Antidepressants for chronic pain

Certain agents may mitigate pain associated with neuropathy, fibromyalgia, headache, and IBS

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Approximately 55 years ago, tricyclic antidepressants (TCAs) began to be used to treat neuropathic pain. Eventually, clinical trials emerged suggesting the utility of TCAs for other chronic pain conditions, such as fibromyalgia (FM) and migraine prophylaxis. However, despite TCAs’ effectiveness in mitigating painful conditions, their adverse effects limited their use.

Pharmacologic advancements have led to the development of other antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), and the use of these agents has come to eclipse that of TCAs. In the realm of pain management, such developments have raised the hope of possible alternative co-analgesic agents that could avoid the adverse effects associated with TCAs. Some of these agents have demonstrated efficacy for managing chronic pain states, while others have demonstrated only limited utility.

This article provides a synopsis of systematic reviews and meta-analyses examining the role of antidepressant therapy for managing several chronic pain conditions, including pain associated with neuropathy, FM, headache, and irritable bowel syndrome (IBS). Because the literature base is rapidly evolving, it is necessary to revisit the information gleaned from clinical data with respect to treatment effectiveness, and to clarify how antidepressants might be positioned in the management of chronic pain.

continued
The effectiveness of antidepressants for pain

The pathophysiologic processes that precipitate and maintain chronic pain conditions are complex (Box 1, page 11). The pain-mitigating effects of antidepressants can be thought of in terms of direct analgesic effects and indirect effects (Box 2, page 12).

During the last several decades, antidepressants have been used to address—and have demonstrated clinical utility for—a variety of chronic pain states. However, antidepressants are not a panacea; some chronic pain conditions are more responsive to antidepressants than are others. The chronic painful states most amenable to antidepressants are those that result primarily from a process of neural sensitization, as opposed to acute somatic or visceral nociception. Hence, several meta-analyses and evidence-based reviews have long suggested the usefulness of antidepressants for mitigating pain associated with neuropathy, headache, FM, and IBS.

Neuropathic pain

Several treatment guidelines advocate for the use of antidepressants for neuropathic pain. For decades, TCAs have been employed off-label to successfully treat many patients with neuropathic pain states. Early investigations suggested that TCAs were robustly efficacious in managing patients with neuropathy. Calculated number-needed-to-treat (NNT) values for TCAs were quite low (ie, reflecting that few patients would need to be treated to yield a positive response in one patient compared with placebo), and were comparable to, if not slightly better than, the NNTs generated for anticonvulsants and α2-δ ligands, such as gabapentin or pregabalin.

Unfortunately, early studies involving TCAs conducted many years ago do not meet contemporary standards of methodological rigor; they featured relatively small samples of patients assessed for brief post-treatment intervals with variable outcome measures. Thus, the NNT values obtained in meta-analyses based on these studies may overestimate treatment benefits. Further, NNT values derived from meta-analyses tended to combine all drugs within a particular antidepressant class (eg, amitriptyline, nortriptyline, desipramine, and imipramine among the TCAs) employed at diverse doses. Taken together, these limitations raise questions about the results of those meta-analyses.

Subsequent meta-analyses, which employed strict criteria to eliminate data from studies with potential sources of bias and used a primary outcome of frequencies of patients reporting at least 30% pain reduction compared with a placebo-controlled sample, suggest that the effectiveness of TCAs as a class for treating neuropathic pain is not as compelling as once was thought. Meta-analyses of studies employing specific TCAs revealed that there was little evidence to support the use of desipramine, imipramine, or nortriptyline in managing diabetic neuropathy or postherpetic neuralgia. Studies evaluating amitriptyline (dose range 12.5 to 150 mg/d), found low-level evidence of effectiveness; the benefit was expected to be present for a small subset (approximately 25%) of patients with neuropathic pain.

There is moderate-quality evidence that duloxetine (60 to 120 mg/d) can produce a ≥50% improvement in pain severity ratings among patients with diabetic peripheral neuropathy. Although head-to-head studies with other antidepressants are limited, it appears that duloxetine and amitriptyline have comparable efficacy, even though the NNTs for amitriptyline were derived from lower-quality studies than those for duloxetine. Duloxetine is the only antidepressant to receive FDA approval for managing diabetic neuropathy. By contrast, studies assessing the utility of venlafaxine in neuropathic pain comprised small samples for brief durations, which limits the ability to draw clear (unbiased) support for its usefulness.

