Antidepressants and Antiepileptic Drugs for Chronic Non-Cancer Pain

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The development of newer classes of antidepressants and second-generation antiepileptic drugs has created unprecedented opportunities for the treatment of chronic pain. These drugs modulate pain transmission by interacting with specific neurotransmitters and ion channels. The actions of antidepressants and antiepileptic drugs differ in neuropathic and non-neuropathic pain, and agents within each medication class have varying degrees of efficacy. Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, desipramine) and certain novel antidepressants (i.e., bupropion, venlafaxine, duloxetine) are effective in the treatment of neuropathic pain. The analgesic effect of these drugs is independent of their antidepressant effect and appears strongest in agents with mixed-receptor or predominantly noradrenergic activity, rather than serotoninergic activity. First-generation antiepileptic drugs (i.e., carbamazepine, phenytoin) and second-generation antiepileptic drugs (e.g., gabapentin, pregabalin) are effective in the treatment of neuropathic pain. The efficacy of antidepressants and antiepileptic drugs in the treatment of neuropathic pain is comparable; tolerability also is comparable, but safety and side effect profiles differ. Tricyclic antidepressants are the most cost-effective agents, but second-generation antiepileptic drugs are associated with fewer safety concerns in elderly patients. Tricyclic antidepressants have documented (although limited) efficacy in the treatment of fibromyalgia and chronic low back pain. Recent evidence suggests that duloxetine and pregabalin have modest efficacy in patients with fibromyalgia. (Am Fam Physician 2005;71:483-90. Copyright© 2005 American Academy of Family Physicians.)

See page 409 for definitions of strength-of-recommendation labels.

Chronic pain affects approximately 86 million Americans, substantially reducing their quality of life.[1] The socioeconomic burden also is significant, with chronic pain estimated to cost $90 billion annually in medical expenses and reduced work productivity.[1]

Our understanding of many chronic pain disorders is evolving rapidly, and the development of newer antidepressant drug classes and second-generation antiepileptic drugs has created unprecedented opportunities for the treatment of chronic pain.

It is important to distinguish between chronic pain that is nociceptive (i.e., resulting from injury or inflammation of somatic or visceral tissue) and chronic pain that is neuropathic (i.e., resulting from neuronal maintenance of pain either peripherally or in the central nervous system).

Chronic and Acute Pain

Chronic and acute pain differ significantly in several important respects and require different treatment approaches. Acute pain is a protective response to injury, whereas chronic pain may be a maladaptive response. Acute pain most often is nociceptive (i.e., resulting from injury or inflammation of somatic or visceral tissue). Chronic pain may be nociceptive or neuropathic (i.e., resulting from neuronal maintenance of pain either peripherally or in the central nervous system [CNS]).

Nociceptive pain usually is treated with anti-inflammatory or analgesic medications. Neuropathic pain typically is treated with medications that influence neurotransmitters (e.g., antidepressants, antiepileptic drugs), and treatment with opioids is reserved for patients with refractory neuropathic pain.

Peripheral neuropathic pain typically is described as burning, sharp, shooting, or aching, and it may be associated with tingling, dysesthesias, or numbness. Allodynia (i.e., a painful sensation from a normally nonpainful stimulus) is common. Pain often is worse at night and may be exacerbated by activity.

Common non-cancer pain syndromes may be neuropathic (peripheral or central) or

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
Tricyclic antidepressants may be used for treatment of chronic neuropathic and non-neuropathic pain syndromes.	A	5, 8, 11, 21
Tricyclic antidepressants are more effective than SSRIs in the treatment of neuropathic pain syndromes. An estimated 2.6 patients must be treated with tricyclic antidepressants and 6.7 patients with SSRIs to have one patient with more than 50 percent pain relief.	B	6, 14
Serotoninergic antidepressants and currently approved antiepileptic drugs have little documented efficacy and therefore should not be used as first-line medications in the treatment of non-neuropathic pain.	B	7, 8, 30-33

SSRIs = selective serotonin reuptake inhibitors.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 409 for more information.

non-neuropathic *(Table 1)*.[2] It is likely that both peripheral and central mechanisms contribute to the persistence of most types of neuropathic pain. Neuropathic pain also may coexist with non-neuropathic pain (e.g., in some patients with chronic low back pain).

