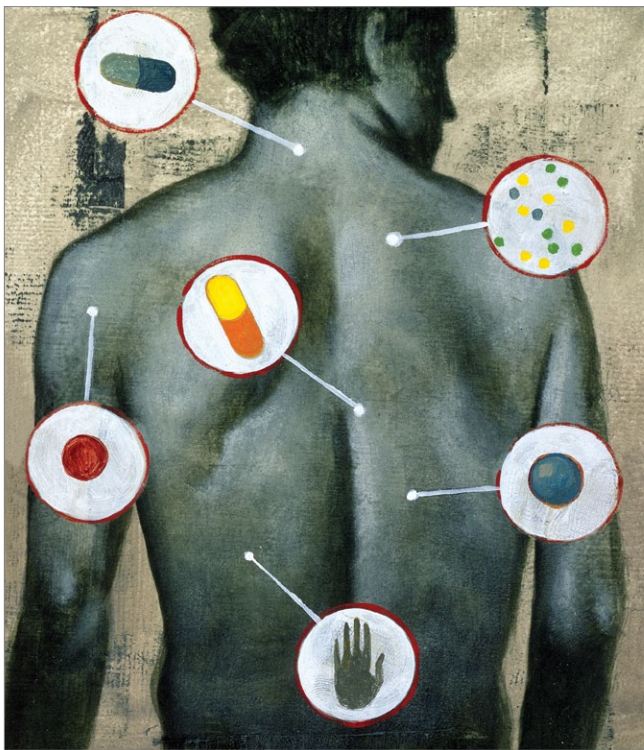


Managing chronic pain: Consider psychotropics and other non-opioids



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For some patients, certain medications may be an alternative to opioids

Of the 56 million American adults who report living with chronic pain almost 60% also exhibit psychiatric disorders such as depression or anxiety.^{1,2} Because patients with chronic pain suffer from a mixture of physical and psychological components, managing such conditions is complicated, and using opioids is tempting. However, treatment needs to address the underlying pathology along with social and psychological factors.

Because substance abuse treatment admissions increased by 400% from 1998 to 2008,³ many physicians look to non-opioids and other treatment modalities to control chronic non-cancer pain. Common pharmacologic therapies used to treat chronic pain include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), antiepileptic drugs (AEDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and, to a lesser extent, atypical antipsychotics. TCAs, SNRIs, AEDs, NSAIDs, and atypical antipsychotics influence a variety of presumed underlying pathophysiological processes, including inflammatory mediators, activity of *N*-methyl-D-aspartate (NMDA) receptors, and voltage-gated calcium channels. In addition, they increase activity of descending inhibitory pain pathways. Animal studies suggest dysfunction of these inhibitory mechanisms contributes to the central sensitization and hyperexcitability of pain transmitting pathways.⁴

In this article, we discuss psychotropics and other non-opioid agents for treating pain. However, no single solution is best for all patients with chronic pain and this article is not a “how to” guide to avoid administer-

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Table 1

Tricyclic antidepressants used to treat pain

Drug	Dosage range for pain (off-label)	Comments
Amitriptyline	10 to 100 mg/d	High sedation, high anticholinergic side effects
Amoxapine	50 to 100 mg/d	Low sedation, moderate anticholinergic side effects
Clomipramine	25 to 100 mg/d	Low sedation, low anticholinergic side effects
Desipramine	25 to 100 mg/d	Low sedation, low anticholinergic side effects
Imipramine	25 to 100 mg/d	Moderate sedation, moderate anticholinergic side effects
Nortriptyline	10 to 75 mg/d	Moderate sedation, low anticholinergic side effects

Source: Reference 8

ing opioid medication. Also incorporate a multimodal, non-pharmacologic approach whenever possible.

