



## Treatment of Neuropathic Pain: The Role of Unique Opioid Agents

Agents that work against central nervous system receptors may be the key to successful pain management in patients with nerve damage or injury.

### Kristen E. Zorn, PharmD

Albany College of Pharmacy and Health Sciences  
Albany, NY

### Jeffrey Fudin, BS, PharmD, FCCP

Adjunct Associate Professor of Pharmacy Practice  
Albany College of Pharmacy and Health Sciences  
Clinical Pharmacy Specialist in Pain Management  
Samuel Stratton VA Medical Center  
Albany, NY

Neuropathic pain often is defined as pain caused by a lesion to or dysfunction of the central or peripheral nervous systems.<sup>1</sup> Neuropathic pain often is chronic in nature, with a complex pathophysiology.<sup>2</sup> Postherpetic neuralgia and diabetic neuropathy are the two most commonly studied and described types of neuropathic pain. In addition to diabetes and the herpes zoster virus, other triggers of neuropathic pain include toxins, trauma, infection, chemotherapy, surgery, tumor infiltration, and immunologic disorders.<sup>3,4</sup>

Differing from nociceptive pain, neuropathic pain is usually described as “burning,” “electric,” “tingling,” and/or “shooting”; it presents as both continuous background pain and spontaneous pain, and it can be impervious to conventional analgesic medications.<sup>4-7</sup>

Nonetheless, several agents have shown substantial

evidence for efficacy in the treatment of neuropathic pain. Selected agents that are most commonly used and studied for the treatment of neuropathic pain can be seen in Table 1.<sup>7-12</sup> Although there is limited data in published guidelines on the use of opioids to treat neuropathic pain,<sup>4,5,8,9,13</sup> several reports suggest that certain unique opioids might be useful in this setting.<sup>14-18</sup>

### Pathophysiology of Nerve Pain

To demonstrate why specific opioids might be beneficial, it is essential to understand the pathophysiology of neuropathic pain and the receptors with which the opioids interact. To facilitate this understanding and draw parallels between the mechanisms of action of older and newer prospective therapies, this article reviews currently approved treatments and off-label treatment options.

**Table 1. Select Medications for the Treatment of Neuropathic Pain**

<b>Drug Name (Brand)</b>	<b>Mechanisms in Neuropathic Pain</b>	<b>Common Adverse Reactions</b>	<b>Special Considerations</b>
<b>Antiepileptics</b>			
Carbamazepine <sup>a,b</sup> (Carbatrol, Eptol, Tegretol, generic)	Decrease synaptic transmission by blocking sodium channels	Drowsiness, dizziness, blurred vision, ataxia, nausea, pruritis, rash	<ul style="list-style-type: none"> <li>• CYP inducer; drug interactions</li> <li>• Monitoring of blood counts and LFTs recommended</li> </ul>
Gabapentin <sup>c</sup> (Neurontin, generic)	Binds to $\alpha_2\delta$ subunit on voltage-gated calcium channels	Somnolence, dizziness, peripheral edema	<ul style="list-style-type: none"> <li>• Dosage adjustments required in renal impairment</li> </ul>
Lamotrigine (Lamictal, generic)	Blocks sodium channels, decreasing release of glutamate	Nausea, somnolence, dizziness, rash, blurred vision	<ul style="list-style-type: none"> <li>• Taper dose over <math>\geq 2</math> wk to discontinue</li> <li>• Risk for teratogenicity</li> </ul>
Levetiracetam (Keppra, generic)	Precise mechanism unknown; may involve binding to synaptic proteins, which modulates neurotransmitter release	Agitation, aggression, anxiety, depression, vomiting, anorexia, fatigue, dizziness, nausea, mood swings	<ul style="list-style-type: none"> <li>• Dosing adjustments required in renal impairment</li> </ul>
Oxcarbazepine (Trileptal, generic)	Blocks sodium channels, stabilizing hyperexcited neuronal membranes	Dizziness, somnolence, headache, vomiting, nausea, tremor, rash	<ul style="list-style-type: none"> <li>• CYP inducer; drug interactions</li> <li>• Risk for Stevens-Johnson syndrome and other dermatologic reactions</li> </ul>
Phenytoin (Dilantin, generic)	Stabilizes neuronal membranes by increasing efflux or decreasing influx of sodium ions across cell membranes	Dizziness, drowsiness, blurred vision, nystagmus, hypotension, bradycardia, psychiatric changes, rash	<ul style="list-style-type: none"> <li>• Monitor serum levels</li> <li>• Many drug interactions</li> </ul>
Pregabalin <sup>a,c,d</sup> (Lyrica)	Binds to $\alpha_2\delta$ subunit on voltage-gated calcium channels	Somnolence, dizziness, peripheral edema	<ul style="list-style-type: none"> <li>• Dosage adjustments required in renal impairment</li> </ul>
Topiramate (Topamax, Topiragen, generic)	Blocks sodium channels, antagonizes glutamate receptors	Dizziness, ataxia, somnolence, psychomotor slowing, paresthesia, weight loss	<ul style="list-style-type: none"> <li>• Associated with metabolic acidosis</li> <li>• Dosage adjustment required in renal impairment</li> <li>• Caution in glaucoma due to increased intra-ocular pressure</li> </ul>
Valproic Acid (Depakene, Depakote, Stavzor, generic)	Enhances action of GABA at postsynaptic receptor sites	Headache, somnolence, dizziness, alopecia, nausea, vomiting, thrombocytopenia, peripheral edema, amnesia	<ul style="list-style-type: none"> <li>• Risk for teratogenicity</li> </ul>
Zonisamide (Zonegran, generic)	May stabilize neuronal membranes through action at calcium and sodium channels	Somnolence, dizziness, anorexia, headache, agitation/irritability	

