

# Assessment and management of chronic pain in patients with depression and anxiety

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## ABSTRACT

This article will review the role of the pharmacist in the management of chronic pain in patients with comorbid mood disorders.

## KEYWORDS

Pain, depression, anxiety

## INTRODUCTION

Chronic pain is a prevalent condition affecting many patients in a range of environments. It can be a debilitating condition causing limitations in mobility which may further inhibit work and recreational activities causing a decrease in quality of life.<sup>1,2</sup> Multiple studies demonstrate that patients with chronic pain are more likely to suffer from a mood disorder. One such recent study examined approximately 1,000 patients with musculoskeletal pain who presented to their primary care provider with uncontrolled pain. This cross-sectional study measured pain intensity and screened for undiagnosed mood disorders. The results showed a high prevalence (>70%) of undiagnosed mood disorders in these uncontrolled pain patients. In addition, a higher pain score was directly related to the diagnosis of a mood disorder.<sup>3</sup> Likewise, patients with depression and anxiety are more likely to suffer from chronic pain. One study estimated that 45% of chronic pain patients have depression and 25% of chronic pain patients have anxiety.<sup>4,5</sup>

Patients with chronic pain and co-morbid mood disorders are often difficult to manage for several reasons. One reason may be a difference in the patient's pain perception. For example, patients with centralized pain disorders like fibromyalgia often report high pain scores.<sup>6,7,8</sup> A recent study published in the *Journal of Pain Research* in 2014 showed that patients with fibromyalgia not only had a higher prevalence of anxiety and depression, but they also had a decrease in ability to perceive the difference between painful stimuli and nonpainful stimuli.<sup>9</sup> Another study, published in *Pain* in 2013, showed that patients with fibromyalgia did not have a significant change in pain rating when exposed to

negative, neutral, and positive pictures whereas the control group showed a decrease in pain scores when viewing positive pictures.<sup>7</sup> This study discussed the possible inability of fibromyalgia patients to change pain perception with attempts to improve affect.<sup>7</sup> Additional difficulties in managing chronic pain and mood disorders come with patients that also have substance abuse history. It has been estimated that patients with moderate to severe depression are 1.8 to 2.4 times more likely to misuse opioid medications.<sup>10</sup> Pharmacists may have several important responsibilities in the management of these patients.

## DEFINITION AND PATHOPHYSIOLOGY

In order to properly assess and manage patients with chronic pain and coexisting mood disorders, it is necessary to first understand the similar pathophysiologic processes underlying these conditions. Chronic pain is defined as pain that lasts beyond the expected course of tissue injury and normal healing.<sup>11,12</sup> It may have many etiologies and may be associated with a chronic medical condition.<sup>1</sup> It may be continuous or recurrent, and it affects the patient's level of functioning as well as his or her quality of life.<sup>13-15</sup>

The pathophysiology of chronic pain is not well understood but may be nociceptive, neuropathic, or mixed in nature.<sup>12</sup> Nociceptive pain occurs when a noxious stimuli (bodily injury) initiates chemical, thermal or mechanical receptors. The signal from these receptors is converted into electrical activity and is transmitted through the central nervous system (CNS).<sup>16</sup> If the injury does not heal or is not treated properly, the resulting pain may become chronic (PP). Chronic pain may also be neuropathic in nature if there is damage to the brain, spinal cord, or peripheral nerves.<sup>12</sup>

The pathophysiology of depression and anxiety may involve the same neurotransmitters that affect pain. Depression is a psychiatric disease state that is thought to be associated with a decrease in serotonin (5HT) output in the CNS and has possibly been linked to reduction in norepinephrine (NE), dopamine (DA), and other neurotransmitters.<sup>17-19</sup> Anxiety may involve gamma aminobutyric acid (GABA), glutamate, 5HT, NE, and other neurotransmitters many of which are targets for treatment of chronic pain.<sup>20</sup> GABA agonism has been shown to reduce pain.<sup>21</sup> Glutamate is an excitotoxic neurotransmitter that is involved in the etiology of anxiety and fibromyalgia.<sup>18</sup> In fact, brain imaging has shown overlap among specific brain regions between activities of chronic pain and anxiety.<sup>22</sup>

