulsant medications.

Serotonin-Norepinephrine Reuptake Inhibitors. Serotonin-norepinephrine reuptake inhibitors are selective for both serotonin and norepinephrine; the selective reuptake of norepinephrine is believed to be responsible for the analgesic effects of SNRIs. The most widely used SNRIs are duloxetine, venlafaxine, and milnacipran (Table 3). The active metabolite of venlafaxine (desvenlafaxine) and the levo enantiomer of milnacipran (levomilnacipran) are commercially available in the United States as antidepressant medications. Proposed mechanisms of action include norepinephrine-mediated activation of descending inhibitory pathways projecting from the supraspinal centers and terminating in the dorsal horn of the spinal cord. Another possible mechanism includes improvement of depressive symptoms. For example, secondary analyses of 4 randomized trials of duloxetine for fibromyalgia revealed that 69% of pain improvement was attributed to the direct analgesic effects of the drug whereas 31% of pain improvement was attributed to reductions in depressive symptoms.[152] In addition to fibromyalgia,[149,153] neuropathic pain,[150] and musculoskeletal pain,[148,154] SNRIs are effective for the treatment of major depressive disorder[155] and anxiety disorders[156] including GAD and panic disorder. As specifically exemplified in the treatment of depression,[157] the effects of antidepressant medications on mental health

TABLE 3. Summary of Medications With Dual Analgesic and Mental Health Effects[a]

Medication	FDA indication		NNT (95% CI)	Dosing
	Pain	Mental health	Pain	
SNRI				
Duloxetine	C-MSP DPN Fibromyalgia	GAD MDD	C-MSP: 6.0 (4.0-11.0)[148] FM: 8.2 (6.0-13.2)[149] NP[b]: 6.4 (5.2-8.4)[150]	60-120 mg/d, single or 2 divided doses
Venlafaxine	—	GAD MDD Panic disorder Social phobia	NP[b]: 6.4 (5.2-8.4)[150]	150-225 mg/d, single dose extended release formulation
Milnacipran	Fibromyalgia	—	FM: 11.0 (8.3-16.3)[149]	100-200 mg/d, 2 divided doses
TCA				
Amitriptyline	—	Depression	NP[b]: 3.6 (3.0-4.4)[150] FM: 3.5 (2.7-5.0)[149]	50-150 mg/d, single dose
Nortriptyline	—	Depression	NP[b]: 3.6 (3.0-4.4)[150]	50-100 mg/d, single dose
Anticonvulsant				
Pregabalin	DPN Fibromyalgia SCI pain PHN	—	NP[b]: 7.7 (6.5-9.4)[150] FM: 6.6 (5.0-9.9)[151]	150-600 mg/d, 2 divided doses
Gabapentin	PHN	—	NP[b]: 7.2 (5.9-9.1)[150] FM: 5.0 (2.8-21.7)[151]	1800-3600 mg/d, 3 divided doses

[a]C-MSP = chronic musculoskeletal pain; DPN = diabetic peripheral neuropathy; FDA = Food and Drug Administration; FM = fibromyalgia; GAD = generalized anxiety disorder; MDD = major depressive disorder; NNT = number needed to treat; NP = neuropathic pain; PHN = postherpetic neuralgia; SCI = spinal cord injury; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

[b]Neuropathic pain diagnostic groups and/or drug class combined to yield a pooled NNT value.

outcomes can be adversely affected by pain, but concurrent behavioral treatment may mitigate these adverse effects.[158]

In individuals with major depressive disorder, duloxetine has been associated with reductions in activation of the ACC and right PFC[159] and milnacipran has been associated with increased activity in brain regions linked to the descending inhibitory pain pathways in adults with fibromyalgia.[160]

Tricyclic Antidepressants. Tricyclic antidepressants were one of the first drug classes used to treat depression and the first antidepressants used to treat pain. Similar to SNRIs, the proposed analgesic effects of TCAs are mediated by activation of descending inhibitory pathways, but other possible mechanisms include blockade of voltage-gated sodium channels,[161] inhibition of *N*-methyl-D-aspartate receptors,[162] and interaction with opioid receptors.[163] The major adverse effects of TCAs are related to blockade of muscarinic (eg, urinary retention, constipation tachycardia, blurred vision, and delirium), histamine (H_1) (eg, sedation and weight gain), and α_1-adrenergic (eg, orthostatic hypotension) receptors. Type 1 antiarrhythmic properties are due to sodium channel blockade, which could, in part, account for the increased rate of sudden cardiac death and myocardial infarction.[164,165] Although neuropathic pain is the most widely recognized pain indication for TCA use,[150] these medications, particularly nortriptyline and amitriptyline, also have proven efficacy for fibromyalgia[149,153] and chronic low back pain.[166] In the present era, TCAs are not generally considered to be first-line treatment agents for mental health disorders because of the availability of other medications with more favorable adverse effect profiles. Amitriptyline has been associated with reduced activation of the ACC and posterior parietal region in adults with chronic abdominal pain.[167]

Anticonvulsants. Numerous anticonvulsants, particularly gabapentin and pregabalin, are used to treat a broad range of pain and mental health disorders. Gabapentin and pregabalin