**Table 1. Select Medications for the Treatment of Neuropathic Pain (continued)**

Drug Name (Brand)	Mechanisms in Neuropathic Pain	Common Adverse Reactions	Special Considerations
<b>SNRIs</b>			
Duloxetine <sup>a,d</sup> (Cymbalta)	Inhibit the reuptake of NE	Sedation, nausea, constipation, ataxia, dry mouth	<ul style="list-style-type: none"> <li>• Contraindicated in patients with glaucoma</li> <li>• Blocks reuptake of 5-HT</li> </ul>
Milnacipran <sup>d</sup> (Savella)		Nausea, insomnia, hypertension, seizures, dizziness, hot flashes	<ul style="list-style-type: none"> <li>• Blocks reuptake of 5-HT</li> </ul>
Venlafaxine (Effexor, generic)		Nausea, dizziness, drowsiness, hyperhidrosis, hypertension, constipation	<ul style="list-style-type: none"> <li>• Dosage adjustments required in renal failure</li> <li>• Blocks reuptake of 5-HT</li> </ul>
<b>TCAs</b>			
Amitriptyline (generic)	Inhibit the reuptake of NE	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	<ul style="list-style-type: none"> <li>• Amitriptyline most likely to produce drowsiness</li> <li>• All but desipramine and nortriptyline also block reuptake of 5-HT</li> <li>• Trimipramine also blocks reuptake of DA</li> </ul>
Desipramine (Norpramin, generic)			
Doxepin (Prudoxin, Silenor, Zonalon, generic)			
Imipramine (Tofranil, generic)			
Nortriptyline (Pamelor, generic)			
Trimipramine (Surmontil, generic)			
<b>Opioids</b>			
Fentanyl (Abstral, Actiq, Duragesic, Fentora, Onsolis, Sublimaze, generic)	μ-opioid agonist	Drowsiness, sedation, constipation, dizziness, nausea/vomiting	<ul style="list-style-type: none"> <li>• Constipation requires concomitant bowel regimen</li> </ul>
Hydrocodone/Acetaminophen <sup>e</sup> (generic)	μ-opioid agonist		
Hydromorphone (Dilaudid, Exalgo, generic)	μ-opioid agonist		
Levorphanol (generic)	μ- and κ-opioid agonist, NMDA receptor antagonist, inhibits reuptake of NE		
Methadone (Dolophine, Methadose, generic)	μ-opioid agonist, NMDA receptor antagonist, inhibits reuptake of NE		

