

Martin A. Katzman MD, BSc, FRCPC; Elizabeth J. Pawluk, MA; Dina Tsirgielis, BSc; Christina D'Ambrosio, BSc; Leena Anand, BA; Melissa Furtado, BSc; Christina Iorio, MA

START Clinic for Mood and Anxiety Disorders, Toronto, Ontario, Canada (Dr. Katzman; Ms. Tsirgielis, D'Ambrosio, Anand, and Furtado); Department of Psychology, Lakehead University, Thunder Bay, Ontario (Dr. Katzman; Ms. Iorio); Department of Psychology, Ryerson University, Toronto (Ms. Pawluk)

mkatzman@startclinic.ca

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Beyond chronic pain: How best to treat psychological comorbidities

When chronic pain is accompanied by disturbances in sleep, a psychiatric disorder, or substance misuse, a single agent with multiple symptom targets may be the best place to start.

PRACTICE RECOMMENDATIONS

› *To achieve optimal outcomes for patients with chronic pain, treat the constellation of symptoms that often accompany it—eg, disordered sleep, depression or anxiety, and/or substance abuse—as well as the pain. (A)*

› *Individualize drug therapy for patients with chronic pain (eg, specific comorbidities and symptoms) while considering drug-based factors, including adverse effect profiles and the potential for interaction with other agents. (A)*

› *Consider using a tricyclic antidepressant, a serotonergic/noradrenergic antidepressant, gabapentin, or pregabalin for patients who have chronic pain and depression or anxiety. (A)*

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Primary care physicians often have the lead role in caring for patients with chronic pain from a myriad of causes, including arthritis, low back injury, migraine, neuropathic pain, and more.¹ To ensure optimal outcomes for such patients, understanding chronic pain syndromes and their negative effect on sleep, mood, and daily functioning is key.

Studies of the interaction of chronic pain, insomnia, and psychiatric disorders are increasing awareness of the way patients with this constellation of comorbidities respond to treatment. What they show is that optimal outcomes are possible only if we treat these co-occurring disorders simultaneously.

Pain affects multiple functions

While pain is thought to originate from a primary dysfunction in the nervous system, the mind and body are involved in the constellation of pain, sleep disturbances, depression, anxiety disorders, and substance abuse/dependence. Patients with chronic pain typically report a higher degree of impairment in all dimensions of quality of life and sleep, and have higher scores on anxiety or depression screens than those without chronic pain.²

■ **Sleep.** About two-thirds (65%) of patients with chronic pain and the vast majority (96%) of those with fibromyalgia report sleep disturbances, with difficulty falling asleep, staying asleep, or both.^{3,4} Sleep deprivation has a hyperalgesic effect, which leads to decreased pain tolerance and greater severity and pain-related disability.^{5,6} While there does not appear to be a causal link between poor sleep and the onset of new pain symptoms, treatment directed toward improving sleep may help to reduce pain severity.

■ **Depression.** In primary care settings, more than 27% of patients with chronic pain meet diagnostic criteria for comorbid depression.⁷ The relationship between pain and depression is bidirectional, whereby chronic pain predicts the onset of new depressive episodes and depression predicts the onset of chronic pain.⁸ Having both conditions is associated with greater pain intensity, greater interference with usual activities, and a lower likelihood of responding to treatment.⁸ That finding highlights the importance of screening for depression in patients who present with somatic complaints, such as fatigue and headache, and in treating both depression and the pain simultaneously.

■ **Anxiety.** The relationship between pain and anxiety also appears to be bidirectional. The prevalence of anxiety disorders—including generalized anxiety disorder (GAD), panic disorder, and social phobia—is about twice as high among patients with chronic pain than in the general population.⁹

In primary care settings, anxiety disorders often are unrecognized and untreated. What's more, anxiety can cause or exacerbate pain symptoms¹⁰; higher prevalence rates for arthritis, migraines, and back pain have been found in patients with a GAD diagnosis than in those without it.⁹ In older adults, pain conditions such as arthritis and migraines are associated with significantly higher rates of anxiety.¹¹

■ **Substance-related disorders.** Substance abuse and dependence are an increasing problem worldwide, especially in developed countries. In North America, according to a 2012 report from the International Narcotics Control Board, approximately one in every 20 deaths of individuals ages 15 to 64 years is related to substance abuse.¹² Canada has been found to have the world's highest per capita consumption of high-potency opioids.¹³ In the United States, prescription drug abuse has been targeted as a public health epidemic.¹⁴ Also of note: Chronic pain affects 24% to 67% of patients with substance use disorders.¹⁵