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are structural analogues of the neurotransmitter γ-aminobutyric acid, but these drugs bind to the α_2-δ subunit of voltage-gated calcium channels. Gabapentin and pregabalin have exhibited efficacy for fibromyalgia[151] and several neuropathic pain conditions including postherpetic neuralgia, diabetic peripheral neuropathy, and neuropathic pain associated with spinal cord injury.[150] Although pregabalin has exhibited efficacy in the treatment of GAD,[168] the drug does not have Food and Drug Administration approval for this indication. Gabapentin may have mild anxiolytic effects, but numerous clinical trials have failed to exhibit clear efficacy for anxiety disorders.[169] In adults with fibromyalgia, pregabalin has been associated with reductions in posterior insular activity.[170]

Serious Adverse Effects. Serotonin syndrome is a medical emergency characterized by the clinical triad of autonomic and neuromuscular hyperactivity with associated delirium.[171] The syndrome is typically associated with selective serotonin reuptake inhibitors, but it has been reported with SNRIs and tramadol use.[172] Laboratory findings include metabolic acidosis and abnormalities consistent with rhabomyolysis, renal failure, and coagulopathy. Although no single symptom or laboratory test is pathognomonic, a clinically oriented diagnostic algorithm has been developed with a sensitivity and specificity of 85% and 97%, respectively (Figure 4).[171]

Serotonin withdrawal syndrome, otherwise referred to as antidepressant discontinuation syndrome, is predominately characterized by sudden onset of dizziness, headache, nausea, fatigue, vomiting, ataxia, and paresthesias after abrupt discontinuation of antidepressant medications with serotonergic activity.[173] Proposed pathophysiological mechanisms include the rapid decline in serotonin availability, but alterations in noradrenergic and cholinergic activity could also be contributing factors. Symptoms may occur with use of SNRIs and TCAs. Regardless of the medication class, drugs with short half-lives are more likely to result in discontinuation symptoms.

The use of duloxetine, venlafaxine, and TCAs by children and adolescents, but not adults, has been associated with increased rates of suicidality and aggressive behavior.[174]

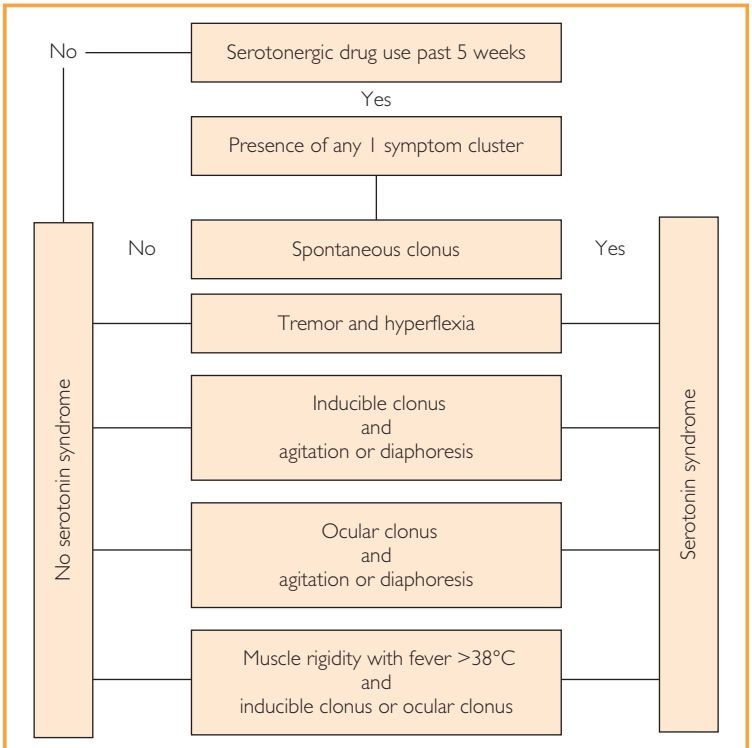

FIGURE 4. Diagnostic algorithm for serotonin syndrome (sensitivity, 85%; specificity, 97%). Adapted from *N Engl J Med*[171] with permission.

In adults, new treatment episodes of gabapentin, but not pregabalin, have been associated with increased rates of attempted suicide, completed suicide, and violent death.[175]

CONCLUSION

Depression, anxiety, and SUDs are highly prevalent in chronic pain conditions frequently encountered in daily clinical practice. Consistent with the governing principles of the pain matrix, functional imaging studies suggest that shared neural mechanisms contribute to the bidirectional relationship between chronic pain and mental health disorders. Although self-report screening questionnaires can facilitate the identification of mental health problems, patients should be routinely questioned about the presence of suicidality and history of sexual violence. Behavioral interventions are associated with sustained improvements in a broad range of functional parameters, and use of analgesic medications with efficacy for both pain and mental health disorders

should be considered first-line agents in patients with chronic pain.

Abbreviations and Acronyms: **ACC** = anterior cingulate cortex; **CBT** = cognitive-behavioral therapy; **GAD** = generalized anxiety disorder; **MPR** = multidisciplinary pain rehabilitation; **PD** = personality disorder; **PFC** = prefrontal cortex; **PTSD** = posttraumatic stress disorder; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **TCA** = tricyclic antidepressant

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