Background: Depression typically affects 5% of the general population, but among patients with chronic pain, 30%-45% experience depression. Studies have shown that the relationship between depression and pain is bidirectional: depression is a positive predictor of the development of chronic pain, and chronic pain increases the risk of developing depression.

Methods: This literature review focuses on the relationship between psychology and pain, covering studies that have investigated the association between depression, pain sensitivity, opioid abuse, and gender differences in pain perception. We conducted a PubMed search pairing the word pain with depression, opioid use, and gender differences.

Results: The relationship between depression and pain is complex, as suggested by numerous studies that propose depression to be a moderator of the relationship between pain severity, physical functioning, and opioid use. Neuroimaging also suggests an anatomic overlap in the pathway of chronic pain and depression. Positive psychological factors, namely hope, pain acceptance, and optimism, affect the adjustment to persistent pain.

Conclusion: The intricate relationship between pain and psychology is evidenced by the clinical overlap in their presentations and the overlap between the anatomic regions in the brain associated with the emotional and sensory features of pain and the areas affected by depression. Studies are beginning to improve our understanding of these two systems, but more studies are needed to elucidate the relationship.

Keywords: Analgesics—opioid, chronic pain, depression, pain, pain perception, psychology
Chronic pain and depression have common comorbidities, including greater levels of stress and sleep disturbance compared to patients without chronic pain or depression.\textsuperscript{16,17} The association between chronic pain and depression can in part be explained by a distorted sensitivity to pain. Although some experimental studies have demonstrated a positive association between negative emotions and greater pain,\textsuperscript{18} there is also evidence that negative emotions can reduce pain sensitivity.\textsuperscript{19,20} Rhudy and Williams have argued that this paradoxical finding can be explained by the type of emotion that is elicited by the degree of arousal or threat.\textsuperscript{21} In this school of thought, greater threats may elicit greater arousal, negative affect, and decreased sensitivity to pain, a phenomenon called stress-induced analgesia.\textsuperscript{22} On the other hand, lesser threats that elicit lower levels of arousal may lead to increased pain sensitivity.\textsuperscript{18} This paradox suggests that the relationship between pain and emotion is more multidimensional and complicated than originally perceived. Studies have shown that the relationship between depression and pain is bidirectional: depression is a positive predictor of the development of chronic pain, and chronic pain increases the risk of developing depression.\textsuperscript{23}

NEUROBIOLOGIC BASIS OF THE RELATIONSHIP BETWEEN DEPRESSION AND PAIN

The dysregulation of noradrenergic and serotonergic pathways is common to both chronic pain and depression.\textsuperscript{24} Hyperactivation in the perigenual anterior cingulate cortex—an area that has been linked to pleasure and receives crucial connections from the dopamine system of the midbrain—has been reported in major depression.\textsuperscript{25} The mesolimbic dopamine system organizes the brain’s response to rewarding vs painful stimuli, thereby driving the system to seek reward-oriented behaviors and avoid those that cause pain or negative feelings such as anxiety or depression.\textsuperscript{2} The mesolimbic dopamine systems and nucleus accumbens are stimulated in response to aversive, painful stimuli as well as to pleasurable stimuli.\textsuperscript{26} This finding suggests that in depression, the mesolimbic system responds to both pain and pleasure. In humans, bilateral activation of the amygdala has been reported to be associated with perceived pain intensity\textsuperscript{27} and has also consistently been reported in depression.\textsuperscript{28}

Studies based on neuroimaging have suggested an intimate relationship between regions in the brain associated with the emotional and sensory features of pain and regions affected by depression.\textsuperscript{29} Other neuroimaging findings indicate that patients with depression may demonstrate greater emotional reactivity than patients without depression, and that greater reactivity, in turn, may lead to a diminished ability to regulate pain.\textsuperscript{30} Further supporting the biologic overlap between the two disorders is evidence suggesting that pain and mood have comparable neuroatomic substrates and neurobiologic mechanisms.\textsuperscript{31}

