

Chronic pain and depression: Treatment of 2 culprits in common

Selected antidepressants address both disorders. Non-drug therapies can be useful adjuncts

Patients who have chronic pain and those with a major depressive disorder (MDD) share clinical features, including fatigue, cognitive complaints, and functional limitation. Sleep disturbance and anxiety are common with both disorders. Because pain and depression share common neurobiological pathways (see Part 1 of this article in the February 2016 issue and at CurrentPsychiatry.com) and clinical manifestations, you can use similar strategies and, often, the same agents to treat both conditions when they occur together (*Table 1, page 47*).

What are the medical options?

Antidepressants. Using an antidepressant to treat chronic pain is a common practice in primary care and specialty practice. Antidepressants that modulate multiple neurotransmitters appear to be more efficacious than those with a single mechanism of action.¹ Convergent evidence from preclinical and clinical studies supports the use of serotonin-norepinephrine reuptake inhibitors (SNRIs) as more effective analgesic agents, compared with the mostly noradrenergic antidepressants, which, in turn, are more effective than selective serotonin reuptake inhibitors (SSRIs).² The mechanism of the

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Vladimir Maletic, MD, MS

Clinical Professor of Neuropsychiatry and Behavioral Science
University of South Carolina School of Medicine
Greenville, South Carolina

Bernadette DeMuri, MD

Clinical Instructor
Department of Psychiatry and Behavioral Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

analgesic action of antidepressants appears to rely on their inhibitory effects of norepinephrine and serotonin reuptake, thereby elevating the performance of endogenous descending pain regulatory pathways.³

Tricyclic antidepressants (TCAs), primarily amitriptyline, nortriptyline, and desipramine, have the advantage of years of clinical experience and low cost. Their side effect burden, however, is higher, especially in geriatric patients. Dose-dependent side effects include sedation, constipation, dry mouth, urinary retention, and orthostatic hypotension.

TCAs must be used with caution in patients with suicidal ideation because of the risk of a potentially lethal intentional overdose.

The key to using a TCA is to start with a low dosage, followed by slow titration. Typically, the dosages of TCAs used in clinical trials that focused on pain have been lower (25 to 100 mg/d of amitriptyline or equivalent) than the dosage typically necessary for treating depression; however, some experts have found that titrating TCAs to higher dosages with an option of monitoring serum levels may benefit some patients.⁴

SNRIs are considered first-line agents for both neuropathic pain and fibromyalgia. Duloxetine has been shown to be effective in both conditions⁵; venlafaxine also has shown efficacy in neuropathic pain.⁶ Milnacipran, another SNRI that blocks 5-HT, and norepinephrine equally and exerts a mild *N*-methyl-*D*-aspartate inhibition, has proven efficacy in fibromyalgia.^{7,8}

SSRIs for alleviating central pain or neuropathic pain are supported by minimal evidence only.⁹ A review of the effectiveness of various antidepressants on pain in diabetic neuropathy concluded that fluoxetine was no more effective than placebo.^{10,11} Schreiber and Pick¹¹ evaluated the antinociceptive properties of several SSRIs and offered the opinion that fluoxetine, fluvoxamine, and citalopram were, at best, weak antinociceptors.

Table 1

Pharmacotherapy of psychiatric disorders in a setting of comorbid pain

Comorbid state	Recommended agents
Depression and pain	SNRIs TCAs
Depression, pain, and anxiety	Duloxetine Venlafaxine
Depression, pain, and cognitive complaints	SNRIs (?)Vortioxetine
Depression, pain, and sleep disturbance	TCAs Adjunctive gabapentin Adjunctive pregabalin
Depression, pain, and fatigue	Milnacipran Adjunctive bupropion Adjunctive modafinil

SNRI: serotonin-norepinephrine reuptake inhibitor;
TCA: tricyclic antidepressant

Opioids. Data on the long-term benefits of opioids are limited, except for use in carefully selected patients; in any case, risk of abuse, diversion, and even death with these agents is quite high.¹² Also, there is evidence that opioid-induced hyperalgesia might limit the usefulness of opioids for controlling chronic pain.¹³

Gabapentin and pregabalin, both anti-convulsants, act by binding to the α -2- σ subunit of voltage-gated calcium channels within the CNS.¹⁴ By reducing calcium influx at nerve terminals, the drugs diminish the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. This mechanism is thought to be the basis for the analgesic, anticonvulsant, and anxiolytic effects of these drugs.¹⁵

Gabapentin and pregabalin have been shown to decrease pain intensity and improve quality of life and function in patients with neuropathic pain conditions. Pregabalin also has shown efficacy in treating central neuropathic pain and fibromyalgia.¹⁶

Added benefits of these drugs is that they have (1) a better side effect profile

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SNRIs are considered first-line agents for fibromyalgia and neuropathic pain