Because of their analgesic effect, opioids often are given to patients with chronic non-cancer pain, but substance misuse is common. Patients with a history of substance abuse or dependence are 4 times more likely to receive

a prescription for opioids than those without such a history, and often are given higher potency opioids at higher doses.¹⁶ What's more, individuals with chronic pain and a history of substance abuse/dependence generally have poorer outcomes, typically because they require more intensive treatment but rarely get it.¹⁷ These findings highlight the need to develop strategies to manage the symptoms of chronic pain in individuals who have a history of substance abuse or dependence—and to prevent addiction in patients without such a history.

Take aim at most—or all—of the patient's symptoms

In treating a patient with multiple comorbidities, it is best to initiate treatment with an agent that will address most—or all—of his or her symptoms. Using one drug whenever possible will reduce costs, prevent drug-drug interactions, and limit the likelihood of adverse effects. The American Psychiatric Association recommends the use of tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for treating chronic pain and comorbid depression.¹⁸ There is evidence of the effectiveness of “unconventional” analgesics, including anticonvulsants and antidepressants, for the treatment of chronic pain, as well. Opioids are, of course, an option too. In addition, nonpharmacologic treatments, such as cognitive-behavioral therapy (CBT), are recommended.¹⁹

Start with an anticonvulsant?

The anticonvulsants gabapentin and pregabalin have been shown to be effective in reducing certain types of neuropathic pain and alleviating insomnia.^{20,21} In studies investigating the use of these drugs in patients with GAD, both gabapentin and pregabalin led to improvement in anxiety symptoms, as well as in pain and sleep.^{20,21} At a dose of about 600 mg/d, pregabalin has been shown to significantly reduce pain levels in patients diagnosed with diabetic peripheral pain syndrome²²; it has also been found to help prevent relapse²³ and reduce sleep disturbances associated with GAD.²⁴

The most common adverse effects of pregabalin are mild-to-moderate somno-



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What percentage of the patients you see each week are seeking care for chronic pain?

- <10%
- 11%-25%
- 26%-50%
- 51%-75%
- >75%

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Avoid prescribing TCAs for depressed patients until you carefully assess their risk of overdose.

lence, dry mouth, headache, dizziness, and peripheral edema^{20,22}; dizziness, somnolence, peripheral edema, and gait disturbance are most commonly associated with gabapentin treatment.²⁵ These tend to stabilize over time, but occasionally the dose must be lowered or the drug discontinued.

■ **Lamotrigine** has been shown to reduce pain in patients with diabetic and sensory neuropathy compared with placebo,²⁶ but was not effective in treating patients with pain due to spinal cord injury. The drug should be initiated at a low dose and slowly titrated to minimize the risk of serious adverse effects such as Stevens-Johnson syndrome.²⁶

Try a tricyclic or an SNRI

TCAs, including amitriptyline, nortriptyline, desipramine, and imipramine, are recommended by the Canadian Pain Society as first-line therapy for chronic pain and often have benefit in the treatment of comorbid mood or anxiety disorders.²⁷ Noradrenergic antidepressants—including TCAs—appear to have particular efficacy in treating moderate to severe neuropathic pain in patients with a comorbid substance disorder who take the drugs regularly, while undergoing frequent assessments.¹⁵

Overdose is a risk associated with TCAs, which have higher toxicity than other classes of antidepressants.²⁸ Thus, it is essential to avoid prescribing TCAs for depressed patients until you carefully assess their risk of overdose. TCAs should not be prescribed for any patient at increased risk for cardiac arrhythmias.²⁹

■ **If you do prescribe a TCA...** The doses of TCAs used to treat mood and anxiety symptoms often are much higher than doses needed for pain relief. As a result patients are often at risk of experiencing side effects.

■ **What about an SNRI?** In general, SNRIs, which target both serotonin and norepinephrine, have a greater analgesic effect than antidepressants targeting either neurotransmitter alone.³⁰ Duloxetine, an SNRI, has been shown to effectively reduce symptoms in patients with pain disorders and comorbid depression.³¹ Other SNRIs studied in the treatment of pain and associated symptoms include venlafaxine, which has been effective in treating patients in

a primary care setting who had both pain and depression,³² and milnacipran, which has been used successfully to treat pain associated with fibromyalgia.³³

■ **SNRIs may interfere with sleep.** SNRIs have been associated with an increase in arousal and in rapid eye movement sleep suppression.³⁴ Thus, another type of medication may be preferable for patients with pain and a sleep disturbance or, if an SNRI is prescribed, it may be necessary to lower the dose or add a sleep aid.