NEUROPATHIC PAIN

Neuropathic pain is defined as a persistent pain syndrome caused by injury to the nervous system, including the dorsal root ganglion, dorsal root, peripheral nerve, or the central nervous system.\textsuperscript{32} The descending monoamine pathway, particularly serotonergic and noradrenergic transmission, is a crucial piece of the endogenous pain modulation system.\textsuperscript{33,34} Neuropathic pain can be considered a type of chronic stress that may share a common neuropathologic mechanism with stress-induced depression and consequently responds to similar treatments. Xu and colleagues demonstrated that using ferulic acid, a major active element in Angelica sinensis, effectively decreased chronic constriction injury–induced neuropathic pain via opioid receptors and the connection with the descending monoamine pathway.\textsuperscript{35} The study also found that the effects of ferulic acid on neuropathic pain are possibly moderated by amelioration of the descending monoamine pathway and the involvement of spinal 5-HT1A and beta-2 receptors.

The development of neuropathic pain stems from lesions of the central or peripheral somatosensory nervous system,\textsuperscript{36} although the location of the lesions is not consistent across individuals, as numerous nonphysical factors seem to influence and affect the development of neuropathic pain.\textsuperscript{37} Some of these factors include psychological components that have been increasingly studied and explored. Studies suggest that these psychological factors influence the perception of pain by affecting individual variations in the sensitivity to pain,\textsuperscript{38-40} as well as the progression of chronic pain.\textsuperscript{41-44} For example, catastrophizing and the anxiety that stems from pain negatively affect neuropathic pain and its management.\textsuperscript{45-49} The inclination to be preoccupied with pain-related somatic sensations (i.e., pain vigilance) has also been linked to the development of chronic pain.\textsuperscript{50,51} Furthermore, positive psychological outlooks and attitudes such as optimism have been associated with a greater ability to cope with pain and a lower severity of pain.\textsuperscript{52-54} On the other hand, distress, anxiety, negative attitudes, and somatization have been associated with the development of chronic pain.\textsuperscript{55-58}

Dispositional optimism is defined as an individual’s general expectation of positive outcomes in various circumstances in life.\textsuperscript{53} Dispositional optimism has been demonstrated to be a positive predictor of health status following psychological trauma,\textsuperscript{59,60} in numerous clinical conditions,\textsuperscript{51-63} and in chronic pain.\textsuperscript{64-66} In fact, dispositional optimism has served as a protective factor, along with low emotional distress and positive affect, against developing neuropathic pain in patients following breast surgery.\textsuperscript{57}

Neuropathic pain commonly does not respond to analgesics but is sensitive to a number of antidepressants, including amitriptyline, a tricyclic antidepressant; moclobemide, a reversible monoamine oxidase A inhibitor; and milnacipran and venlafaxine, serotonin-noradrenaline reuptake inhibitors.\textsuperscript{68} The complex relationship between depression and pain demonstrates that multitargeted therapy can aid in the management of neuropathic pain with enhanced efficacy compared to therapies that target single pathways.\textsuperscript{69} A number of herbal medicines have been used as psychiatric drugs as well,\textsuperscript{34,70,71} including curcumin and St. John’s wort, and have shown similar efficacy in ameliorating depressive symptoms with fewer adverse side effects compared to prescription drugs.\textsuperscript{35}

Experimental Inducibility of Neuropathic Pain

A study conducted by L"otsch et al demonstrated that for 60%-70% of 11 standardly analyzed Quantitative Sensory

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Testing (QST) parameters, clinical patterns similar to those of neuropathic pain could be mimicked in healthy volunteers following the application of topical capsaicin.72 However, only 18% of the participants in the Lötsch et al study demonstrated neuropathy-like symptoms, thereby posing the question, what factors contribute to this clinical presentation? Dimova et al conducted an observational study of healthy subjects who were assessed based on a set of psychological variables that make up pain-related cognitive-emotional and general psychological mechanisms.73 Dispositional optimism was quantified using the Life Orientation Test (LOT). Dimova et al found that LOT scores differed significantly between groups in which a neuropathy-like pattern of pain could or could not be partly induced, assessed via QST. Thus, they concluded that the likelihood of being able to induce the clinical presentation of neuropathic pain using topical capsaicin application depended on psychological factors, namely pessimistic disposition.