Mechanism of Action of Antidepressants and Antiepileptic Drugs in Pain Syndromes

Transmission of painful stimuli through the spinal column and CNS is modulated by excitatory and inhibitory neurotransmitters, as well as actions at sodium and calcium channels. Norepinephrine and serotonin may be excitatory or inhibitory, but they are functionally inhibitory on pain transmission; glutamate is the other important excitatory neurotransmitter. The most important inhibitory neurotransmitter is γ-aminobutyric acid (GABA). Antidepressants and antiepileptic drugs are thought to relieve neuropathic pain through interaction with specific neurotransmitters and ion channels *(Table 2)*.[3]

TABLE 1
Common Non-Cancer Pain Syndromes

Peripheral neuropathic pain	*Central neuropathic pain*	*Non-neuropathic pain**
Complex regional pain syndrome	Multiple sclerosis	Arthritis
Human immunodeficiency virus sensory neuropathy	Myelopathies	Inflammatory arthritis
Idiopathic peripheral neuropathy	Parkinson's disease	Osteoarthritis
Infection	Poststroke pain	Chronic low back pain
Metabolic disorders		Chronic neck pain
Alcohol and other toxins		Fibromyalgia
Diabetic neuropathy		Post-traumatic pain
Nutritional deficiencies		
Nerve compression or entrapment		
Phantom limb pain		
Postherpetic neuralgia		
Trigeminal neuralgia		

**—Elements of neuropathic pain may be superimposed on the underlying disorder*

Information from reference 2..

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants are thought to affect pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin, both of which influence descending pain pathways. In addition, histamine H_1-receptor affinity (associated with sedation) may be correlated with the analgesic effect of antidepressants. Amitriptyline (Elavil) also has an analgesic effect in patients with acute pain.[4]

Tricyclic antidepressants may be categorized as secondary or tertiary amines. Secondary amines such as nortriptyline (Pamelor) and desipramine (Norpramin) show relatively selective inhibition of norepinephrine reuptake. Tertiary amines such as amitriptyline and imipramine (Tofranil) show more balanced inhibition of norepinephrine and serotonin, but they also have greater anticholinergic side effects.

The novel antidepressants venlafaxine (Effexor) and duloxetine (Cymbalta) have balanced inhibition of serotonin and norepinephrine reuptake without blockade of other

neuroreceptors that are responsible for typical tricyclic side effects. The mechanism of action of bupropion (Wellbutrin) is uncertain but involves blockade of dopamine uptake.

ANTIEPILEPTIC DRUGS

Antiepileptic drugs act at several sites that may be relevant to pain, but the precise mechanism of their analgesic effect remains unclear. These agents are thought to limit neuronal excitation and enhance inhibition. Relevant sites of action include voltage-gated ion channels (i.e., sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and N-methyl-D-aspartate, and the inhibitory receptors for GABA and glycine *(Table 2)*.[3]

Antiepileptic drugs may be categorized as first or second generation. The second-generation agents are better tolerated, cause less sedation, and have fewer CNS side effects.

Clinical Efficacy

The efficacy of antidepressants and antiepileptic drugs varies dramatically in neuropathic and non-neuropathic pain syndromes. Specific agents within each medication class can vary in effectiveness. *Table 3* lists typical dosages and side effects of medications commonly used to treat chronic pain. *Table 4*[4-19] reviews the levels of evidence for these agents.

NEUROPATHIC PAIN

Antidepressants. Meta-analyses[5,6] have confirmed the efficacy of tricyclic antidepressants in the treatment of neuropathic pain. Nontricyclic antidepressants show variable degrees of efficacy in patients with neuropathic pain.