**Table 1. Select Medications for the Treatment of Neuropathic Pain (continued)**

Drug Name (Brand)	Mechanisms in Neuropathic Pain	Common Adverse Reactions	Special Considerations
<b>Opioids</b>			
Morphine (Astramorph, Avinza, Kadian, MS Contin, Oramorph, generic)	$\mu$ -opioid agonist	Drowsiness, sedation, constipation, dizziness, nausea/vomiting	<ul style="list-style-type: none"> <li>• Constipation requires concomitant bowel regimen</li> <li>• Tramadol also blocks reuptake of 5-HT; Note that the opioid receptor binding affinity is low, 6000x &lt; that of morphine.</li> </ul>
Oxycodone (Oxycontin, Roxicodone, generic)	$\mu$ -opioid agonist		
Oxymorphone (Opana, Opana ER, generic)	$\mu$ -opioid agonist		
Tapentadol (Nucynta)	$\mu$ -opioid agonist, inhibits reuptake of NE		
Tramadol (Rybix, Ryzolt, Ultram, Ultram ER, generic)	$\mu$ -opioid agonist, inhibits reuptake of NE		
<b>Miscellaneous</b>			
Capsaicin <sup>a,c</sup> (Qutenza, generic)	Depletes and prevents accumulation of substance P in peripheral sensory neurons	Transient skin irritation, paresthesias, contact dermatitis, cough	
Ketamine (Ketalar, generic)	NMDA receptor antagonist; high doses stimulate $\mu$ and $\Sigma$ receptors		
Memantine (Namenda, Namenda XR)	NMDA receptor antagonist	Dizziness, headache, fatigue, drowsiness, rash	
Lidocaine patch <sup>c</sup> (Lidoderm, generic)	Blocks initiation and conduction of nerve impulses by decreasing membrane permeability to Na <sup>+</sup>	Local rash and erythema	No systemic side effects

<sup>a</sup> FDA-approved to treat diabetic neuropathy

<sup>b</sup> FDA-approved to treat trigeminal neuralgia

<sup>c</sup> FDA-approved to treat postherpetic neuralgia

<sup>d</sup> FDA-approved to treat fibromyalgia

<sup>e</sup> Maximum daily dosage is dependent on acetaminophen content. (Nerenberg DM, Fudin J. Maximum daily dose of hydrocodone. Letter to the editor. *Am J Health-Syst Pharm.* 2010;67(19):1587-1588.)

CYP, cytochrome P450; DA, dopamine; GABA, gamma-aminobutyric acid; 5-HT, serotonin; LFTs, liver function tests; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant  
Based on references 7-12.

### Location, Location, Location

Based on lesion location in the nervous system, the pain originates centrally, peripherally, or may be mixed. Peripherally, a local inflammatory response will occur after direct damage to a nerve. This inflammation causes nociceptors to become more sensitive to normal stimuli, to undergo a lengthened response when stimulated, and to discharge spontaneously. More specifically, calcium channels that regulate the release of neurotransmitters from terminals of sensory neurons become altered. Overactivity of these channels causes a decrease in neurotransmitter release and, subsequently, abnormal firing at the nerve ending.<sup>13</sup>

## Opioids do not act by altering pain threshold, or transduction, rather they change the way pain is perceived in the afferent pathway of the central nervous system.

Normally, when a person experiences a painful stimulus, excitatory amino acids such as glutamate are released. Glutamate can interact with the *N*-methyl-D-aspartate (NMDA) receptor in the central nervous system. Prolonged and repeated activation by glutamate on the NMDA receptor leads to an increase in neuronal signal transduction to the central nervous system and strengthened synapses between neurons. This sensitization of spinal cord neurons causes a heightened responsiveness to certain signal inputs that are received.<sup>19</sup> Further changes in nerve function, chemistry, and structure can occur, triggering the spontaneous pain and allodynia that are

characteristic of neuropathic pain.<sup>13</sup>

It is known that opioids act primarily as agonists at endogenous opioid receptors. The various opioid receptors include delta, kappa, and mu, with mu playing the largest role in analgesia. The physiological effects that opioids have when binding to these receptors generally are well understood. Depending on the receptor and the opioid-binding affinity, varying levels of analgesia and adverse effects can occur. Opioids do not act by altering pain threshold, or transduction, rather they change the way pain is perceived in the afferent pathway of the central nervous system.<sup>20</sup> The aforementioned changes to the pain-transmitting system

that occur in neuropathic pain are likely what makes treatment so challenging.

