Ochsner Journal 17:173–180, 2017
© Academic Division of Ochsner Clinic Foundation

Pain and Psychology—A Reciprocal Relationship

Nalini Vadivelu, MD,[1] Alice M. Kai, BA,[2] Gopal Kodumudi, BS, MS,[3] Karine Babayan, BA,[4] Manuel Fontes, MD,[1] Matthew M. Burg, PhD[1]

[1]Department of Anesthesiology, Yale University, New Haven, CT [2]Stony Brook School of Medicine, Stony Brook, NY [3]California Northstate University College of Medicine, Elk Grove, CA [4]The University of Southern California Rossier School of Education, Los Angeles, CA

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*

Address correspondence to Nalini Vadivelu, MD, Department of Anesthesiology, Yale University, TMP3, 333 Cedar Street, New Haven, CT 06520. Tel: (203) 785-2802. Email: nalini.vadivelu@yale.edu

INTRODUCTION

A significant reciprocal relationship between depressive symptoms and pain exists. Chronic pain is associated with a greater risk of developing or having depression,[1] and epidemiologic studies indicate that up to 75% of patients with depression also report pain.[2,3] Chronic pain is costly. Based on the 2008 Medical Expenditure Panel Survey, approximately 100 million adults in the United States reported chronic pain, and the estimated national annual cost is $635-$650 billion.[4]

Depression typically affects 5% of the general population, but among patients with chronic pain, 30%-45% experience depression.[5,6] In a study of 18,980 subjects, 43.4% of individuals who met the criteria for major depressive disorder also met the criteria for chronic painful physical condition (CPPC), a percentage significantly higher than the 16.1% of the general population with CPPC.[7] To meet the criteria for CPPC, the patient must have had pain for 6 months that led to medication use or consultation with a healthcare specialist. Of note, people who report CPPC also report worse symptoms of fatigue, diminished concentration, insomnia, and psychomotor retardation compared to people without pain.[8]

Depression is a mental disorder that consists of both somatic and emotional symptoms. The prevalence of physical and somatic symptoms existing concurrently in patients with major depressive disorder in tertiary care ranges from 30%-54%.[9-11] Despite this knowledge, numerous studies have reported that depression is not assessed in up to half of patients experiencing physical symptoms,[12] thereby increasing the risk of these patients developing more severe depression and greater treatment resistance.[13]

Chronic pain has been linked to reduced benefits from antidepressants and decreased quality of life.[13] A population-based study reported that patients experiencing both depression and pain sought 20% more initial visits to medical providers and had higher total medical costs compared to patients with depression but no reports of pain.[14] The findings of these studies show that patients with both pain and depression have higher medical costs and less treatment benefit than patients with depression only, creating problems with utilization of medical care and medical management. Another study furthered this point, reporting that more severe and longer duration depressive episodes occur among individuals who also report the presence of pain.[15]

Chronic pain and depression have common comorbidities, including greater levels of stress and sleep disturbance compared to patients without chronic pain or depression.[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,[18] there is also evidence that negative emotions can reduce pain sensitivity.[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.[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.[22] On the other hand, lesser threats that elicit lower levels of arousal may lead to increased pain sensitivity.[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.[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.[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.[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.[2] The mesolimbic dopamine systems and nucleus accumbens are stimulated in response to aversive, painful stimuli as well as to pleasurable stimuli.[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[27] and has also consistently been reported in depression.[28]

Studies based on neuroimages have suggested an intimate relationship between regions in the brain associated with the emotional and sensory features of pain and regions affected by depression.[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.[30] Further supporting the biologic overlap between the two disorders is evidence suggesting that pain and mood have comparable neuroanatomic substrates and neurobiologic mechanisms.[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.[32] The descending monoamine pathway, particularly serotonergic and noradrenergic transmission, is a crucial piece of the endogenous pain modulation system.[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.[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,[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.[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,[38-40] as well as the progression of chronic pain.[41-44] For example, catastrophizing and the anxiety that stems from pain negatively affect neuropathic pain and its management.[45-49] The inclination to be preoccupied with pain-related somatic sensations (ie, pain vigilance) has also been linked to the development of chronic pain.[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.[52-54] On the other hand, distress, anxiety, negative attitudes, and somatization have been associated with the development of chronic pain.[55-58]