### ASSESSMENT OF CHRONIC PAIN

In the simplest form, chronic pain assessment is accomplished using a one-dimensional scale such as the visual analog scale (VAS), numeric rating scale (NRS), or verbal descriptor scale (VDS).<sup>1</sup> These scales are self-rated and give a snapshot of the intensity of a patient's pain. However, it has been shown that chronic pain is highly complex, with multiple factors affecting what the patient experiences with his or her pain,<sup>23-28</sup> and one-dimensional measures may over-simplify the assessment. Factors affecting chronic pain experience include psychiatric comorbidities such as depression and anxiety.<sup>23,29-31</sup> These disorders may also carry overlap in somatic symptoms with chronic pain,<sup>32</sup> and may worsen pain outcomes.<sup>28,33-35</sup> Thus it is beneficial to include psychiatric, emotional, and psychological components as part of a multidimensional assessment of chronic pain patients.<sup>9,26,29,32,36-39</sup> In fact, in 2005, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group of pain professionals recommended that six core domains be assessed for chronic pain outcomes. Among these was emotional functioning alongside pain and physical functioning.<sup>14</sup>

A variety of measurement scales are available that more globally describe a patient's chronic pain compared to the more simplistic measures mentioned previously. One example of a multi-dimensional pain scale is the McGill Pain Questionnaire.<sup>40</sup> In this scale, patients select word descriptors of pain like "throbbing" and "shooting" that describe their pain, and they rate pain from mild to excruciating.<sup>40</sup> Another useful scale is the West Haven-Yale Multidimensional Pain Inventory. In addition to questions that assess intensity of pain, this scale utilizes questions addressing social functioning, mood, physical functioning, and the effect of chronic pain on

relationships,<sup>41</sup> and it has been used in clinical studies that correlate pain with psychiatric co-morbidities.<sup>42,43</sup> The Brief Pain Inventory is a third tool that has been used clinically to assess pain in patients with depression and anxiety.<sup>44</sup> It is shorter than previous scales mentioned, yet still includes questions about emotional and social function of the patient.<sup>44</sup> These multidimensional scales may help pharmacists consider the non-physical consequences of pain, and this may help the pharmacist treat and monitor pain more appropriately in these co-existing conditions.

### TREATMENT OF CHRONIC PAIN

It is crucial that treatment of chronic pain focuses on the involvement of the patient and the need for their cooperation and participation. The treatment course should be presented as a process of rehabilitation from a biopsychosocial perspective. This involves physical and/or occupational therapy to increase function, psychological treatment like cognitive behavioral therapy, and pharmacologic treatment.<sup>5</sup> Pharmacists can provide education to the patient on realistic goals of pain medication management and the importance of adherence with all aspects of the pain rehabilitation process. The patient should be informed that pain medication will not relieve all pain but help decrease pain intensity and frequency so the patient can improve functional ability.

Medications can be used to treat both chronic pain and comorbid mood disorders. A study in *The Journal of the American Medical Association (JAMA)* in 2009 showed an improvement in depression scores and pain severity with use of antidepressants and a self-management pain program for musculoskeletal pain.<sup>45</sup> A self-management pain program focuses on the responsibility of the patient to be adherent with recommended medications and to participate in physical exercise. As part of this self-management pain program, the pharmacist can provide information to the patient on the biological processes involved in their pain and potential options for the treatment of their pain.<sup>45</sup> The pharmacist may also educate patients on the appropriate use of their medications and potential side effects.

Antidepressants have the most evidence in treating chronic pain with comorbid anxiety or depression. Serotonin-norepinephrine reuptake inhibitors (SNRI's) may be considered as first line treatment in these patients.<sup>46-50</sup> The SNRI's venlafaxine, duloxetine, and milnacipran have been shown to attenuate neuropathic pain and fibromyalgia with and without coexisting depression.<sup>46-50</sup> Lower doses of duloxetine (ex. 20 mg)

may be sufficient for pain, but doses of up to 120 mg daily may be necessary.<sup>51</sup> Venlafaxine may be considered, but the dose may need to be titrated up for efficacy likely due to lack of norepinephrine reuptake inhibition at doses less than 150 mg.<sup>2,52,53</sup>

Selective serotonin reuptake inhibitors (SSRIs) have some efficacy in treatment of chronic pain.<sup>4,8,50,52</sup> It is theorized that SSRIs may not be as efficacious for pain due to lack of NE activity.<sup>1</sup> However, they are still a good option in patients with comorbid depression and/or anxiety. Their side effect profile is most favorable among the antidepressants.<sup>54</sup> A systematic review of four comparative studies with SSRIs in patients with major depressive disorder and chronic pain did not reveal any differences in efficacy between SSRIs.<sup>55</sup>

