

Chronic pain and depression: Understanding 2 culprits in common



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Does a shared pathophysiology hold the key to managing these conditions when they coexist?

Any discussion of the relationship between major depressive disorder (MDD) and chronic pain encounters an obstacle immediately: Neither has a singular pathophysiology. Furthermore, MDD and, to a significant extent, chronic pain are defined more by their symptoms than by a presumed etiology and pathogenesis.

Why does this matter to a busy clinician?

Explicitly or implicitly, we often align our treatment approaches with what we assume is the underlying pathophysiology of the conditions we are addressing. An overview of shared pathophysiology of chronic pain conditions and MDD therefore can be useful in practice.

What is chronic pain? Defined as “pain that persists past the healing phase following an injury,”¹ chronic pain often is subdivided into 4 types^{2,3}:

- *nociceptive* (caused by a lesion or potential tissue damage)
- *inflammatory*
- *neuropathic* (spontaneous pain or hypersensitivity to pain related to neurologic illness or injury)
- *functional* (hypersensitivity to pain due to abnormal central processing of a normal input).

Disclosures

Dr. Maletic has served as a consultant to FORUM Pharmaceuticals; Eli Lilly and Company; Lundbeck; Merck & Co.; Otsuka; Pamlab, Inc.; Sunovion Pharmaceuticals; Takeda Pharmaceutical; and Teva Pharmaceuticals. He has served on the promotional speakers' bureau of Eli Lilly and Company; Lundbeck; Merck & Co.; Sunovion Pharmaceuticals; Otsuka; Pamlab, Inc.; Takeda Pharmaceutical; and Teva Pharmaceuticals.

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Although fibromyalgia often is categorized as a dysfunctional pain syndrome, persons who suffer from it, much like those who suffer neuropathic pain, commonly report *hyperalgesia* (augmented sensitivity to painful stimuli), *allodynia* (abnormal pain response to non-noxious stimuli), and *paresthesias*. These shared clinical features of fibromyalgia and neuropathic pain are consistent with central sensitization, which suggests overlapping pathophysiology.⁴

Comorbidity between depression and pain is common. A 30% to 60% co-occurrence rate of MDD and chronic pain has been reported.⁵ Some subtypes of chronic pain, such as fibromyalgia, are so commonly comorbid with psychiatric conditions that they have spawned a scientific debate as to whether the conditions are most parsimoniously considered (1) separate illnesses with high comorbidity or (2) different symptomatic manifestations of a single underlying condition.⁶ Moreover, cumulative evidence suggests that chronic pain and depression do not just co-occur; each one facilitates development of the other, such that chronic pain is a strong predictor of subsequent onset of MDD, and vice versa.

When pain and depression are comorbid, they also tend to make treatment of each condition more difficult. For example, pain presents (1) a major obstacle to achieving remission when treating depression^{7,8} and (2) significant risk of relapse.⁹ A 3-year longitudinal study showed that painful symptoms substantially reduced the chance of recovery in a group of older depressed patients ($n = 327$). A substantially greater percentage of patients with MDD alone attained recovery (47%), compared with only 9% in whom MDD and painful symptoms were comorbid.¹⁰ Furthermore, a higher level of pain can delay remission when treating MDD,¹¹ thus reducing the likelihood of an optimal outcome.¹²

Understanding shared processes. Recent developments in neuroscience and psychoimmunology point to the fact that comorbid pain and depression might be driven by overlapping pathophysiological processes in the brain and body. In the 2 parts of

this article, we (1) review scientific understanding of these shared processes and (2) demonstrate how recent advances in the epidemiology, phenomenology, and etiology of chronic pain and MDD provide important clues for more effective diagnosis (Part 1) and treatment (Part 2, March 2016)—and, therefore, better outcomes. Our focus is primarily on the relationship between MDD and the best-studied comorbid chronic pain conditions: fibromyalgia, neuropathic pain, chronic back pain, and rheumatoid arthritis.