Tricyclic antidepressants

Although this class acts primarily by increasing serotonin levels, norepinephrine and dopamine also are affected depending on the particular medication. Studies have shown that amitriptyline, nortriptyline, and desipramine function well as analgesics independent of their antidepressant effects.⁵ TCAs may improve pain symptoms at lower therapeutic dosages than those used for treating depression.⁵

Although researchers have not elucidated TCAs' mechanism of action with regards to analgesia, they are thought to act within the concept of the gating theory of pain control,⁶ which functions by activation and inhibition of pain signal transmission. It is believed TCAs act on nociceptive pathways by blocking serotonin and norepinephrine reuptake. Although researchers previously thought that TCAs' analgesic mechanism was correlated to serotonin reuptake inhibition, this theory has changed. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have not demonstrated substantial effectiveness in neuropathic pain when compared with TCAs and SNRIs. Recent studies have shown that TCAs may work by blocking sodium channels, similar to local anesthetics and antiarrhythmic agents.⁷

Psychiatrists prescribe TCAs infrequently because of these drugs' unfavor-

able side effect profile compared with SSRIs and SNRIs. However, TCAs often are prescribed for pain management as an adjunct to other medications for neuropathic conditions and at lower dosages than those used for treating depression (Table 1).⁸

SNRIs

Evidence supports using duloxetine, a potent SNRI that mediates pain inhibition in the descending pathways, for 4 chronic pain conditions:

- diabetic peripheral neuropathic pain
- fibromyalgia
- mechanical low back pain
- pain associated with osteoarthritis.⁹

Titrate the dosage to 60 mg/d and maintain the patient at this dose for at least 4 weeks. Thereafter, according to patient response, the dosage may be titrated to 120 mg/d (off-label) with appropriate vital sign monitoring and routine lab analysis.

Venlafaxine also can mediate pain response in a similar manner to duloxetine, but is not FDA-approved for treating pain. Use caution when prescribing venlafaxine for patients with a history of hypertension. Milnacipran is a relatively new SNRI that has been shown to be effective in treating fibromyalgia in divided doses of 100 to 200 mg/d (Table 2, page 40).⁹⁻¹¹

Antiepileptic drugs

Several AEDs are used for pain management (Table 3, page 41).¹²⁻¹⁶ Gabapentin and

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TCAs may improve pain symptoms at lower therapeutic dosages than those used for treating depression



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Treating chronic pain

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Evidence supports using the SNRI duloxetine for 4 types of chronic pain

Table 2

Treating pain with serotonin-norepinephrine reuptake inhibitors

Drug	Dosage range for pain	Comments
Duloxetine	60 to 120 mg/d ⁹	FDA maximum recommended dose is 60 mg/d
Milnacipran	25 to 200 mg/d ¹⁰	Approved for treating depression outside the United States
Venlafaxine	75 to 225 mg/d ¹¹	Monitor blood pressure, LFTs, and kidney function

LFTs: liver function tests

pregabalin work by binding to voltage-gated calcium channels and decreasing excitatory neurotransmitter release. Along with TCAs, they are considered a first-line treatment for managing neuropathic pain.¹⁷ Gabapentin is FDA-approved for seizures and postherpetic neuralgia, but evidence supports its use in most types of neuropathic pain. Pregabalin is FDA-approved for treating seizures, diabetic peripheral neuropathy, central neuropathic pain, postherpetic neuralgia, and fibromyalgia.

Topiramate inhibits excitatory neurotransmission by enhancing the effects of gamma-aminobutyric acid, and also by blocking NMDA receptors. Topiramate is FDA-approved for seizures and migraine prophylaxis, and is used off-label for treating neuropathic pain. A 12-week trial of topiramate for diabetic neuropathy found significant analgesia in 50% of patients taking the drug, compared with 34% receiving placebo.¹⁸

Lamotrigine is approved for several types of seizures and maintenance of bipolar I disorder, and is used off-label for neuropathic pain. A recent Cochrane database review concluded that lamotrigine is ineffective for neuropathic pain¹⁴; however, some guidelines recommend using lamotrigine to treat neuropathies that do not respond to treatment with carbamazepine.¹⁹

Carbamazepine is a complex AED that is structurally similar to TCAs. It blocks sodium channels and has various pharmacologic properties, including anticholinergic, muscle relaxant, antidepressant, and sedative effects. Carbamazepine has analgesic effects through blockade of synaptic transmission in the trigeminal nucleus

and is FDA-approved for seizures, bipolar disorder, neuropathic pain, and trigeminal neuralgia. In a systematic review of 12 trials of carbamazepine that included 4 placebo-controlled trials for trigeminal neuralgia, 2 studies showed a number needed to treat (NNT) of 1.8.²⁰ For diabetic neuropathy, there was insufficient data to calculate NNT.