The role of SSRIs

Despite the recognized utility and widespread use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depressive and anxiety disorders, their role in managing neuropathic pain is less clear. Although some agents, such as escitalopram, have demonstrated mild pain-relieving effects in patients with painful polyneuropathy, the magnitude of the effect was clinically relevant at best for only a small number of patients.³⁵ The effectiveness of other SSRIs in painful diabetic neuropathy has been shown to be less than that of TCAs.³⁶ SSRIs generally are not recommended for the treatment of chronic neuropathic pain, even when it is associated with mood and anxiety symptoms.²⁷

Opioids for which patients?

Chronic pain often is treated with opioids. Particular caution is required, however, when treating patients with pain and substance abuse or dependence.^{15,37} In order to prevent relapse in such individuals when they're suffering from chronic pain, opioids should be used only if:^{15,38}

- the pain is moderate to severe and has a significant impact on the patient's functioning and overall quality of life;
- nonopioid medications have been tried but were unsuccessful; and
- the patient agrees to be closely monitored while taking opioids.

The opioids tramadol and methadone are recommended as third-line therapy, along with nonopioid medications such as cannabinoids, lamotrigine, topiramate, and valproic acid.²⁷

■ **Use a comprehensive pain scale**, such as the Brief Pain Inventory, to assess the pain of any patient with a history of a substance-related disorder rather than asking him or her to rate the pain level on a general Likert-type scale.¹⁵

Long-acting opioids, such as sustained-release morphine, oxycodone, or fentanyl patch, are preferable to short-acting immediate-release opioids, which have a higher addictive profile because of their fast onset of action.¹⁵ Keep in mind, however, that long-acting opioids also have the potential for abuse, and patients taking them must be carefully monitored, as well.

Nonpharmacologic therapy often helps, too

Evidence suggests that even the most potent drugs significantly decrease pain in only about half of those taking them.³⁹ And whether or not adequate pain relief is achieved, patients with the constellation of pain and sleep, mood, anxiety, and/or substance disorders can benefit from nonpharmacologic interventions, as well. Let patients know that CBT, in particular, has been shown to have a positive effect on psychological function and comorbid psychological disorders, particularly when it is combined with pharmacologic therapy.⁴⁰ In addition, other nonpharmacologic treatments, including biofeedback⁴¹⁻⁴⁴ and meditation,⁴⁵⁻⁴⁷ have shown preliminary value in managing pain.

Further research is needed to understand the effectiveness of CBT in the management of chronic pain; however, it appears that

CBT may have a positive effect on psychological functioning and comorbid psychological disorders.

The bottom line: Don't overlook mood, anxiety symptoms in pain patients

In epidemiological studies of chronic pain, it is apparent that sleep, depressive, substance abuse/dependence, and anxiety syndromes often occur together, which supports the necessity of considering psychosocial dynamics to understand pain. Although there has been some inconsistency observed across findings (eg, Romano and Turner),⁴⁸ clarifying the relationships amongst these disorders may be an avenue for future research. The literature to date suggests that mood- and anxiety-related symptoms should not be overlooked in pain patients, as there is a negative effect on prognosis when these disorders co-occur.⁶

Treatment should be based on individual patient factors, such as presenting symptoms and potential for drug side effects. Some pharmacologic agents have been shown to be effective in treating several symptoms of this pyramid. Such drugs offer the best success and relapse rates, and reduce the likelihood of drug interactions. CBT appears to offer added benefits, especially if combined with pharmacology. However, few controlled trials have been conducted in this area and further research is required to appropriately guide clinical management. **JFP**

CORRESPONDENCE

Martin A. Katzman, MD, FRCPC, START Clinic for Mood and Anxiety Disorders, 32 Park Road, Toronto, Ontario, Canada M4W 2N4; mkatzman@startclinic.ca



Instead of using a Likert-type scale, use a comprehensive pain scale, such as the Brief Pain Inventory, to assess pain in patients with a history of a substance-related disorder.

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CBT has a positive effect on psychological comorbidities, especially when combined with medication.

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