The societal burden of chronic pain conditions is enormous

A recent epidemiological study¹³ projected that as many as 100 million people in the United States—30.7% of the population—suffer some form of chronic pain, including arthritis and joint pain. A World Health Organization survey yielded a similar (and staggering) 37% prevalence of chronic pain in the population of 10 developed countries.¹⁴

Estimates are that various forms of neuropathic pain, including diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, spinal cord injury, and radiculopathy, alone afflict as many as 26 million people worldwide, including approximately 1.5% of the U.S. population.^{15,16}

Chronic low back pain is epidemic. With a projected point prevalence of 30%, the condition is the most common cause of activity limitation among people age <45, and the most frequent reason in the United States for visiting a physician.¹

Functional somatic syndromes, including fibromyalgia and irritable bowel syndrome, impose an astounding strain on health care: These syndromes account for 25% to 50% of all outpatient visits, or approximately 400 million clinic visits annually in the United States.¹⁷

Why should you care about these numbers? The answer is that comorbidity among chronic pain, mood disorders, anxiety disorders, sleep disorders, cognitive impairment, fatigue, and chronic stress presents an enormous clinical challenge because it not only complicates the diag-

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Evidence suggests that chronic pain and depression do not just co-occur: each one facilitates development of the other



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Depression and chronic pain

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Pharmacotherapeutic and non-drug pain interventions might ameliorate sleep problems, low energy, anxiety, depression, and anhedonia

Box

Major depressive disorder, chronic pain, and risk of suicide

Major depressive disorder (MDD) and chronic pain each have a well-established association with suicide attempts and completion. The paucity of research evaluating the effect of MDD–chronic pain comorbidity on the risk of suicide is somewhat astounding. Consistent evidence suggests that people who suffer chronic pain have a 2-fold to 3-fold increase in the risk of suicide compared with healthy controls.³⁵ Other studies have noted 20% lifetime prevalence of suicide attempts among chronic pain patients.³⁵

Should we expect to find a suicide-promoting synergy between MDD and chronic pain at a basic pathophysiological level? Theories based on pathophysiological

understanding of these conditions state that both chronic pain and MDD tend to produce a so-called “reward deficiency syndrome,” while generating sensitivity to stress and maladaptive suppression of dopamine signaling in the principal reward brain areas.³⁶ Some authors emphasize loss of social attachments as an aggravating factor common to chronic pain and MDD³⁶; others point to a combination of physical and psychological pain as a precipitant of suicidal behavior, whereby patients seek relief and escape from incessant anguish.³⁷

Regardless of the origin of this phenomenon, from a clinical standpoint, a high risk of suicide with comorbid MDD and chronic pain demands attention and thorough evaluation.

agnosis of these conditions but also compromises treatment outcomes and imposes severe limitations on daily functioning and quality of life of those afflicted.^{5,17-24}

A complex relationship and a daunting clinical challenge

Chronic pain enhances the risk of MDD by 2-fold to 5-fold. The risk appears to be mediated by the number of pain conditions rather than by the severity of pain.²³ Some authors have noted a kind of dose-response relationship among pain, depression, and anxiety. Among patients who experienced chronic pain that affected 1 body region, the prevalence of generalized anxiety disorder (GAD) and MDD was 30% and 20%, respectively; in patients who experienced pain in ≥ 2 regions, the prevalence of GAD and MDD was elevated to 54% and 32%.²⁵ Moreover, patients with fibromyalgia were 4.3 times more likely than healthy controls to develop MDD at some point in their lives and 4.7 times more likely to develop an anxiety disorder.²⁶

Although women are more likely to suffer from fibromyalgia, the risk for people of either sex of developing subsequent MDD is comparable once the condition has developed.²⁷ Overall, depression and anxiety are among the most common comorbidities of fibromyalgia, with prevalence ranging from 20% to 80% and 13% to 63.8%, respectively.²⁸

High comorbidity between depression and pain also is relevant for patients with neuropathic pain. A survey from Australia reported depression in 34% and anxiety in 25% of patients with neuropathic pain.²⁹ Pain severity tended to be enduring and associated with significantly impaired functioning. A significant percentage of patients suffering from rheumatoid arthritis and systemic lupus erythematosus tend to manifest anxiety and depression (93% to 94%), cognitive impairment (66%), fatigue (40%), and sleep disorders (72%).²²