Given the diversity of pathophysiologic processes underlying the disturbances that cause neuropathic pain disorders, it is unsurprising that the effectiveness of amitriptyline and duloxetine were not generalizable to all neuropathic pain states. Although amitriptyline produced pain-mitigating effects in patients with diabetic neuropathy and
post-herpetic neuralgia, and duloxetine mitigated pain among patients with diabetic neuropathy, there was no evidence to suggest their effectiveness in phantom limb pain or human immunodeficiency virus-related and spinal cord-related neuropathies.

Fibromyalgia

As with the issues encountered in interpreting the effectiveness of antidepressants in neuropathic pain, interpreting results gleaned from clinical trials of antidepressants for treating FM are fraught with similar difficulties. Although amitriptyline has been a first-line treatment for FM for many years, the evidence upon which such recommendations were based consisted of low-level studies that had a significant potential for bias.59 Large randomized trials would offer more compelling data regarding the efficacy of amitriptyline, but the prohibitive costs of such studies makes it unlikely they will be conducted. Amitriptyline (25 to 50 mg/d) was effective in mitigating FM-related pain in a small percentage of patients studied, with an estimated NNT of 4.59 Adverse effects, often contributing to treatment discontinuation, were encountered more frequently among patients who received amitriptyline compared with placebo.

Selective serotonin reuptake inhibitors failed to demonstrate significant pain relief (estimated NNT of 10), or improvement in fatigue or sleep problems, even though the studies upon which such conclusions were based were low-level studies with a high potential for bias.60 Although SSRIs have limited utility for mitigating pain, they are still quite useful for reducing depression among patients with FM.60

By contrast, the SNRIs duloxetine and milnacipran provided clinically relevant pain relief.
Antidepressants for chronic pain

Clinical Point
Pain relief in patients with irritable bowel syndrome is possible with both TCAs as well as SSRIs

Box 2
Antidepressants’ direct and indirect pain-mitigating effects and psychiatric comorbidities

The pain-mitigating effects of antidepressants can be thought of in terms of direct analgesic effects (impacting neurotransmission of descending pathways independent of influences on mood) and indirect effects (presumably impacting cortical and limbic output to the periaqueductal gray area, the rostroventral medulla, and the dorsolateral pontomesencephalic tegmentum brought about by improvement in mood and/or cognitive appraisals) (Figure 2,3,8,10,11,15,20,22,28,29). Support for the direct analgesic effects has been garnered from initial empirical work that demonstrated pain relief among patients with pain who are not depressed. Additionally, among patients who have depression and experience pain, analgesia reportedly often occurs within 2 weeks, which is before antidepressant effects are appreciated, and, at least for some antidepressants, occurs at doses far lower than those required to produce mood-elevating effects. On the other hand, it is well established that significant comorbidities exist between chronic pain states and psychiatric disorders (eg, depression and somatic symptom and related disorders). There may be common physiological substrates underlying chronic pain and depression. There are bidirectional influences of limbic (affective) systems and those CNS structures involved in pain processing and integration. The effects of pain and depression are reciprocal; the presence of one makes the management of the other more challenging. Mood disturbances can, therefore, impact pain processing by acting as affective and cognitive amplifiers of pain by leading to catastrophizing, pain severity augmentation, poor coping with pain-related stress, etc. It is plausible that the mood-elevating effects of antidepressants can improve pain by indirect effects, by modulating limbic activity, which in turn, impacts coping, cognitive appraisals of pain, etc.

Patients with somatoform disorders (using pre-DSM-5 terminology) frequently present with chronic pain, often in multiple sites. Such patients are characterized by hypervigilance for, and a predisposition to focus on, physical sensations and to appraise these sensations as reflecting a pathological state. Neuroimaging studies have begun to identify those neural circuits involved in somatoform disorders, many of which act as cognitive and affective amplifiers of visceral-somatic sensory processing. Many of these neural circuits overlap, and interact with, those involved in pain processing. Antidepressants can mitigate the severity of unexplained physical complaints, including pain, among patients who somatize; however, due to the heterogeneity of studies upon which this claim is based, the quality of the evidence is reportedly low. There is uncertainty whether, or to what extent, antidepressant benefits among patients who somatize are due to a direct impact on pain modulation, or indirect effects on mood or cognitive appraisals/perceptions.