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Beneficial effects of antidepressants may be 'pseudo-specific': that is, a reflection of improvement in mood overall

than TCAs and (2) fewer drug interactions when they are used as a component of combination therapy. Pregabalin has the additional advantage of less-frequent dosing, linear pharmacokinetics, and a predictable dose-response relationship.¹⁷

Addressing other comorbid psychiatric conditions

Sleep disturbance is common among patients with chronic pain. Sleep deprivation causes a hyperexcitable state that amplifies the pain response.¹⁸

When a patient presents with chronic pain, depression, and disturbed sleep, consider using a sedating antidepressant, such as a TCA. Alternatively, gabapentin or pregabalin can be added to an SNRI; anticonvulsants have been shown to improve quality of sleep.¹⁹ Cognitive-behavioral interventions targeting sleep disturbance may be a helpful adjunct in these patients.²⁰

When anxiety is comorbid with chronic pain, antidepressants with proven efficacy in treating anxiety disorders, such as duloxetine or venlafaxine, can be used. When chronic pain coexists with a specific anxiety disorder (social anxiety disorder, obsessive-compulsive disorder, panic disorder), an SSRI might be more advantageous than an SNRI,²¹ especially if it is combined with a more efficacious analgesic.

Benzodiazepines should be avoided as a routine treatment for comorbid anxiety and pain, because these agents can produce sedation and cognitive interference, and carry the potential for dependence.

Fatigue. In patients who, in addition to pain and depression, complain of fatigue, an activating agent such as milnacipran or adjunct bupropion might be preferable to other agents. Modafinil has been shown to be a well-tolerated and potentially effective augmenting agent for antidepressants when fatigue and sleepiness are present as residual symptoms²²; consider them as adjuncts when managing patients who have chronic pain and depression that manifests as excessive sleepiness and/or fatigue.

Cognitive complaints. We have noted that disturbances of cognition are common in patients with depression and chronic pain, and that cognitive dysfunction might improve after antidepressant treatment.

Studies suggest that SSRIs, duloxetine, and other antidepressants, such as bupropion, might exert a positive effect on learning, memory, and executive function in depressed patients.²³ Beneficial effects of antidepressants may be "pseudo-specific," however—that is, predominantly a reflection of overall improvement in mood, not on specific amelioration of the cognitive disturbance.

Vortioxetine has shown promise in improving cognitive function in adults with MDD; its cognitive benefits are largely independent of its antidepressant effect.²⁴ The utility of vortioxetine in chronic pain patients has not been studied, but its positive impact on mood, anxiety, sleep, and cognition might make it a consideration for patients with comorbid depression—although it is uncertain at this time whether putative noradrenergic activity makes it suitable for use in chronic pain disorders.

Last, avoid TCAs in patients who have cognitive complaints. These agents have anticholinergic effects that can have an adverse impact on cognitive function.

Cautions: Drug–drug interactions, suicide risk, disrupted sleep

Avoiding drug–drug interactions is an important consideration when treating comorbid disorders. Many chronic pain patients take over-the-counter or prescribed nonsteroidal anti-inflammatory drugs for analgesia; these agents can increase the risk of gastrointestinal bleeding when they are combined with an SSRI or an SNRI.

The use of the opioid tramadol with an SNRI or a TCA is discouraged because of the risk of serotonin syndrome.

Combining a sedating antidepressant, such as a TCA, with gabapentin or pregabalin can increase the risk of CNS depression and psychomotor impairment, especially in geriatric patients. An opioid analgesic is likely to amplify these effects.

Table 2

Non-drug options for treating chronic pain and major depressive disorder (MDD)

Cognitive-behavioral therapy

- Has established efficacy as stand-alone or adjunct treatment of chronic pain, MDD, anxiety disorders, and insomnia
- Diminishes catastrophizing and ruminations
- Supports maintenance of improvement

Mindfulness-based therapy

- Established efficacy as monotherapy or adjunctive treatment of chronic pain, MDD, and anxiety disorders

Other behavioral and psychological approaches^a

- Acupuncture
- Biofeedback
- Deep diaphragmatic breathing and relaxation training
- Guided imagery
- Hypnosis
- Supportive group therapy

Exercise and restorative therapies

- Evidence supports adjunct use in treatment of MDD and chronic pain. Exercise improves pain control, mood, cognition, strength, functionality, and cardiometabolic and bone health

^aThese are mostly helpful as components of a mind–body integrated treatment of chronic pain and depression

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Complaints of sleep disturbance and anxiety can compound the risk of suicide in a patient with chronic pain

Suicidal ideation is not uncommon in patients with chronic pain and depression. To minimize the risk of suicide in patients with a chronic pain disorder, you should ensure optimal pain control by combining the most efficacious analgesic agent with psychotherapeutic interventions and optimal antidepressant treatment. Furthermore, cognitive-behavioral therapy (CBT) (see the discussion below) might not only improve pain coping skills, but also ameliorate catastrophizing, anxiety, and concomitant sleep disturbance.