Dispositional optimism is defined as an individual's general expectation of positive outcomes in various circumstances in life.[53] Dispositional optimism has been demonstrated to be a positive predictor of health status following psychological trauma,[59,60] in numerous clinical conditions,[61-63] and in chronic pain.[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.[67]

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.[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.[69] A number of herbal medicines have been used as psychiatric drugs as well,[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.[35]

Experimental Inducibility of Neuropathic Pain

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

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%, $P<0.001$). 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 study[81] 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.[77-79] 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 sclerosis[98] and cancer.[93,99] 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 studies[115-117] 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 Esteve 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 Esteve 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] Taenzer 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.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

REFERENCES

1. Lépine JP, Briley M. The epidemiology of pain in depression. *Hum Psychopharmacol*. 2004 Oct;19 Suppl 1:S3-S7.
2. Agüera-Ortiz L, Failde I, Mico JA, Cervilla J, López-Ibor JJ. Pain as a symptom of depression: prevalence and clinical correlates in patients attending psychiatric clinics. *J Affect Disord*. 2011 Apr;130(1-2):106-112. doi: 10.1016/j.jad.2010.10.022.
3. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003 Nov 10;163(20):2433-2445.
4. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012 Aug;13(8):715-724. doi: 10.1016/j.jpain.2012.03.009.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994:143-147.
6. Demyttenaere K, Bruffaerts R, Lee S, et al. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. *Pain*. 2007 Jun;129(3):332-342.
7. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003 Jan;60(1):39-47.