Oxcarbazepine, an analog of carbamazepine, also is FDA-approved for seizures and is used off-label for neuropathic pain. In the only double-blind trial with positive results, oxcarbazepine titrated to 1,800 mg/d reduced diabetic neuropathy pain scores on a visual analog scale by 24 points—roughly 25%.¹⁵

Non-opioid analgesics

NSAIDs have antipyretic, analgesic, and anti-inflammatory effects and are used for fever, headache, mild-to-moderate pain, musculoskeletal pain, menstrual pain, and dental pain. They are particularly useful in treating acute pain, often in combination with opioid analgesics. NSAIDs exert their analgesic action through blockade of prostaglandin production via reversible inhibition of cyclooxygenase-1 and cyclooxygenase-2.

The most common side effects of NSAIDs are the result of gastrointestinal (GI) toxicity and include dyspepsia, heartburn, nausea, anorexia, and epigastric pain.²¹ GI ulceration and bleeding are rare but serious complications. To decrease these risks, tell patients to take NSAIDs with food. Add a GI protective agent, such as an H2 blocker or proton pump inhibitor, for patients at higher risk for GI complications.²²

Table 3

Antiepileptic drugs for pain treatment

Drug	Dosage range for pain	Comments
Carbamazepine	Starting dose: 100 mg twice a day, doses titrated to 400 to 800 mg/d usually are adequate. Maximum of 1,200 mg/d ¹²	Anticholinergic effects, blood dyscrasias, hyponatremia, increase in LFTs, ECG changes. CYP450 inducer, many DDIs
Gabapentin	Starting dose: 100 to 300 mg at bedtime or 100 to 300 mg 3 times a day, slow titration, maximum of 3,600 mg/d ¹³	Dizziness, sedation, weight gain, peripheral edema. Adjust dose in renal insufficiency
Lamotrigine	200 to 400 mg/d ¹⁴	Sedation, headache, dizziness, ataxia, GI upset, blurred vision. Risk of life-threatening rash
Oxcarbazepine	Starting dose: 300 mg/d, then titrated as tolerated to a maximum of 1,800 mg/d ¹⁵	Adverse drug reactions similar to carbamazepine, less anticholinergic effects, more hyponatremia. Fewer DDIs than carbamazepine
Pregabalin	Starting dose: 50 mg 3 times a day or 75 mg twice a day, may increase every 3 to 7 days as tolerated, maximum of 600 mg/d ¹³	Same adverse drug reactions as gabapentin, less sedation. Adjust dose in renal insufficiency. More costly than gabapentin
Topiramate	Starting dose: 12.5 to 25 mg once or twice a day for 4 weeks; then double the dose every 4 weeks to reach a maximum dose of 100 to 200 mg/d in divided doses ¹⁶	Weight loss, anorexia, nephrolithiasis, cognitive impairment

CYP450: cytochrome P450; DDIs: drug-drug interactions; GI: gastrointestinal; LFTs: liver function tests

In addition, inhibition of renal prostaglandins by NSAIDs can cause renal toxicity, fluid retention, and edema, potentially exacerbating existing cardiovascular conditions such as hypertension and heart failure. NSAIDs may increase the risk of serious thrombotic events such as myocardial infarction and stroke. Use NSAIDs at the lowest effective dose for the shortest duration possible and generally avoid prescribing in patients at high risk for cardiovascular disease and pregnant women, especially those in their third trimester.^{23,24}

NSAIDs may cause pharmacodynamic and pharmacokinetic drug-drug interactions. The risk of GI toxicity and bleeding increases when NSAIDs are administered with drugs that also irritate the gastric mucosa or have antiplatelet/anticoagulant effects.²¹ Plasma concentrations of drugs with a narrow therapeutic index that are renally eliminated, such as methotrexate and lithium, can increase to potentially toxic levels with concurrent NSAID use because NSAIDs decrease renal perfusion.²¹ Also, the therapeutic effects of anti-

hypertensives may be attenuated because NSAIDs cause fluid retention.²⁵

Acetaminophen (APAP) is available in several dosage forms as a single ingredient and in combination with opioids in prescription products. For more information about APAP, see this article at CurrentPsychiatry.com.