Antidepressants with mixed-receptor or noradrenergic activity appear to have the greatest analgesic effect in patients with neuropathic pain. Predominantly serotoninergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), often are ineffective in treating chronic pain.[5,20] Amitriptyline and its metabolite nortriptyline have the best documented efficacy in the treatment of neuropathic and non-neuropathic pain syndromes.[4] The novel antidepressants bupropion,[10] venlafaxine,[11] and duloxetine[12] also have proved effective in patients with neuropathic pain.

The efficacy of tricyclic antidepressants in the treatment of neuropathic pain appears to be independent of their antidepressant effect,[21] and patients with pain but no depression respond to these agents. Although pain reduction occurs at dosages lower than those typically used to treat depression, a dose response between 25 and 100 mg has been noted.[22] Some experts recommend documenting a therapeutic level of a tricyclic antidepressant before concluding that the drug is clinically ineffective in a patient with chronic pain.

Nociceptive pain usually is treated with anti-inflammatory or analgesic medications, whereas neuropathic pain typically is treated with antidepressants or antiepileptic drugs.

Antiepileptic Drugs. Specific antiepileptic drugs are effective in the treatment of patients with neuropathic pain.[14] Of the first-generation agents, carbamazepine (Tegretol) is indicated for the treatment of trigeminal neuralgia. Carbamazepine also has shown modest efficacy in trials involving patients with diabetic neuropathy or postherpetic neuralgia.[14] Phenytoin (Dilantin) is used infrequently to treat chronic pain.

Of the second-generation antiepileptic drugs, gabapentin (Neurontin) has the best

TABLE 2
Suggested Mechanisms of Action for Antidepressants and Antiepileptic Drugs Used to Treat Chronic Pain

Mechanism of action	*Drugs*
Inhibition of norepinephrine reuptake	Tricyclic antidepressants (secondary amines): desipramine (Norpramin), nortriptyline (Pamelor)
Inhibition of norepinephrine and serotonin reuptake	Tricyclic antidepressants (tertiary amines): amitriptyline (Elavil), imipramine (Tofranil) Novel antidepressants: venlafaxine (Effexor), duloxetine (Cymbalta) Cyclobenzaprine (Flexeril)
Blockade of sodium channel	Antiepileptic drugs: carbamazepine (Tegretol), gabapentin (Neurontin), lamotrigine (Lamictal)
Blockade of calcium channel	Antiepileptic drugs: gabapentin, pregabalin (Lyrica)*
Enhancement of γ-aminobutyric acid	Antiepileptic drug: carbamazepine Spasmolytic drug: baclofen (Lioresal)

**—Investigational drug (approval pending from U.S. Food and Drug Administration).*

Adapted with permission from Ross EL. The evolving role of antiepileptic drugs in treating neuropathic pain. Neurology 2002;55(5 suppl 1):S42.