8. Ohayon MM. Specific characteristics of the pain/depression association in the general population. *J Clin Psychiatry*. 2004; 65 Suppl 12:5-9.
9. Brecht S, Courtecuisse C, Debieuvre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry*. 2007 Nov;68(11):1707-1716.
10. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum*. 2005 May;52(5):1577-1584.
11. Lee P, Zhang M, Hong JP, et al. Frequency of painful physical symptoms with major depressive disorder in Asia: relationship with disease severity and quality of life. *J Clin Psychiatry*. 2009 Jan;70(1):83-91.
12. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003 Jun 18;289(23):3095-3105.
13. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med*. 2004 Jan-Feb;66(1):17-22.
14. Bao Y, Sturm R, Croghan TW. A national study of the effect of chronic pain on the use of health care by depressed persons. *Psychiatr Serv*. 2003 May;54(5):693-697.
15. Karp JF, Scott J, Houck P, Reynolds CF 3rd, Kupfer DJ, Frank E. Pain predicts longer time to remission during treatment of recurrent depression. *J Clin Psychiatry*. 2005 May;66(5): 591-597.
16. Miller LR, Cano A. Comorbid chronic pain and depression: who is at risk? *J Pain*. 2009 Jun;10(6):619-627. doi: 10.1016/j.jpain.2008.12.007.
17. Ohayon MM, Schatzberg AF. Chronic pain and major depressive disorder in the general population. *J Psychiatr Res*. 2010 May;44(7):454-461. doi: 10.1016/j.jpsychires.2009.10.013.
18. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage*. 2009 Sep;47(3):987-994. doi: 10.1016/j.neuroimage.2009.05.059.
19. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain*. 2000 Jan;84(1):65-75.
20. Rhudy JL, Meagher MW. Individual differences in the emotional reaction to shock determine whether hypoalgesia is observed. *Pain Med*. 2003 Sep;4(3):244-256.
21. Rhudy JL, Williams AE. Gender differences in pain: do emotions play a role? *Gend Med*. 2005 Dec;2(4):208-226.
22. Martenson ME, Cetas JS, Heinricher MM. A possible neural basis for stress-induced hyperalgesia. *Pain*. 2009 Apr;142(3): 236-244.
23. Von Korff M, Simon G. The relationship between pain and depression. *Br J Psychiatry Suppl*. 1996 Jun;(30):101-108.
24. Stahl S, Briley M. Understanding pain in depression. *Hum Psychopharmacol*. 2004 Oct;19 Suppl 1:S9-S13.
25. Mayberg HS. Defining the neural circuitry of depression: toward a new nosology with therapeutic implications. *Biol Psychiatry*. 2007 Mar 15;61(6):729-730.
26. Berridge K, Winkielman P. What is an unconscious emotion? (The case for unconscious ''liking''). *Cogn Emot*. 2003;17(2): 181-211. doi: 10.1080/02699930302289.
27. Bornhövd K, Quante M, Glauche V, Bromm B, Weiller C, Büchel C. Painful stimuli evoke different stimulus–response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain*. 2002 Jun;125(Pt 6):1326-1336.
28. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry*. 2003 Aug 1;54(3):338-352.
29. Ehnvall A, Mitchell PB, Hadzi-Pavlovic D, Malhi GS, Parker G. Pain during depression and relationship to rejection sensitivity. *Acta Psychiatr Scand*. 2009 May;119(5):375-382. doi: 10.1111/j.1600-0447.2008.01316.x.
30. Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Arch Gen Psychiatry*. 2008 Nov;65(11):1275-1284. doi: 10.1001/archpsyc.65.11.1275.
31. Micó JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. *Trends Pharmacol Sci*. 2006 Jul;27(7):348-354.
32. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999 Jun 5;353(9168):1959-1964.
33. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL. Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Methods*. 1994 Jul;53(1):55-63.
34. Zhao X, Wang C, Zhang JF, et al. Chronic curcumin treatment normalizes depression-like behaviors in mice with mononeuropathy: involvement of supraspinal serotonergic system and GABAA receptor. *Psychopharmacology (Berl)*. 2014 May;231(10):2171-2187. doi: 10.1007/s00213-013-3368-2.
35. Xu Y, Lin D, Yu X, et al. The antinociceptive effects of ferulic acid on neuropathic pain: involvement of descending monoaminergic system and opioid receptors. *Oncotarget*. 2016 Apr 12;7(15):20455-20468. doi: 10.18632/oncotarget.7973.
36. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol*. 2010 Aug;9(8):807-819. doi: 10.1016/S1474-4422(10)70143-5.
37. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. *Neuron*. 2012 Feb 23;73(4):638-652. doi: 10.1016/j.neuron.2012.02.008.
38. George SZ, Hirsh AT. Psychologic influence on experimental pain sensitivity and clinical pain intensity for patients with shoulder pain. *J Pain*. 2009 Mar;10(3):293-299. doi: 10.1016/j.jpain.2008.09.004.
39. Hanssen MM, Vancleef LM, Vlaeyen JW, Peters ML. More optimism, less pain! The influence of generalized and pain-specific expectations on experienced cold-pressor pain. *J Behav Med*. 2014 Feb;37(1):47-58. doi: 10.1007/s10865-012-9463-8.
40. Hirsh AT, George SZ, Bialosky JE, Robinson ME. Fear of pain, pain catastrophizing, and acute pain perception: relative prediction and timing of assessment. *J Pain*. 2008 Sep;9(9): 806-812. doi: 10.1016/j.jpain.2008.03.012.
41. Keogh E, Book K, Thomas J, Giddins G, Eccleston C. Predicting pain and disability in patients with hand fractures: comparing pain anxiety, anxiety sensitivity and pain catastrophizing. *Eur J Pain*. 2010 Apr;14(4):446-451. doi: 10.1016/j.ejpain.2009.08.001.
42. Lautenbacher S, Huber C, Schöfer D, et al. Attentional and emotional mechanisms related to pain as predictors of chronic postoperative pain: a comparison with other psychological and physiological predictors. *Pain*. 2010 Dec; 151(3):722-731. doi: 10.1016/j.pain.2010.08.041.
43. Peters ML, Sommer M, van Kleef M, Marcus MA. Predictors of physical and emotional recovery 6 and 12 months after surgery. *Br J Surg*. 2010 Oct;97(10):1518-1527. doi: 10.1002/bjs.7152.
44. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine (Phila Pa 1976)*. 2002 Mar 1;27(5):E109-E120.
45. Mankovsky T, Lynch M, Clark A, Sawynok J, Sullivan MJ. Pain catastrophizing predicts poor response to topical analgesics in patients with neuropathic pain. *Pain Res Manag*. 2012 Jan-Feb;17(1):10-14.
46. Phillips TJ, Brown M, Ramirez JD, et al. Sensory, psychological, and metabolic dysfunction in HIV-associated peripheral neuropathy: a cross-sectional deep profiling study. *Pain*. 2014 Sep;155(9):1846-1860. doi: 10.1016/j.pain.2014.06.014.