The relationship between depression and pain appears to be bidirectional. For example, recent studies demonstrate that 30% to 60% of depressed patients also suffer from a painful condition.⁵

The complex history of patients presenting with concomitant complaints of depression, anxiety, chronic pain, sleep disturbance, cognitive impairment, and fatigue present a daunting diagnostic task. Pain tends to be associated with greater fatigue and sleep disturbance, which in turn depletes a patient’s ability to enjoy life and enhances negative affect.^{19,20,30} The take-home message might be to screen all chronic pain patients for MDD, anxiety, and sleep disorders, and vice versa.

Furthermore, comorbidity among chronic pain, MDD, anxiety, and sleep disorders can introduce specific intricacies into our treatment approach. Although, in general, comorbidities tend to have a nega-

tive impact on treatment outcomes, many pharmacotherapeutic and non-drug interventions targeting chronic pain might ameliorate sleep problems, low energy, anxiety, depression, and anhedonia.^{18,20,30-32} On the other hand, we should consider that opioid treatment for chronic pain might represent a risk factor for subsequent depression. It is conceivable that chronic opioid treatment and associated sedation can erode self-efficacy and social relationships, thereby compromising sources of support.^{33,34} It is equally important to keep in mind that, even if we are successful in attaining remission when treating depression and pain, residual pain symptoms might persist, requiring more specific interventions.²⁴

MDD and chronic pain each have, on their own, a well-established association with suicide attempts and completion. Researchers are investigating whether a pathophysiologic suicide-promoting synergy between the 2 disorders exists when they are comorbid (*Box*³⁵⁻³⁷).

Shared genetics and pathophysiology

Several candidate genes have been identified as risk genes for chronic pain, depression, and anxiety. One of those studied the most is 5-HTTLPR, involved in regulating synthesis of serotonin transporter. The short form of this gene has been implicated in a diverse set of conditions, including MDD, anxiety disorders, and substance abuse—and fibromyalgia. Other genes associated with the risk of MDD and pain disorders are ones that code for:

- serotonin 5-HT_{2A} and 5-HT_{1A} receptors
- catechol-O-methyltransferase, an enzyme involved in catecholamine metabolism
- dopamine D₄ receptor
- proinflammatory cytokines interleukin-1 and interleukin-6.⁴

Both monoamines and inflammatory cytokines play a role in modulating γ -aminobutyric acid (GABA) and glutamate neurons, as well as glia cells constituting peripheral pain pathways and central circuits that participate in the pain response and regulation of mood.^{4,17,38}

The ‘pain matrix’

Brain circuitry that is involved in processing pain stimuli—often referred to as the *pain matrix*—shares many structural components with circuitry involved in the stress response and emotional modulation.⁴ Emerging evidence indicates that the pain matrix might not be pain-specific but, instead, a complex aggregate of interconnected brain structures involved in evoking defensive responses to a number of offending stimuli, including pain, threat, danger, loss, and social rejection or isolation.

It is remarkable, in this regard, that imaging studies show that the dorsal anterior cingulate, central to experiencing negative affect in response to physical pain, also mediates distress in response to the “pain” of social exclusion.³⁹ Emerging functional and structural imaging provides evidence of continuous reorganization of prefrontal cortices as a consequence of enduring chronic pain.¹ Of particular interest are findings of (1) a reduction of gray matter in the dorsolateral prefrontal cortex (DLPFC) and (2) functional activation of the medial prefrontal cortex (mPFC), both of which correlate with the duration and experience of chronic back pain.¹ It is tempting to speculate that structural decline of the DLPFC, observed in MDD and chronic pain, is linked to cognitive and executive function deficits, which are readily observed in patients with either disorder—given that DLPFC is a “hub” of the so-called “cognitive-executive functional network.”^{1,4}

Likewise, the mPFC is a key component of the *default mode network* (DMN), a functional network also comprising the posterior cingulate cortex and hippocampus. DMN performs a diverse set of activities, including self-reflection, daydreaming, reminiscing, planning, processing of social information, and creative thinking. Negative neuroplastic changes in the DMN are a common finding in MDD and chronic pain, and might be associated with a tendency toward rumination and catastrophizing—key clinical manifestations of MDD and chronic pain—and linked with pervasive negative affect and sleep disturbance.^{4,32}