TABLE 3

Antidepressants and Antiepileptic Drugs Used in Chronic Pain Syndromes

Drug	*Dosage*	*Side effects, contraindications, and comments*
Antidepressants		
Tricyclic antidepressants	—	Side effects: dry mouth, constipation, urinary retention, sedation, weight gain Contraindications: cardiac conduction abnormalities, recent cardiac events, narrow-angle glaucoma
Amitriptyline (Elavil),* imipramine (Tofranil)*	10 to 25 mg at bedtime; increase by 10 to 25 mg per week up to 75 to 150 mg at bedtime or a therapeutic drug level.	Tertiary amines have greater anticholinergic side effects; therefore, these agents should not be used in elderly patients.
Desipramine (Norpramin),* nortriptyline (Pamelor)*	25 mg in the morning or at bedtime; increase by 25 mg per week up to 150 mg per day or a therapeutic drug level.	Secondary amines have fewer anticholinergic side effects.
Selective serotonin reuptake inhibitors		
Fluoxetine (Prozac),* paroxetine (Paxil)*	10 to 20 mg per day; up to 80 mg per day for fibromyalgia.	Side effects: nausea, sedation, decreased libido, sexual dysfunction, headache, weight gain Efficacy in pain syndromes is relatively poor.
Novel antidepressants		
Bupropion (Wellbutrin)*	100 mg per day; increase by 100 mg per week up to 200 mg twice daily (400 mg per day).	Side effects: anxiety, insomnia or sedation, weight loss, seizures (at dosages above 450 mg per day)
Venlafaxine (Effexor)*	37.5 mg per day; increase by 37.5 mg per week up to 300 mg per day.	Side effects: headache, nausea, sweating, sedation, hypertension, seizures Serotoninergic properties in dosages below 150 mg per day; mixed serotoninergic and noradrenergic properties in dosages above 150 mg per day
Duloxetine (Cymbalta)*	20 to 60 mg per day taken once or twice daily in divided doses (for depression); 60 mg twice daily for fibromyalgia	Side effects: nausea, dry mouth, constipation, dizziness, insomnia
Antiepileptic drugs		
First-generation agents		
Carbamazepine (Tegretol)	200 mg per day; increase by 200 mg per week up to 400 mg three times daily (1,200 mg per day).	Side effects: dizziness, diplopia, nausea Treatment can result in aplastic anemia.
Phenytoin (Dilantin)*	100 mg at bedtime; increase weekly up to 500 mg at bedtime.	Side effects: dizziness, ataxia, slurred speech, confusion, nausea, rash Treatment can result in blood dyscrasias and hepatotoxicity.
Second-generation agents		
Gabapentin (Neurontin)	100 to 300 mg at bedtime; increase by 100 mg every 3 days up to 1,800 to 3,600 mg per day taken in divided doses three times daily.	Side effects: drowsiness, dizziness, fatigue, nausea, sedation, weight gain
Pregabalin (Lyrica)	150 mg at bedtime for diabetic neuropathy; 300 mg twice daily for postherpetic neuralgia.	Side effects: drowsiness, dizziness, fatigue, nausea, sedation, weight gain
Lamotrigine (Lamictal)*	50 mg per day; increase by 50 mg every 2 weeks up to 400 mg per day.	Side effects: dizziness, constipation, nausea; rarely, life-threatening rashes

**—Not approved by the U.S. Food and Drug Administration for treatment of neuropathic pain.*

TABLE 4
Study-Quality Ratings for Antidepressants and Antiepileptic Drugs in Chronic Pain Syndromes

	Neuropathic pain		*Non-neuropathic pain*	
Drug	*Trigeminal neuralgia*	*Diabetic neuropathy or postherpetic neuralgia*	*Fibromyalgia*	*Low back or other pain*
Antidepressants				
Amitriptyline (Elavil)[4-8]		1	1	2
Fluoxetine (Prozac)[9]			3	
Bupropion (Wellbutrin)[10]		2		
Venlafaxine (Effexor)[11]		2		
Duloxetine (Cymbalta)[12,13]		1	1	
Antiepileptics				
First generation				
Carbamazepine (Tegretol)[14]	1	3		
Phenytoin (Dilantin)[14]	3			
Second generation				
Gabapentin (Neurontin)[15,16]		1		
Lamotrigine (Lamictal)[17]*	3			
Pregabalin (Lyrica)[18,19]†		2	2	

1 = good-quality patient-oriented evidence; 2 = limited-quality patient-oriented evidence; 3 = other evidence. See page 0000 for more information on ratings.

**—Efficacy of lamotrigine as an adjunct to carbamazepine or phenytoin.*

†*—Investigational drug (approval pending from U.S. Food and Drug Administration).*

Information from references 4 through 19.

documented efficacy in the treatment of neuropathic pain. Gabapentin has been proved superior to placebo in patients with painful diabetic neuropathy[15] or postherpetic neuralgia.[16] In these trials,[15,16] effective dosages have ranged from 2,400 to 3,600 mg per day.