Other antidepressants that may be utilized for chronic pain and comorbid anxiety or depression include bupropion, mirtazapine, and tricyclic antidepressants (TCAs).<sup>55</sup> TCAs are effective for neuropathic pain and migraine prophylaxis but are not first-line due to their side effect profile.<sup>56</sup> The TCAs that have broader spectrum inhibition of neurotransmitters, like amitriptyline, appear to be more effective than secondary amines like desipramine.<sup>1,56</sup> Analgesic efficacy seems to be dose-related but adverse effects may limit dose increases. Trazodone shows minimal efficacy for pain, but nefazodone has shown promise.<sup>1,55</sup> However, this medication carries the risk of liver toxicity.<sup>1</sup>

Anticonvulsants are a good option for treatment of chronic pain and psychiatric disorders. A recent Cochrane Database systematic review reported that pregabalin for generalized anxiety disorder had the best tolerability when compared to SSRIs and SNRIs.<sup>57</sup> Pregabalin is also effective for neuropathic pain so it could be considered as an option when a patient has both neuropathic pain and generalized anxiety.<sup>52,58,59</sup> Other anticonvulsants may also be used for pain. Gabapentin is useful for neuropathic pain with minimal adverse effects and may also help with substance abuse disorders.<sup>60,61</sup> Topiramate and valproic acid are useful for migraine prophylaxis and mood stabilization.<sup>62,63</sup>

Certain opiate analgesics may be used for severe uncontrolled chronic pain while also potentially affecting psychiatric disorders. Tramadol has unique pharmacologic properties. It is a weak mu-agonist and inhibits NE and 5HT reuptake and may be especially useful for neuropathic pain.<sup>53,64</sup> A study in rats and human case studies have shown a possible antidepressant effect.<sup>53,64</sup> However, there is still risk of abuse and misuse

with this medication. A particular opiate analgesic, tapentadol, has NE reuptake inhibiting properties and is a mu opioid agonist. There is an extended release form that may be especially useful for patients that have chronic neuropathic pain.<sup>65</sup> There are no current studies on its use for psychiatric disorders but this may be a future area of study. Tapentadol would not be an ideal medication for patients with uncontrolled anxiety or depression due to an increased risk of misuse and abuse.

## DRUG ABUSE

In the past 20 years, there has been an increase in the use of opioids for pain management. Practitioners have been educated to recognize and treat pain as the 5th vital sign.<sup>66,67</sup> With this increased awareness and treatment of pain there has been an increase in the misuse and abuse of pain medications. Patients with chronic pain and mood disorders are at much higher risk of substance abuse, including misuse of opioid pain medications.<sup>68</sup> A literature review published in *General Hospital Psychiatry* in 2013 revealed that patients with psychiatric diagnoses and substance abuse disorders are more likely to receive long-term opioid therapy for chronic pain and are more likely to suffer from adverse events like accidental overdose from this use.<sup>69</sup> Opioid involvement in emergency department (ED) admissions has risen 183% since 2004 and an estimated 15,000 deaths in 2008 were related to pain medications.<sup>69</sup> It is thought that a person may abuse substances initially to experience euphoria. This may be an attempt to mask depression or anxiety, decrease pain, or to alleviate stress. However, after time the pleasurable effects of these drugs decrease and may cause anhedonia in daily activities.<sup>70</sup> Opioid therapy may help with anxiety and depression in the short-term but long-term use can exacerbate psychiatric illness and decrease functional ability.<sup>69</sup>

For patients that have a substance abuse history, including opioid abuse, it is important to address pain complaints with nonpharmacologic approaches and medications with low abuse potential. Other substance abuse issues including use of alcohol, illicit drugs, and other addictive prescription medications like stimulants and benzodiazepines should be addressed. Medications like SNRI's and nonopioid analgesics discussed previously should be considered first-line options to address chronic pain and coexisting mood disorders. When deciding whether or not to use an opioid medication for pain some considerations should include the patient's pain diagnosis, risk of opioid abuse, and history of efficacy of opioids and non-opioid medications for the patient's pain.<sup>71</sup>

Pharmacists can provide a valuable service to patients by educating on the proper use of opioids. Patients should be instructed not to crush long-acting opioids and not to exceed the recommended dose. The patient should be informed of potential side effects including hyperalgesia, constipation, and sedation. In addition, patients should be educated on the risks of addiction and tolerance, and interactions with other sedating medications or alcohol.