Furthermore, functional and structural changes in the amygdala and hippocampus

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Brain circuits that process pain stimuli share structural components with circuits related to emotional modulation



Depression and chronic pain

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Convergent evidence indicates that MDD and chronic pain amplify each other, contributing to treatment resistance in both disorders

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for a figure showing a possible common pathophysiology between MDD and chronic pain

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- Nelson TK, Krahn LE. Treating affective illness in patients with chronic pain. *Current Psychiatry*. 2004;3(5):51-54,59-62,67-68.

have been described in MDD, fibromyalgia, and neuropathic pain.⁴ Dysfunction of these limbic formations may be a contributing factor in the disruption of neuroendocrine, autonomic, and immune function, which could further contribute to aggravated mood and pain symptoms.^{4,17,40}

Consequently, excessive hypothalamic-pituitary-adrenal axis and sympathetic activation, combined with elevation of proinflammatory cytokine production and release, likely plays a role in the pathophysiology of MDD and chronic pain disorders.^{4,17,40} Moreover, at cellular, sub-cellular, and molecular levels, chronic pain and MDD are associated with:

- perturbed neuron-glia relationships
- altered glutamatergic, GABA, glycine, substance-P, opioid, 5-HT, norepinephrine, and dopamine signaling
- dysfunction of intracellular signaling cascades and neurotrophic signaling.^{4,20,30,31,38}

(This article at CurrentPsychiatry.com includes a *Figure* that describes how homeostatic function of prefrontal cortical-limbic circuitry is compromised in MDD and chronic pain—thus disrupting autonomic, neuroendocrine, and neuroimmune regulation.)

Disturbance in monoamine signaling in chronic pain and MDD might give rise to profound anhedonia, cognitive impairment, anxiety, insomnia, sensitiv-

ity to stress, and inadequate functioning of descending pain-regulatory pathways, which primarily use norepinephrine and 5-HT.^{4,9,20,30,31,38} Using pharmacotherapeutic agents that successfully modulate monoamines, therefore, might ameliorate the function of brain networks innervated by neurotransmitter systems involved in the regulation of pain, mood, cognition, stress response, and sleep. Notably, the same monoamines serve as transmitters in descending pain pathways.

In summary, convergent evidence indicates that MDD and chronic pain states amplify each other, thus contributing to treatment resistance in both disorders.

On the bright side, timely and effective treatment of MDD might optimize the chance of remission and minimize the risk of enduring structural brain changes in MDD and chronic pain.^{1,4,31,32} The obverse is also true: Emphasizing the importance of the resolution of painful symptoms in the context of MDD, a study reported a significantly greater remission rate of 36.2% in those who had >50% reduction of pain on a visual analogue scale following treatment with a serotonin-norepinephrine reuptake inhibitor, compared with a 17.8% remission rate in persons who experienced <50% pain reduction on the scale.³

Editors' note: In Part 2 of this article (March 2016), the authors review pharmacotherapeutic and non-drug strategies for managing comorbid chronic pain conditions and MDD.