Despite the uncertainties about the exact mechanisms through which antidepressants exert analgesic effects, antidepressants can be appropriately used to treat patients with selected chronic pain syndromes, regardless of whether or not the patient has a psychiatric comorbidity. For those patients with pain and psychiatric comorbidities, the benefits may be brought about via direct mechanisms, indirect mechanisms, or a combination of both.

life, reducing sleep problems, or improving fatigue. Nonetheless, duloxetine and milnacipran are FDA-approved for managing pain in FM. Studies assessing the efficacy of venlafaxine in the treatment of FM to date have been limited by small sample sizes, inconsistent dosing, lack of a placebo control, and lack of blinding, which limits the ability to clearly delineate the role of venlafaxine in managing FM.

Mirtazapine (15 to 45 mg/d) showed a clinically relevant benefit compared with placebo for participant-reported pain relief of ≥30% and sleep disturbances. There was no benefit in terms of participant-reported improvement of quality of life, fatigue, or negative mood. The evidence was considered to be of low quality overall.

Headache
Amitriptyline has been employed off-label to address headache prophylaxis since 1964. Compared with placebo, it is efficacious in ameliorating migraine frequency and intensity as well as the frequency of tension headache. However, SSRIs and SNRIs (venlafaxine) failed to produce significant reductions in migraine frequency or severity or the frequencies of tension headache when compared with placebo.
Irritable bowel syndrome

Early studies addressing antidepressant efficacy in IBS reveal inconsistencies. For example, whereas some suggest that TCAs are effective in mitigating chronic, severe abdominal pain,\(^39,40\) others concluded that TCAs failed to demonstrate a significant analgesic benefit.\(^69\) A recent meta-analysis that restricted analysis of efficacy to randomized controlled trials (RCTs) with more rigorous methodological adherence found that pain relief in IBS is possible with both TCAs as well as SSRIs. However, adverse effects were more commonly encountered with TCAs than with SSRIs. Some of the inconsistencies in treatment efficacy reported in early studies may be due to variations in responsiveness of subsets of IBS patients. Specifically, the utility of TCAs appears to be best among patients with diarrheal-type (as opposed to constipation-type) IBS.\(^40,70\)

Other chronic pain conditions

Antidepressants have been used to assist in the management of several other pain conditions, including oral-facial pain, interstitial cystitis, non-cardiac chest pain, and others. The role of antidepressants for such conditions remains unclear due to limitations in the prevailing empirical work, such as few trials, small sample sizes, variations in outcome measures, and insufficient randomization and blinding.\(^71-76\) The interpretation of results from systematic reviews and meta-analyses is limited because of these shortcomings.\(^77\) Hence, it has not always been possible to determine whether, and to what extent, patients with such conditions may benefit from antidepressants.

Neuromodulatory effects and efficacy for pain

The interplay of norepinephrine (NE) and serotonin (5-HT) neurotransmitter systems and cellular mechanisms involved in
Antidepressants that influence both NE and 5-HT transmission have greater analgesic effects

Clinical Point

The descending modulation of pain pathways is complex. Experimental animal models of pain modulation suggest that 5-HT can both inhibit as well as promote pain perception by different physiological mechanisms, in contrast to NE, which is predominately inhibitory. While 5-HT in the descending modulating system can inhibit pain transmission ascending to the brain from the periphery, it appears that an intact noradrenergic system is necessary for the inhibitory influences of the serotonergic system to be appreciated.\(^\text{16,78,79}\) Deficiencies in one or both of these neurotransmitter systems may contribute to hyperactive pain processing, and thereby precipitate or maintain chronic pain. Pain mitigation may be achieved best by enhancing both neurotransmitters simultaneously, less so by enhancing NE alone, and least by enhancing 5-HT alone.\(^\text{6}\) The ability to impact pain modulation would, therefore, depend on the degree to which an antidepressant capitalizes on both noradrenergic and serotonergic neurotransmission. Antidepressants commonly employed to manage pain are presented in Table 1\(^\text{47,60,68,80-88}\) according to their primary neurotransmitter effects. Thus, the literature summarized above suggests that antidepressants that influence both NE and 5-HT transmission have greater analgesic effects than antidepressants with more specific effects, such as influencing 5-HT reuptake alone.\(^\text{80-85}\) It is unsurprising, therefore, that the SSRIs have not been demonstrated to be as consistently analgesic.\(^\text{47,60,68,80-88}\)