Pharmacists can help in recognition of potential substance abuse issues. Some drug-seeking behaviors may include obtaining medications from multiple sources, acquisition of medications from family members, friends, or other illegal sources, and forgery or theft of medications.<sup>72</sup> These patients may frequently complain of lost or stolen narcotics or attempt to refill their pain medications from their provider after hours, which leads to visits to urgent care or the emergency room with requests for narcotics.<sup>72</sup> It was estimated in 2011 that about 25% of controlled substance prescriptions came from the emergency room.<sup>70</sup> Use of the emergency room for chronic pain issues encourages the use of multiple prescribers and lack of followup with the primary physician.

If an opioid is appropriate for treatment of a patient's chronic pain, it would be prudent to consider employing a pain treatment contract.<sup>73</sup> A pain contract should contain both patient and physician responsibilities. Some examples of items that may be included in the contract are a patient agreement not to use illegal substances, a specified time frame for follow-up clinic visits with the physician, and an understanding that there would be no allowances for lost or stolen medication. The contract should be signed by both physician and patient and include ramifications if the contract is breached. Often the patient-provider relationship is discontinued if the contract is not held by the patient. Regular follow-up and monitoring of the patient's progress is necessary. Random urine drug tests may also be part of the pain contract.<sup>73</sup> Pharmacists can assist the provider in development of a pain contract and in interpreting urine drug test results.

Monitoring of controlled substance use can now be done by using the Prescription (Drug) Monitoring Program (PMP or PDMP). The PMP is a database that is maintained by individual states. Currently there are 49 states that have a PMP or are currently in the process of implementing a PMP and 21 of these states share information.<sup>74</sup> Licensed prescribers and dispensers (pharmacists) can access the PMP and search by patient name or provider. The PMP is updated daily or weekly

depending on the state. Medications monitored include all controlled substances scheduled II-IV in addition to schedule V controlled substances and tramadol in some cases.<sup>74</sup> Pharmacists can use the PMP to look for signs of diversion, abuse, or doctor shopping by looking for early fills, multiple prescribers, multiple pharmacies, rapid dose escalation, and significant increases in quantities dispensed. Outpatient pharmacists can use the PMP to assess for fraudulent prescriptions or alterations to a prescription. Pharmacists can also use the PMP to monitor appropriate use of opioids for patients under a pain contract. A "patient alert" can be entered into the PMP system by prescribers or pharmacists for patients with diversion or abuse issues.<sup>74</sup> It is important to remember that the PMP information is confidential and cannot be provided to the patient or law enforcement and only current or prospective patients can be searched by the practitioner.<sup>74</sup>

Pharmacists can also provide assistance in developing an opioid taper protocol for patients that need to discontinue opioid use. Opioid tapers can be done on an inpatient or outpatient basis. Advantages of inpatient tapers are rapid completion over several days to weeks and close supervision of the patient's progress. One strategy for a fast opioid taper would be to decrease the dose by 25-50% every 3-7 days.<sup>71</sup> Patients undergoing an outpatient taper need to be responsible for adherence to the taper and should be educated on potential withdrawal symptoms. An outpatient taper may take 6 months for complete discontinuation of opioids. An example of a slow taper might be a decrease in dose of 10% every week.<sup>71</sup> There are guidelines to assist in opioid tapering like the 2010 Veterans Affairs/Department of Defence (VA/DoD) Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain.<sup>74,75</sup>

## CONCLUSION

Chronic pain and mood disorders commonly coexist, possibly due to the pathophysiologic similarities relating to neurotransmitters in the CNS. Assessment of pain in patients with mood disorders is best done comprehensively taking into account several factors including emotional, social, and psychological issues. These patients can be difficult to treat due to a difference in perception of pain, negative coping skills, and the risk of drug abuse. Treatment of chronic pain in patients with anxiety and/or depression is best done by a pain management team that focuses on the patient's responsibility to actively take part in the rehabilitation process. In order for the patient to reach his or her goals, it is important to make sure he or she is properly informed

of the condition and realistic expectations of pain control are set. Pharmacists can play a valuable role as part of the pain management team in a variety of areas ranging from inpatient to outpatient settings and medical to psychiatric environments. Some of these pharmacist roles include selection of an appropriate opioid regimen, recognition of potential opioid abuse, assistance with developing a pain contract, analysis of urine drug screen results, monitoring of controlled substance use, and providing education to patients.

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