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Bottom Line

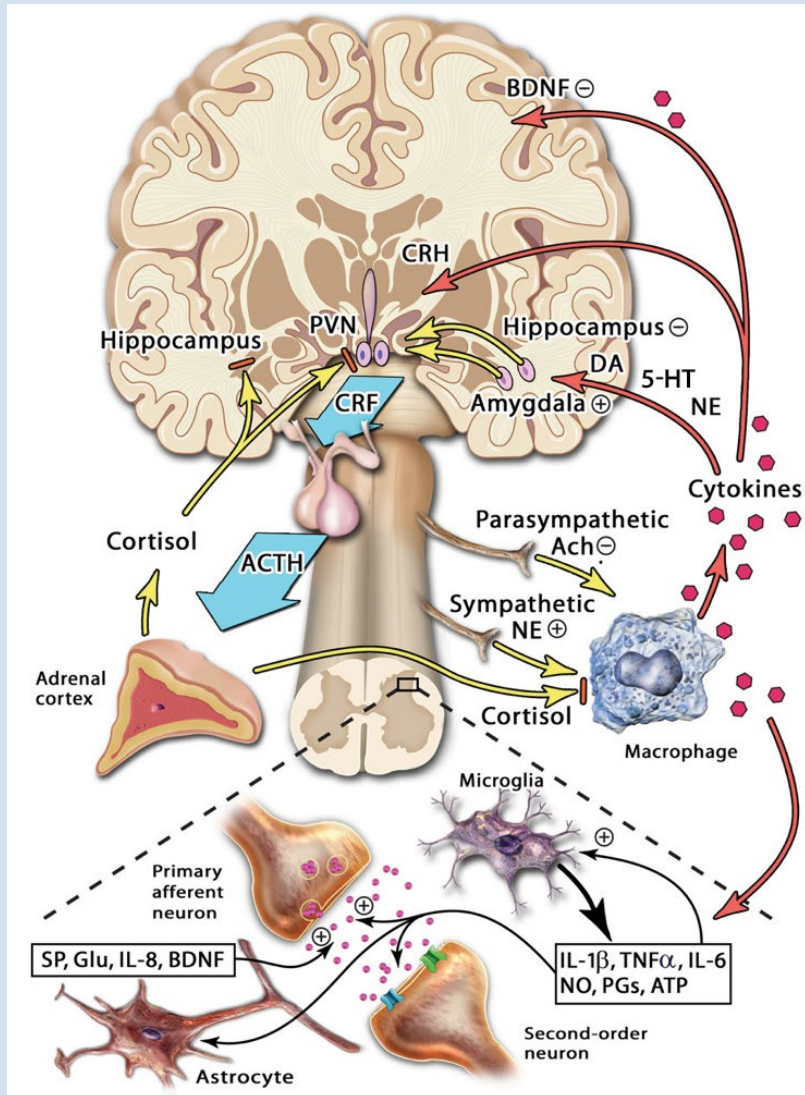
Comorbidity between major depressive disorder (MDD) and pain is common, and the 2 conditions exhibit substantial epidemiological, clinical, and neurobiological overlap. They also appear to facilitate development of each other, and chronic pain is a strong predictor of subsequent onset of MDD (and vice versa). Understanding shared pathophysiology can guide individualized, integrated treatment.



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Major depression and chronic pain disorders—common pathophysiology?



Compromised homeostatic function of prefrontal cortical-limbic circuitry in major depressive disorder (MDD) and chronic pain disrupts autonomic, neuroendocrine, and neuroimmune regulation, shown here.

1. Stress, pain, and depression lead to excessive, untimely release of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and glucocorticoids
2. Sympathetic overactivity, combined with diminished parasympathetic tone, contributes to immune activation and release of proinflammatory cytokines (eg, tumor necrosis factor- α [TNF- α], interleukin-1 [IL-1], and interleukin-6 [IL-6]) from macrophages and other immune cells
3. Inflammatory cytokines further interfere with monoaminergic and neurotrophic signaling. Proinflammatory cytokines also can reduce central glucocorticoid receptor sensitivity, leading to further disruption of (1) the hypothalamic-pituitary-adrenal (HPA) axis and (2) immune system regulation
4. Disturbances of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) signaling in MDD and chronic pain impair the function of descending pain modulatory pathways. Elevated mediators of the inflammatory response, combined with excessive sympathetic tone, can further affect dorsal column processing of pain signals by contributing to activation of microglia and astroglia
5. Activated microglia exchange chemical signals with astrocytes and nociceptive neurons, thus amplifying pain-related transmission of glutamate (Glu), substance P (SP), adenosine triphosphate (ATP), brain-derived neurotrophic factor (BDNF), pro-inflammatory cytokines (IL-1, IL-6, interleukin-8, TNF- α , nitrogen oxide (NO), and prostaglandins (PGs)

Ach: acetylcholine; ATP: adenosine triphosphate; CRF: corticotropin releasing factor; PVN: paraventricular nucleus of hypothalamus

Source: Reference 4