Atypical antipsychotics

Although atypical antipsychotics are not often used to treat pain, studies indicate that fibromyalgia patients may benefit from ziprasidone²⁶ and olanzapine,²⁷ most often as an adjunctive treatment rather than monotherapy. Randomized controlled studies indicate poor tolerability with several atypical antipsychotics. Weight gain, akathisia, and somnolence are side effects of some atypical antipsychotics. Additionally, ziprasidone has been associated with QTc prolongation. For chronic pain patients, atypical antipsychotics are most useful for treating psychiatric comorbidities.

Clinical Point

Along with TCAs, antiepileptic drugs are considered first-line for treating neuropathic pain



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Treating chronic pain

Clinical Point

Use NSAIDs at the lowest effective dose possible because they may increase the risk of myocardial infarction and stroke

Related Resources

- Leo RJ. Chronic nonmalignant pain: How to 'turn down' its physiologic triggers. *Current Psychiatry*. 2008;7(8):19-36.
- Nikolaus T, Zeyfang A. Pharmacological treatments for persistent non-malignant pain in older persons. *Drugs Aging*. 2004;21(1):19-41.
- World Health Organization. WHO's pain ladder. www.who.int/cancer/palliative/painladder/en.

Drug Brand Names

Acetaminophen • Tylenol	Lithium • Eskalith, Lithobid
Amitriptyline • Elavil, others	Methotrexate • Rheumatrex, Trexall
Amoxapine • Asendin	
Carbamazepine • Tegretol, Carbatrol, others	Milnacipran • Savella
Clomipramine • Anafranil	Nortriptyline • Aventyl, Pamelor
Desipramine • Norpramin	Olanzapine • Zyprexa
Duloxetine • Cymbalta	Oxcarbazepine • Trileptal
Fluoxetine • Prozac	Pregabalin • Lyrica
Gabapentin • Neurontin, Gralise	Topiramate • Topamax, Topiragen
Imipramine • Tofranil	Venlafaxine • Effexor
Lamotrigine • Lamictal	Ziprasidone • Geodon

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Bottom Line

For patients with chronic pain, certain non-opioid medications—including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, antiepileptic drugs, and nonsteroidal anti-inflammatory drugs—may eliminate the need for opioid analgesics. Consider the risks and benefits of these medications, as well as the individual characteristics of the patient's presenting problem.

Box

Acetaminophen : Safe and effective for treating pain

Although its mechanism of action is not well understood, acetaminophen (APAP) works by blocking prostaglandin syntheses via inhibition of cyclooxygenase-1 and cyclooxygenase-2 in the CNS.^a Therefore, in contrast to NSAIDs, APAP does not possess peripheral anti-inflammatory effects or affect platelet function and is effective for treating fever, headache, and acute and chronic mild pain. The American Geriatrics Society recommends APAP for minor and persistent pain in older patients^b and the American College of Rheumatology recommends it as first-line therapy for osteoarthritis of the hip or knee.^c

APAP has few clinically significant drug interactions, an excellent safety profile, and a long history of safe and effective use.

When used within the recommended dosage range, APAP has few side effects. However, overuse of APAP is the leading cause of acute liver failure in the United States.^d APAP hepatotoxicity can be accompanied by nephrotoxicity, is dose-dependent, and can be caused by acute overdose or chronic ingestion at doses over the recommended maximum of 4 g/d. Patients have experienced elevated liver transaminases with coadministration of APAP with phenytoin and phenobarbital.^{e,f} Alcohol and other potentially hepatotoxic drugs also can increase the risk of liver toxicity when combined with APAP.^g APAP is pregnancy category B and is considered the drug of choice for treating pain or fever during pregnancy and breast-feeding.⁹

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