Similarly, pharmacodynamic and pharmacokinetic differences within antidepressant classes may influence analgesic effectiveness. Simultaneous effects on NE and 5-HT are achieved at low doses with duloxetine and milnacipran. By contrast, 5-HT effects predominate at low doses for venlafaxine. To achieve pain-mitigating effects, higher doses of venlafaxine generally are required.\(^\text{90}\) Therefore, inconsistencies across studies regarding the analgesic benefits of venlafaxine may be attributable to variability in dosing; patients treated with lower doses may not have experienced sufficient NE effects to garner positive results.

The differences in analgesic efficacy among specific TCAs may be understood in a similar fashion. Specifically, tertiary TCAs (imipramine and amitriptyline) inhibit both 5-HT and NE reuptake.\(^\text{5,90}\) Secondary amines (desipramine and nortriptyline) predominantly impact NE reuptake, possibly accounting for the lesser pain-mitigating benefit achieved with these agents, such as for treating neuropathic pain. Further, in vivo imipramine and amitriptyline are rapidly metabolized to secondary amines that are potent and selective NE reuptake inhibitors. In this way, the secondary amines may substantially lose the ability to modulate pain transmission because of the loss of concurrent 5-HT influences.\(^\text{90}\)

Table 1

<table>
<thead>
<tr>
<th>Antidepressant class or agent</th>
<th>Serotonergic activity</th>
<th>Noradrenergic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs (eg, fluoxetine, paroxetine)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>SNRIs (eg, duloxetine, milnacipran)(^a)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tertiary TCAs (eg, amitriptyline, imipramine)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Secondary TCAs (eg, nortriptyline, desipramine)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Trazodone</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

\(^a\)Duloxetine is FDA-approved for treating chronic musculoskeletal pain, fibromyalgia, and diabetic neuropathic pain, and milnacipran is FDA-approved for managing fibromyalgia

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: References 47,60,68,80-88
Clinical pearls

The following practical points can help guide clinicians regarding the usefulness of antidepressants for pain management:

• **Antidepressants can alleviate symptoms of depression and pain.** The pain-mitigating effects of antidepressants are possible even among chronic pain patients who are not depressed. Antidepressants may confer benefits for chronic pain patients with depression and other comorbid conditions, such as somatic symptom and related disorders.

• **Antidepressants are useful for select chronic pain states.** Although the noradrenergic and serotonergic antidepressants (SNRIs and, to some extent, amitriptyline) appear to have efficacy for neuropathic pain and FM, the benefits of SSRIs appear to be less robust. On the other hand, SSRIs and TCAs may have potential benefit for patients with IBS. However, the results of meta-analyses are limited in the ability to provide information about which patients will best respond to which specific antidepressant or how well. Future research directed at identifying characteristics that can predict which patients are likely to benefit from one antidepressant vs another would help inform how best to tailor treatment to individual needs.

• **The pain-mitigating effects of antidepressants often emerge early in the course of treatment (often before mood-elevating effects are observed).** For example, in the case of amitriptyline, pain relief may be possible for some patients at doses generally lower than those required for mood-elevating effects. To date, there is limited information in the literature to determine what constitutes a sufficient duration of treatment, or when treatment should be modified.

• **Failure to reduce pain should raise questions about whether the dose should be increased, an alternative agent should be tried, or combinations with other analgesic agents should be considered.** Failure to achieve pain-mitigating effects with one antidepressant does not mean failure with others. Hence, failure to achieve desired effects with one agent might warrant an empirical trial with another agent. Presently, too few double-blind RCTs have been conducted to assess the pain-mitigating effects of other antidepressants (eg, bupropion and newer SNRIs such as desvenlafaxine and levomilnacipran). Meta-analysis of the analgesic effectiveness of these agents or