47. Schlereth T, Heiland A, Breimhorst M, et al. Association between pain, central sensitization and anxiety in postherpetic neuralgia. *Eur J Pain*. 2015 Feb;19(2):193-201. doi: 10.1002/ejp.537.
48. Selvarajah D, Cash T, Sankar A, et al. The contributors of emotional distress in painful diabetic neuropathy. *Diab Vasc Dis Res*. 2014 Jul;11(4):218-225.
49. Toth C, Brady S, Hatfield M. The importance of catastrophizing for successful pharmacological treatment of peripheral neuropathic pain. *J Pain Res*. 2014 Jun 24;7:327-338. doi: 10.2147/JPR.S56883.
50. Lautenbacher S, Huber C, Baum C, Rossaint R, Hochrein S, Heesen M. Attentional avoidance of negative experiences as predictor of postoperative pain ratings and consumption of analgesics: comparison with other psychological predictors. *Pain Med*. 2011 Apr;12(4):645-653. doi: 10.1111/j.1526-4637.2011.01076.x.
51. Lautenbacher S, Huber C, Kunz M, et al. Hypervigilance as predictor of postoperative acute pain: its predictive potency compared with experimental pain sensitivity, cortisol reactivity, and affective state. *Clin J Pain*. 2009 Feb;25(2):92-100. doi: 10.1097/AJP.0b013e3181850dce.
52. Boselie JJ, Vancleef LM, Smeets T, Peters ML. Increasing optimism abolishes pain-induced impairments in executive task performance. *Pain*. 2014 Feb;155(2):334-340. doi: 10.1016/j.pain.2013.10.014.
53. Goodin BR, Bulls HW. Optimism and the experience of pain: benefits of seeing the glass as half full. *Curr Pain Headache Rep*. 2013 May;17(5):329. doi: 10.1007/s11916-013-0329-8.
54. Goodin BR, Glover TL, Sotolongo A, et al. The association of greater dispositional optimism with less endogenous pain facilitation is indirectly transmitted through lower levels of pain catastrophizing. *J Pain*. 2013 Feb;14(2):126-135. doi: 10.1016/j.jpain.2012.10.007.
55. Diatchenko L, Fillingim RB, Smith SB, Maixner W. The phenotypic and genetic signatures of common musculoskeletal pain conditions. *Nat Rev Rheumatol*. 2013 Jun;9(6):340-350. doi: 10.1038/nrrheum.2013.43.
56. Finan PH, Quartana PJ, Smith MT. Positive and negative affect dimensions in chronic knee osteoarthritis: effects on clinical and laboratory pain. *Psychosom Med*. 2013 Jun;75(5):463-470. doi: 10.1097/PSY.0b013e31828ef1d6.
57. Shedden Mora M, Weber D, Borkowski S, Rief W. Nocturnal masseter muscle activity is related to symptoms and somatization in temporomandibular disorders. *J Psychosom Res*. 2012 Oct;73(4):307-312. doi: 10.1016/j.jpsychores.2012.07.008.
58. Sullivan MJ, Thorn B, Rodgers W, Ward LC. Path model of psychological antecedents to pain experience: experimental and clinical findings. *Clin J Pain*. 2004 May-Jun;20(3):164-173.
59. Iacoviello BM, Charney DS. Psychosocial facets of resilience: implications for preventing posttrauma psychopathology, treating trauma survivors, and enhancing community resilience. *Eur J Psychotraumatol*. 2014 Oct 1;5. doi: 10.3402/ejpt.v5.23970.
60. Segovia F, Moore JL, Linnville SE, Hoyt RE, Hain RE. Optimism predicts resilience in repatriated prisoners of war: a 37-year longitudinal study. *J Trauma Stress*. 2012 Jun;25(3):330-336. doi: 10.1002/jts.21691.
61. Beitel M, Savant JD, Cutter CJ, Peters S, Belisle N, Barry DT. Psychopathology and pain correlates of dispositional optimism in methadone-maintained patients. *Am J Addict*. 2012 Nov;21 Suppl 1:S56-S62. doi: 10.1111/j.1521-0391.2012.00293.x.