FACTORS AFFECTING THE RELATIONSHIP BETWEEN DEPRESSION AND PAIN Opioid Use

The use of opioids for the management of chronic and acute pain has increased dramatically. In fact, from 1997 to 2005, hydrocodone prescriptions increased 198%, oxycodone prescriptions increased 588%, and methadone prescriptions increased 933%.74 In 2014, more than 10 million Americans aged 12 years and older used opioid analgesics nonmedically.75 Although opioids can be used effectively for short-term management of cancer pain and acute pain,76 a paucity of evidence supports the administration of opioids for long-term management of chronic noncancer pain.77-80 Because of the risk of addiction and unfavorable side effects, opioids should only be used continuously when the benefit to the patient is very clear. For instance, continuing opioid treatment is advisable if the patient shows clear improvement across multiple domains including better quality of life, decreased pain, and improved functioning.81 Commonly, patients find that after prolonged use, opioids are ineffective in reducing pain, and dosing needs to be steadily increased. Understanding that many patients increase their doses rather than discontinuing a medication that no longer effectively controls their pain, making clinical decisions regarding the maintenance of an opioid regimen in patients suffering from chronic pain can be difficult.81

Because patients with psychiatric diagnoses are commonly excluded from efficacy trials with opioids,82 assessment of the safety and efficacy of opioid use in patients with chronic pain and mental health diagnoses remains fairly unexplored. Some studies have suggested that the prototypical patient who is prescribed opioids in clinical practice contrasts with patients selected to participate in clinical trials, thereby muddling the data. For example, numerous studies have demonstrated that patients with depression are more likely to be given opioids and in higher doses than patients without depression in various settings, including the emergency department and primary care offices.83-85 Howe and Sullivan have proposed that this finding may be a contributing factor to the adverse usage of opioids.86

The link between the use of opioids and depression is likely multifactorial and complicated. Accordingly, there are numerous modes of thought regarding their relationship, including one that argues that patients with depression experience more severe pain compared to patients without depression, thus requiring higher doses of opioids and increasing the likelihood of having opioids prescribed.87 Howe and Sullivan have proposed that patients with mental health comorbidities are prescribed opioids more frequently, a process referred to as adverse selection.86 A study by Edlund et al showed that patients with mental health disorders are more at risk for developing an addiction to opioids.88 Sullivan et al believe that the added burden of emotional pain experienced by patients with mental health disorders affects the individual’s and the healthcare provider’s discernment of distress, resulting in the initiation of opioids to manage both physical and emotional pain.89

Goesling and colleagues investigated the relationship between depression, opioid use, and pain in patients at a university-based outpatient pain clinic, and their findings support the idea that the presence of depression may favor the initiation and continuation of opioid administration.81 Of the 2,104 patients who participated, 55.89% were using opioids at the time of the study. Compared to the nonopioid users in the study, the opioid-using subjects reported a worse phenotypic profile: worse physical functioning and greater severity of pain. Furthermore, a greater portion of opioid users reported depressive symptoms compared to those not taking opioids (43.6% vs 26.8%, P <.001). Pain severity was linked with a greater likelihood of taking opioids, but this finding was moderated by depression. Among patients without depression, the researchers reported a positive correlation between the predicted probabilities of using opioids as pain severity increased, but this probability was not dependent on pain severity in the patients with symptoms of depression.

The findings of the Goesling et al study81 have important implications for the reevaluation of continued opioid use in patients with chronic pain, particularly when evidence suggests that opioids do not adequately control chronic pain.77,78 Goesling et al argue that although selection bias can explain higher rates of depression among the clinical population that is already taking opioids compared to the population not on opioids, another possibility worth considering is that longitudinal usage of opioids may propagate or worsen depression. A longitudinal study conducted in a nonmedical prescription opioid population found that worsening depression was associated with greater mean daily doses of opioids.90 Another study based on a cohort of patients with low back pain found that a greater daily dose of opioids led to a greater risk for new-onset depression.91

Scherrer et al conducted a retrospective study of two large patient cohorts with substantial differences in comorbidity burdens and demographics.92 They observed that in both groups, subjects who were in remission from depression had a roughly 2-fold increased risk of depression recurrence if they had started opioid therapy relative to those who had not. The authors suggest that a possible explanation for this finding is that opioid use may counteract complete remission and increase the chances of recurrent depression. Given the lack of clarity regarding the relationship between chronic opioid use and depression, additional studies must be conducted to assess this relationship.
Positive Psychological Factors