### Table 2

**Antidepressants used to manage pain: Adverse effects and potential drug interactions**

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>Potential drug interactions (effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>Anticholinergic; alpha-adrenergic influences</td>
<td>Opioids; benzodiazepines; sedative hypnotics; selected muscle relaxants (sedation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclobenzaprine (anticholinergic effects and sedation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methadone (QT prolongation)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Nausea, dry mouth, nervousness, constipation, and somnolence</td>
<td>Tapentadol, tramadol, or triptans (serotonin syndrome)</td>
</tr>
<tr>
<td></td>
<td>Weight loss and elevations in diastolic blood pressure (venlafaxine); hepatic toxicity ( duloxetine)</td>
<td>Aspirin, non-steroidal anti-inflammatory drugs, or warfarin (increased risk for bleeding)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioids or sedatives (eg, benzodiazepines) (sedation)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Nausea, diarrhea, insomnia or sedation, tremors, sexual dysfunction, and restless legs syndrome</td>
<td>Tapentadol, tramadol, or triptans (serotonin syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin, non-steroidal anti-inflammatory drugs, or warfarin (increased risk for bleeding)</td>
</tr>
</tbody>
</table>

SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

| Source: Reference 95 |
Antidepressants for chronic pain

Clinical Point
Evidence regarding which patients will best respond to which specific antidepressant is limited.

Bottom Line
Antidepressants can alleviate symptoms of depression and pain. Noradrenergic and serotonergic antidepressants appear to have efficacy for pain associated with neuropathy and fibromyalgia, while selective serotonin reuptake inhibitors and tricyclic antidepressants may have benefit for patients with irritable bowel syndrome. However, evidence regarding which patients will best respond to which specific antidepressant is limited.

Related Resources

Drug Brand Names

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Brand Name</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Elavil, Endep</td>
</tr>
<tr>
<td>Buproprion</td>
<td>Wellbutrin, Zyban</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>Rela, Soma</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Amrix, Flexeril</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Pristiq</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Horizant, Neurontin</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>Fetzima</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dolophine, Methadose</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Savella</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Remeron</td>
</tr>
<tr>
<td>Nortriptiline</td>
<td>Patelon</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Lyrica, Lyrica CR</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Nucynta</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Ultram</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel, Oleptro</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin, Jantoven</td>
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</tbody>
</table>

Comparisons to the efficacy of other antidepressant classes is, therefore, impossible at this time. Because many chronic pain states are complex, patients will seldom experience clinically relevant benefit from any one intervention.\(^{20}\) The bigger implication for clinical research is to determine whether there is a sequence or combination of medication use that will provide overall better clinical effectiveness.\(^{52}\) Only limited data are available exploring the utility of combining pharmacologic approaches to address pain.\(^{91}\) For example, preliminary evidence suggests that combinations of complementary strategies, such as duloxetine combined with pregabalin, may result in significantly greater numbers of FM patients achieving ≥30% pain reduction compared with monotherapy with either agent alone or placebo.\(^{52}\)

Antidepressant selection may need to be based on medication-related adverse effect profiles and the potential for drug interactions. These factors are useful to consider in delineating multimodal treatment regimens for chronic pain in light of patients’ comorbidities and co-medication regimen. For example, the adverse effects of TCAs (anticholinergic and alpha-adrenergic influences) limit their utility for treating pain. Some of these effects can be more problematic in select populations, such as older adults or those with orthostatic difficulties, among others. TCAs are contraindicated in patients with closed-angle glaucoma, recent myocardial infarction, cardiac arrhythmias, poorly controlled seizures, or severe benign prostatic hypertrophy. Although the pain-mitigating effects of SNRIs have not been demonstrated to significantly exceed those of TCAs,\(^{68,93,94}\) SNRIs would offer an advantage of greater tolerability of adverse effects and relative safety in patients with comorbid medical conditions that would otherwise preclude TCA use. The adverse effects and common drug interactions associated with antidepressants are summarized in Table 2\(^{95}\) (page 15).

Conclusion
Chronic, nonmalignant pain conditions afflict many patients and significantly impair their ability to function. Because of heightened concerns related to the appropriateness of, and restricting inordinate access to, long-term opioid analgesics, clinicians need to explore the usefulness of co-analgesic agents, such as antidepressants. Significant comorbidities exist between psychiatric disorders and chronic pain, and psychiatrists...
are uniquely positioned to diagnose and treat psychiatric comorbidities, as well as pain, among their patients, especially since they understand the kinetics and dynamics of antidepressants.

References

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Clinical Point
Chronic pain states are complex, and patients will seldom experience clinically relevant benefit from any one intervention.