62. Gison A, Dall'Armi V, Donati V, Rizza F, Giaquinto S. Dispositional optimism, depression, disability and quality of life in Parkinson's disease. *Funct Neurol*. 2014 Apr-Jun;29(2):113-119.
63. Vassend O, Quale AJ, Rise O, Schanke AK. Predicting the long-term impact of acquired severe injuries on functional health status: the role of optimism, emotional distress and pain. *Spinal Cord*. 2011 Dec;49(12):1193-1197. doi: 10.1038/sc.2011.70.
64. Cruz-Almeida Y, King CD, Goodin BR, et al. Psychological profiles and pain characteristics of older adults with knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2013 Nov;65(11):1786-1794.
65. Hoofwijk DM, Fiddelers AA, Peters ML, et al. Prevalence and predictive factors of chronic postsurgical pain and poor global recovery 1 year after outpatient surgery. *Clin J Pain*. 2015 Dec;31(12):1017-1025. doi: 10.1097/AJP.0000000000000207.
66. Ramírez-Maestre C, Esteve R. Disposition and adjustment to chronic pain. *Curr Pain Headache Rep*. 2013 Mar;17(3):312. doi: 10.1007/s11916-012-0312-9.
67. Bruce J, Thornton AJ, Powell R, et al; Recovery Study Group. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. *Pain*. 2014 Feb;155(2):232-243. doi: 10.1016/j.pain.2013.09.028.
68. Villarinho JG, Pinheiro Kde V, Pinheiro Fde V, et al. The antinociceptive effect of reversible monoamine oxidase-A inhibitors in a mouse neuropathic pain model. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013 Jul 1;44:136-142. doi: 10.1016/j.pnpbp.2013.02.005.
69. Xu Y, Zhang L, Shao T, et al. Ferulic acid increases pain threshold and ameliorates depression-like behaviors in reserpine-treated mice: behavioral and neurobiological analyses. *Metab Brain Dis*. 2013 Dec;28(4):571-583. doi: 10.1007/s11011-013-9404-4.
70. Chiappedi M, Bejor M. Herbals and natural dietary supplements in psychiatric practice. *Recent Pat CNS Drug Discov*. 2010 Jun;5(2):164-171.
71. Xu Y, Ku BS, Yao HY, et al. The effects of curcumin on depressive-like behaviors in mice. *Eur J Pharmacol*. 2005 Jul 25;518(1):40-46.
72. Lötsch J, Dimova V, Hermens H, et al. Pattern of neuropathic pain induced by topical capsaicin application in healthy subjects. *Pain*. 2015 Mar;156(3):405-414. doi: 10.1097/01.j.pain.0000460328.10515.c9.
73. Dimova V, Oertel BG, Kabakci G, et al. A more pessimistic life orientation is associated with experimental inducibility of a neuropathy-like pain pattern in healthy individuals. *J Pain*. 2015 Aug;16(8):791-800. doi: 10.1016/j.jpain.2015.05.004.
74. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. *Pain Physician*. 2007 Mar;10(3):399-424.
75. Pezalla EJ, Rosen D, Erensen JG, Haddox JD, Mayne TJ. Secular trends in opioid prescribing in the USA. *J Pain Res*. 2017 Feb;10:383-387. doi: 10.2147/JPR.S129553.
76. Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009 Feb;10(2):113-130. doi: 10.1016/j.jpain.2008.10.008.
77. Ballantyne JC. Opioids for chronic pain: taking stock. *Pain*. 2006 Nov;125(1-2):3-4.
78. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. 2008 Jul-Aug;24(6):469-478. doi: 10.1097/AJP.0b013e31816b2f26.
79. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013 Aug 27;(8):CD004959. doi: 10.1002/14651858.CD004959.pub4.
80. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006 May 23;174(11):1589-1594.