An increasing number of studies recognize the positive psychological factors that affect how individuals adjust to persistent pain, including hope, pain acceptance, and optimism.93-96

Snyder et al define hope as a mental belief in one’s ability to initiate and propagate actions and the belief in one’s ability to initiate pathways to attain goals.97 Hope has been associated with decreased pain and symptoms in patients with chronic diseases including multiple sclerosis98 and cancer.99,100 Hope has also been linked to decreased functional disability, distress, and physical weakening in patients with pain secondary to traumatic injuries.100-102

Pain acceptance is defined as accepting what cannot be altered, getting involved in meaningful activities despite the pain, and decreasing ineffective endeavors to eliminate pain.103,104 The literature suggests that subjects with higher levels of pain acceptance experience substantially lower levels of pain, pain-associated disability, and distress.105-107

Gender

Research has begun to explore and support findings of gender differences in relation to pain, including differences in effectiveness of analgesia, vulnerability to diseases associated with pain, and recovery from anesthesia.108-110 In studies of experimentally induced pain, women have demonstrated lower tolerance for and diminished thresholds to a broad assortment of noxious stimuli relative to men.111,112 In addition, epidemiologic studies suggest that women report more negative responses to pain and more numerous pain experiences than men.113,114 A number of studies115-117 have attributed the gender differences in pain experiences to biologic differences, although the argument supporting psychological and social factors has also grown considerably.

A study by Ramírez-Maestre and Estève of 400 patients with chronic spinal pain attending primary care units found that women scored considerably higher than men on pain intensity and pain anxiety.118 In regards to chronic pain, a higher report of pain intensity has been considered an indication of maladjustment to chronic pain.118 However, in an earlier study, the authors suggest that the level of daily functioning may serve as a more accurate indicator of adjustment and capacity in patients who report pain.119

Gender roles have had an impact on reports of pain intensity because of female gender norms being structured so that the expression of pain is more acceptable in females than in males and a routine part of life, whereas male gender norms demand greater tolerance to pain compared to females.111,115,116 Therefore, Ramírez-Maestre and Estève concluded that although men in their study reported lower levels of pain intensity and pain anxiety relative to women, the women demonstrated greater adaptation to chronic pain as indicated by their levels of functioning and levels of anxiety and depression compared to the men in the study.118

Acute Postoperative Pain

The relationship between psychological morbidity and acute postoperative pain is largely unexplored and requires investigation. Despite advancements in pain management, patients continue to report moderate to severe pain postoperatively. Severe pain has been associated with prolonged postoperative recovery-to-ambulation time; progression to chronic postoperative pain; lower patient satisfaction; and greater mortality, morbidity, and risk of cardiac and pulmonary complications.120,121 Taenzler et al demonstrated that patients with depression prior to surgery had significantly greater analgesic requirements and postoperative pain compared to patients without depression.122 Consistent with these findings, De Cosmo et al found that subjects with depression and preoperative anxiety consumed greater amounts of tramadol and postoperatively reported greater pain intensities compared to subjects without depression.123

Royse et al found that adequate postoperative analgesia administration may be a factor in postoperative depression.124 They compared the outcomes of patients receiving high thoracic epidural analgesics to those of patients who received patient-controlled intravenous analgesics for 3 days after coronary artery bypass surgery. Patients who received high thoracic epidural analgesia reported better pain relief and had a lower likelihood of developing depression compared to those on patient-controlled analgesics.

CONCLUSION

The relationship between pain and psychology is complex and multifactorial. The intricate relationship between the two processes is evidenced by the clinical overlap in their presentations and the overlap between the anatomic regions in the brain associated with the emotional and sensory features of pain and the areas affected by depression. Studies are beginning to improve our understanding of these two systems, but more studies are needed to elucidate the relationship with the goal of optimizing treatment for patients with depression and concurrent chronic pain and thereby reducing hospital stay and healthcare costs.

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REFERENCES


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