Complaints of sleep disturbance and anxiety can compound the risk of suicide in a chronic pain patient. When possible, these complex patients should be treated by a multidisciplinary team that includes a pain management specialist, psychotherapist, and primary care clinician. It is important to strengthen the clinician–patient relationship to facilitate close monitoring of symptoms and to provide a trusting environment in which patients feel free to discuss thoughts of suicide or self-harm. For such patients, prescribing opiates and TCAs in small quantities is a prudent action.

When a patient struggles with suicidal thoughts, his (her) family might need to dispense these medications. Most important, if a patient is actively suicidal, consider referral to an inpatient facility or intensive outpatient program, where aggressive treatment of depressive symptoms and intensive monitoring and support can be provided.²⁵

Usefulness of non-drug interventions

There is, of course, a diversity of non-drug treatments for MDD and for chronic pain; discussion here focuses primarily on modalities with established efficacy in *both* disease states (*Table 2*). On rare occasions, non-drug treatments can constitute a stand-alone approach; most often, they are incorporated into a multimodal treatment plan or applied as an adjunct intervention.²⁶

Psychotherapy. The most robust evidence supports the use of CBT in addressing MDD and chronic pain—occurring individually and comorbidly.^{26–28} Efficacy is well established in MDD, as monotherapy



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Cognitive-behavioral therapy has demonstrated value for relieving pain-related disability

and adjunct treatment, spanning acute and maintenance phases.

Furthermore, CBT also has support from randomized trials, meta-analyses, and treatment guidelines, either as monotherapy or co-therapy for both short-term relief and long-term pain reduction. Additionally, CBT has demonstrated value for relieving pain-related disability.^{26,28}

Combination of a special form of CBT, *ruminant-focused CBT* with ongoing pharmacological therapy over a 26-week period in a group of medication-refractory MDD patients produced a remission rate of 62%, compared with 21% in a treatment-as-usual group.²⁹ This is of particular interest in chronic pain patients, because rumination-related phenomena of *pain catastrophizing* and *avoidance* facilitate a transition from acute to chronic pain, while augmenting pain severity and associated disability.³⁰

Catastrophizing also has been implicated in mediating the relationship between pain and sleep disturbance. Not surprisingly, a randomized controlled study demonstrated the benefit of 8-week, Internet-delivered CBT in patients suffering from comorbid chronic pain, depression, and anxiety. Treatment significantly diminished pain catastrophizing, depression, and anxiety; maintenance of improvement was demonstrated after 1 year of follow-up.³¹

Other behavioral and psychological approaches. Biofeedback, mindfulness-based stress reduction, relaxation training and diaphragmatic breathing, guided imagery, hypnosis, and supportive groups might play an important role as components of an integrated mind-body approach to chronic pain,^{28,32,33} while also providing mood benefits.

Exercise. The role of exercise as a primary treatment of MDD continues to be controversial, but its benefits as an add-on intervention are indisputable. Exercise not only complements pharmacotherapy to produce greater reduction in depressive scores and improvement in quality of life, it might aid in reestablishing social contacts when conducted in a group setting—

an effect that can be of great value in both MDD and chronic pain.³⁴

Exercise and restorative therapies provide several benefits for chronic pain patients, including:

- improved pain control, cognition, and mood
- greater strength and endurance
- cardiovascular and metabolic benefits
- improved bone health and functionality.^{26,28,32,33,35}

To achieve optimal benefit, an exercise program must be customized to fit the patient's physical condition, level of fitness, and specific type of pain.³⁵ Preliminary evidence suggests that, beyond improvement in pain and functionality, exercise might reduce depressive symptoms in chronic pain patients.³⁶

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Benefits of exercise as an add-on intervention in MDD are indisputable; exercise also provides improved pain control

Related Resources

- Maletic V, DeMuri B. Chronic pain and depression: Understanding 2 culprits in common. *Current Psychiatry*. 2013;15(2):40-44,52.
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Drug Brand Names

Amitriptyline • Elavil	Milnacipran • Savella
Bupropion • Wellbutrin	Modafinil • Provigil
Citalopram • Celexa	Nortriptyline • Aventyl,
Desipramine • Norpramin	Pamelor
Duloxetine • Cymbalta	Pregabalin • Lyrica
Fluoxetine • Prozac	Tramadol • Ultram
Fluvoxamine • Luvox	Venlafaxine • Effexor
Gabapentin • Neurontin,	Vortioxetine • Brintellix
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Bottom Line

Because pain and depression share common neurobiological pathways and clinical manifestations, similar strategies and agents are used to treat these conditions, including when they are comorbid. Use of antidepressants for treatment of chronic pain is a common practice. Long-term benefit of opioids is limited, although the risk of these drugs is high. Gabapentin and pregabalin decrease pain intensity and improve quality of life and function neuropathic pain. Non-drug approaches can be used as stand-alone, but are more commonly incorporated into a multimodal treatment plan or applied as an adjunct.