81. Goesling J, Henry MJ, Moser SE, et al. Symptoms of depression are associated with opioid use regardless of pain severity and physical functioning among treatment-seeking patients with chronic pain. *J Pain*. 2015 Sep;16(9):844-851. doi: 10.1016/j.jpain.2015.05.010.
82. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004 Dec;112(3):372-380.
83. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clin J Pain*. 2010 Jan;26(1):1-8. doi: 10.1097/AJP.0b013e3181b99f35.
84. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. 2012 Mar 7;307(9):940-947. doi: 10.1001/jama.2012.234.
85. Sullivan MD, Edlund MJ, Steffick D, Unützer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005 Dec 15;119(1-3):95-103.
86. Howe CQ, Sullivan MD. The missing 'P' in pain management: how the current opioid epidemic highlights the need for psychiatric services in chronic pain care. *Gen Hosp Psychiatry*. 2014 Jan-Feb;36(1):99-104. doi: 10.1016/j.genhosppsych.2013.10.003.
87. Börsbo B, Peolsson M, Gerdle B. The complex interplay between pain intensity, depression, anxiety and catastrophising with respect to quality of life and disability. *Disabil Rehabil*. 2009;31(19):1605-1613.
88. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007 Jun;129(3):355-362.
89. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006 Oct 23;166(19):2087-2093.
90. Martins SS, Fenton MC, Keyes KM, Blanco C, Zhu H, Storr CL. Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. *Psychol Med*. 2012 Jun;42(6):1261-1272. doi: 10.1017/S0033291711002145.
91. Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD; Residency Research Network of Texas (RRNeT) Investigators. Change in opioid dose and change in depression in a longitudinal primary care patient cohort. *Pain*. 2015 Feb;156(2):348-355. doi: 10.1097/01.j.pain.0000460316.58110.a0.
92. Scherrer JF, Salas J, Copeland LA, et al. Increased risk of depression recurrence after initiation of prescription opioids in noncancer pain patients. *J Pain*. 2016 Apr;17(4):473-482. doi: 10.1016/j.jpain.2015.12.012.
93. Berendes D, Keefe FJ, Somers TJ, Kothadia SM, Porter LS, Cheavens JS. Hope in the context of lung cancer: relationships of hope to symptoms and psychological distress. *J Pain Symptom Manage*. 2010 Aug;40(2):174-182. doi: 10.1016/j.jpainsymman.2010.01.014.
94. Elander J, Robinson G, Mitchell K, Morris J. An assessment of the relative influence of pain coping, negative thoughts about pain, and pain acceptance on health-related quality of life among people with hemophilia. *Pain*. 2009 Sep;145(1-2):169-175. doi: 10.1016/j.pain.2009.06.004.
95. Ferreira VM, Sherman AM. The relationship of optimism, pain and social support to well-being in older adults with osteoarthritis. *Aging Ment Health*. 2007 Jan;11(1):89-98.
96. Gauthier LR, Rodin G, Zimmermann C, et al. Acceptance of pain: a study in patients with advanced cancer. *Pain*. 2009 May;143(1-2):147-154. doi: 10.1016/j.pain.2009.02.009.
97. Snyder CR, Harris C, Anderson JR, et al. The will and the ways: development and validation of an individual-differences measure of hope. *J Pers Soc Psychol*. 1991 Apr;60(4):570-585.
98. Tree HA. Multiple sclerosis severity, pain intensity, and psychosocial factors: Associations with perceived social support, hope, optimism, depression, and fatigue. 2009. http://search.proquest.com/docview/304917622. Accessed April 12, 2017.
99. Stanton AL, Danoff-Burg S, Cameron CL, et al. Emotionally expressive coping predicts psychological and physical adjustment to breast cancer. *J Consult Clin Psychol*. 2000 Oct;68(5):875-882.
100. Creamer M, O'Donnell ML, Carboon I, et al. Evaluation of the Dispositional Hope Scale in injury survivors. *J Res Pers*. 2009 Aug;43(4):613-617. doi: 10.1016/j.jrp.2009.03.002.
101. Elliott TR, Witty TE, Herrick S, Hoffman JT. Negotiating reality after physical loss: hope, depression, and disability. *J Pers Soc Psychol*. 1991 Oct;61(4):608-613.
102. Peleg G, Barak O, Harel Y, Rochberg J, Hoofien D. Hope, dispositional optimism and severity of depression following traumatic brain injury. *Brain Inj*. 2009 Sep;23(10):800-808. doi: 10.1080/02699050903196696.
103. Forman EM, Butryn ML, Hoffman KL, Herbert JD. An open trial of an acceptance-based behavioral intervention for weight loss. *Cogn Behav Pract*. 2009 May;16(2):223-235. doi: 10.1016/j.cbpra.2008.09.005.
104. McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. *Pain*. 2004 Jan;107(1-2):159-166.
105. McCracken LM. Learning to live with the pain: acceptance of pain predicts adjustment in persons with chronic pain. *Pain*. 1998 Jan;74(1):21-27.
106. McCracken LM, Vowles KE, Eccleston C. Acceptance-based treatment for persons with complex, long standing chronic pain: a preliminary analysis of treatment outcome in comparison to a waiting phase. *Behav Res Ther*. 2005 Oct;43(10):1335-1346.
107. Viane I, Crombez G, Eccleston C, et al. Acceptance of pain is an independent predictor of mental well-being in patients with chronic pain: empirical evidence and reappraisal. *Pain*. 2003 Nov;106(1-2):65-72.
108. Ciccone GK, Holdcroft A. Drugs and sex differences: a review of drugs relating to anaesthesia. *Br J Anaesth*. 1999 Feb;82(2):255-265.
109. Fillingim RB, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. *Neurosci Biobehav Rev*. 2000 Jun;24(4):485-501.
110. Myles PS, McLeod AD, Hunt JO, Fletcher H. Sex differences in speed of emergence and quality of recovery after anaesthesia: cohort study. *BMJ*. 2001 Mar 24;322(7288):710-711.
111. Alabas OA, Tashani OA, Tabasam G, Johnson MI. Gender role affects experimental pain responses: a systematic review with meta-analysis. *Eur J Pain*. 2012 Oct;16(9):1211-1223. doi: 10.1002/j.1532-2149.2012.00121.x.
112. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. *Pain Forum*. 1995 Winter;4(4):209-221. doi: 10.1016/S1082-3174(11)80022-X.
113. Holdcroft A, Berkley KJ. Sex and gender differences in pain and its relief. In: McMahon S, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Edinburgh: Elsevier Churchill Livingstone; 2005:1181-1197.
114. Unruh AM. Gender variations in clinical pain experience. *Pain*. 1996 May-Jun;65(2):123-167.
115. Bernardes SF, Keogh E, Lima ML. Bridging the gap between pain and gender research: a selective literature review. *Eur J Pain*. 2008 May;12(4):427-440.
116. Bernardes SF, Lima ML. Being less of a man or less of a woman: perceptions of chronic pain patients' gender identities. *Eur J Pain*. 2010 Feb;14(2):194-199. doi: 10.1016/j.ejpain.2009.04.009.