One study[23] of patients with painful diabetic neuropathy found no significant effect for gabapentin in a dosage of 900 mg per day. The efficacy of this drug in other pain syndromes that may have a neuropathic component (e.g., persistent postoperative pain) has been of borderline statistical significance.[24]

The investigational drug pregabalin (Lyrica) has documented efficacy in the treatment of diabetic neuropathy[18] and postherpetic neuralgia.[19] Approval of pregabalin by the U.S. Food and Drug Administration is pending.

Lamotrigine (Lamictal) has been proved modestly effective in patients with trigeminal neuralgia,[17] neuropathy associated with human immunodeficiency virus infection,[25] and poststroke pain.[26] The drug is ineffective in patients with unspecified refractory neuropathic pain.[27] The use of lamotrigine is limited by potentially life-threatening rashes.

Comparative Efficacies. Antidepressants and antiepileptic drugs have comparable efficacy in patients with neuropathic pain. However, the drug classes (and individual agents within each class) differ in safety, tolerability, and side effect profiles.[28]

Second-generation antiepileptic drugs are better tolerated than first-generation agents, cause less sedation, and have fewer central nervous system side effects.

In a meta-analysis[28] of trials of antidepressants and antiepileptic drugs in patients with neuropathic pain, the estimated number needed to treat for significant reduction of pain was 2.6 with tricyclic antidepressants, 6.7 with SSRIs, 2.5 with

sodium channel–blocking antiepileptic drugs (i.e., phenytoin and carbamazepine), and 4.1 with gabapentin. Another meta-analysis[5] found no significant difference between antidepressants and antiepileptic drugs in the reduction of neuropathic pain.

A small randomized, double-blind, controlled trial[29] of gabapentin and amitriptyline in patients with diabetic neuropathy found that both agents were effective, with no significant differences. Tolerability also was comparable.

NON-NEUROPATHIC PAIN

The efficacy of tricyclic antidepressants has been documented in a variety of non-neuropathic pain syndromes. Most other antidepressants and most antiepileptic drugs have little or no documented efficacy in the treatment of non-neuropathic pain.

Fibromyalgia. Analysis of controlled trials on the treatment of fibromyalgia is limited by differences in outcome measures, inconsistent reporting of associated depression, and conflicting results.[30] A meta-analysis[31] found that antidepressants were mildly beneficial in reducing pain severity and improving sleep and overall well-being, and mildly effective in reducing fatigue; treatment with these agents also showed a trend for a beneficial effect on tender points.

In one study,[32] 30 to 47 percent of patients with fibromyalgia who were treated with amitriptyline reported moderate or marked improvement of pain. However, similar efficacy was reported for other antidepressants, tranquilizers, cyclobenzaprine (Flexeril), nonsteroidal anti-inflammatory drugs, exercise, and physical therapy.

Tricyclic antidepressants have the best documented efficacy in patients with fibromyalgia, but the treatment effect is modest and tends to wane over time.[33] Although fluoxetine (Prozac) has shown no efficacy in a conventional dosage (20 mg per day), a study[9] of dosages of up to 80 mg per day showed significant efficacy. Cyclobenzaprine, a muscle relaxant that structurally is a tricyclic agent, also has shown modest efficacy in patients with fibromyalgia.[34]

Recently, duloxetine in a dosage of 60 mg twice daily was shown to improve pain and global measures of fibromyalgia, compared with placebo.[13] The improvement occurred regardless of baseline depression status.

Of the antiepileptic drugs, only pregabalin has demonstrated efficacy in the treatment of fibromyalgia. Patients taking 450 mg per day reported reduced pain and fatigue, and improved sleep.[34]

Low Back Pain. A recent meta-analysis[7] found that patients with chronic back pain who were treated with antidepressants had a small but significant decrease in pain. However, their ability to perform activities of daily living did not improve. Efficacy was less for antidepressants with predominantly serotoninergic activity.

Other Chronic Pain Disorders. One review[8] evaluated the efficacy of antidepressants in the treatment of a variety of pain disorders. The non-neuropathic pain disorders included osteoarthritis and rheumatoid arthritis, chronic low back pain, and other chronic pain disorders (not specified). In the arthritis studies, 26 to 68 percent of patients were noted to have a 50 percent or greater improvement in pain; however, the studies had small sample sizes and methodologic flaws.[8]

Clinical Considerations

Because efficacy in neuropathic pain is similar for antidepressants and antiepileptic drugs,

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TABLE 5
Clinical Guidelines for the Treatment of Chronic Pain

All chronic pain
Use of a pain scale facilitates clinical evaluation of the patient's response to a therapeutic drug trial.
An assessment of quality of life and activities of daily living should be incorporated into the clinical evaluation of the therapeutic drug trial.
Identification of psychiatric comorbidity may suggest the use of an antidepressant for nonpain indications.
Neuropathic pain
A tricyclic antidepressant is the preferred initial therapy if the patient has coexisting insomnia, anxiety, or depression, or if cost is a consideration.
An antiepileptic drug (e.g., gabapentin [Neurontin]) is preferred if the patient cannot tolerate the side effects of tricyclic antidepressants, has cardiac contraindications to the use of tricyclic antidepressants (e.g., conduction abnormalities, recent cardiac event), or is a "frail elder."
Titrate the selected medication to achieve clinical effect or to the maximum tolerated dosage (see Table 3). With gabapentin, if no effect is seen at a dosage of 1,800 mg per day, discontinue the drug; if a partial effect occurs, titrate the drug to a dosage of 2,400 to 3,600 mg per day.
Monitor response to treatment.
If monotherapy is tolerated but only partially effective, combine an antidepressant with an antiepileptic drug.
If monotherapy is poorly tolerated or ineffective, choose a first-line agent from a different medication class or use a second-line agent (e.g., bupropion [Wellbutrin], venlafaxine [Effexor]).
If pain relief remains inadequate, consider use of a short-acting or long-acting opioid or tramadol (Ultram).
Non-neuropathic pain
Exercise is the primary therapy for chronic low back pain and fibromyalgia.
Begin treatment of low back pain with a nonsteroidal anti-inflammatory drug (not effective in the treatment of fibromyalgia).
Consider use of a tricyclic antidepressant as a pain adjuvant to promote sleep and alleviate muscle spasm.
In appropriately selected patients, consider use of a short- or long-acting opioid or tramadol.
Empiric use of antiepileptic drugs such as gabapentin is not justified by the current literature but is common practice in pain clinics.

Information from reference 2.

initial drug selection is based on side effects, contraindications, coexisting conditions, and cost *(Table 5)*.[2] Patients with associated anxiety, depression, or sleep disturbance may benefit from a tricyclic or novel antidepressant, although gabapentin and pregabalin also appear to reduce anxiety. Tricyclic antidepressants are significantly less expensive than second-generation antiepileptic drugs.

Sedation and weight gain are common side effects of tricyclic antidepressants and gabapentin. Tricyclic antidepressants should not be used in patients with cardiac conduction abnormalities, recent cardiac events, or narrow-angle glaucoma. Elderly patients should not be treated with tertiary amines because of the greater anticholinergic effects of these agents.

Even when drug therapies for painful neuropathies are successful, there is only a 30 to 50 percent reduction of pain. A combination of drugs that target different sites and receptors may be reasonable, although this approach has not been evaluated.[2] Opiates[2,35] and tramadol (Ultram)[2] have been proved effective in the treatment of neuropathic and non-neuropathic pain.

Nonpharmacologic treatments (e.g., exercise, behavioral therapies) are particularly important in patients with non-neuropathic pain syndromes. Currently available medications have limited benefit in these syndromes.

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