117. Forsythe LP, Thorn B, Day M, Shelby G. Race and sex differences in primary appraisals, catastrophizing, and experimental pain outcomes. *J Pain*. 2011 May;12(5):563-572. doi: 10.1016/j.jpain.2010.11.003.
118. Ramírez-Maestre C, Esteve R. The role of sex/gender in the experience of pain: resilience, fear, and acceptance as central variables in the adjustment of men and women with chronic pain. *J Pain*. 2014 Jun;15(6):608-618.e1. doi: 10.1016/j.jpain.2014.02.006.
119. Ramírez-Maestre C, Esteve R, López AE. Cognitive appraisal and coping in chronic pain patients. *Eur J Pain*. 2008 Aug;12(6):749-756.
120. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology*. 2013 Apr;118(4):934-944. doi: 10.1097/ALN.0b013e31828866b3.
121. Joshi GP, Kehlet H. Procedure-specific pain management: the road to improve postsurgical pain management? *Anesthesiology*. 2013 Apr;118(4):780-782. doi: 10.1097/ALN.0b013e31828866e1.
122. Taenzer P, Melzack R, Jeans ME. Influence of psychological factors on postoperative pain, mood and analgesic requirements. *Pain*. 1986 Mar;24(3):331-342.
123. De Cosmo G, Congedo E, Lai C, Primieri P, Dottarelli A, Aceto P. Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain*. 2008 Jun;24(5):399-405. doi: 10.1097/AJP.0b013e3181671a08.
124. Royse C, Remedios C, Royse A. High thoracic epidural analgesia reduces the risk of long-term depression in patients undergoing coronary artery bypass surgery. *Ann Thorac Cardiovasc Surg*. 2007 Feb;13(1):32-35.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.