In spite of an opioid's ability to alter nociceptive signals, neuronal excitation still occurs. Failure of most opioids, especially as single agents, to treat neuropathic pain, happens all too often. There are, however, distinctive opioids that bind to receptors other than the mu-opioid receptor and have non-opioid properties that are relevant to the pathophysiology of neuropathic pain.<sup>14</sup> Although a recent meta-analysis indicates possible efficacy of various opioids without these unique mechanisms, the usefulness of these medications, such as oxycodone or morphine, in neuropathic pain remains

equivocal.<sup>21</sup> This review will focus on those opioids with nonopioid properties and unique mechanisms of action.

### Unique Mechanism

Methadone and levorphanol are two opioids that have unique mechanisms in addition to their conventional opioid receptor actions. Both of these opioids additionally work by antagonizing NMDA receptors and inhibiting the reuptake of norepinephrine, the latter being the mechanism by which certain antidepressants purportedly work to treat neuropathic pain.<sup>22,23</sup> Levorphanol also has additional unique qualities, in that it has a high affinity for the kappa-opioid receptor, possibly adding to its analgesic activity.<sup>24</sup>

These properties have provided an incentive to design clinical trials that assess the treatment efficacy of methadone and levorphanol. In one double-blinded, randomized, controlled crossover trial, a low dose of methadone was used to demonstrate its efficacy in patients with chronic nonmalignant neuropathic pain.<sup>14</sup> Compared with the placebo group, the group receiving 20 mg of methadone daily experienced statistically significant improvements in subjective scale ratings of maximum pain intensity, average pain intensity, and pain relief. The improvements in all three outcomes extended for more than 48 hours and demonstrated a significant analgesic effect of methadone in neuropathic pain.<sup>14</sup>

A small study assessing allodynia and spontaneous pain in 18 patients with neuropathic pain also revealed similar results. Pretreatment pain scores were significantly lowered with methadone therapy, from 7.7 to 1.4. Patients who experienced "shooting pain" reported a complete response, and 9 of 13 patients with allodynia reported complete resolution.<sup>15</sup> A retrospective review of 13 patients over a 12-month study period suggested that methadone

is also effective. Although four patients discontinued methadone before the 12-month study period ended, the remaining nine patients reported, on average, a 47% improvement in quality of life, a 43% increase in pain relief, and a 30% improvement in sleep.<sup>16</sup>

### The Forgotten Opioid

Although methadone often is considered a stigmatized opioid, it still is more commonly prescribed than levorphanol, which is sometimes referred to as “the forgotten opioid.”<sup>22-24</sup> Because levorphanol shares the unique non-opioid properties of methadone, it also, theoretically, should be useful in the treatment of neuropathic pain. A case series during a 5-year period looked at neuropathic pain patients treated with levorphanol after inadequate treatment responses to other opioids, including methadone. In this review, 31 of 1,752 patients were treated with oral levorphanol. Of the 31 patients, 52% indicated their pain relief was “excellent” and 22% indicated their pain relief was “fair.” These outcomes correlated to a 74% response rate and suggested a pattern of relief that is similar to that of methadone.<sup>17</sup>

In a double-blind study in which 81 patients were allowed to maintain their non-opioid analgesics, levorphanol was added for 8 weeks of therapy. The group that received a higher strength of levorphanol reported a 36% reduction in pain, compared with a 21% reduction in pain in a lower-strength group ( $P=0.02$ ).<sup>18</sup> Many other subjective outcome measures were improved, such as sleep and affective distress, but no significant differences existed between the high- and low-strength groups with respect to these measures.

The scarce available data on levorphanol suggests, minimally, that it could be used in treating neuropathic pain when other therapies are ineffective. Bearing in mind levorphanol’s unique

mechanism, further assessment of its clinical utility should continue because it could potentially play a larger role in the treatment of refractory neuropathic pain.

### Opioids With NMDA Antagonist Properties

Considering the available evidence for methadone and levorphanol, it is equally important to review the literature on non-opioids that also have NMDA antagonistic properties. This will provide further evidence for the NMDA receptor’s role in neuropathic pain and increase the likelihood that

these opioids could be more highly considered as treatment options.

Memantine (Namenda) is a medication typically used to treat Alzheimer’s disease by way of NMDA receptor antagonism.<sup>25</sup> Growing evidence suggests that NMDA antagonists may be useful in neuropathic pain; memantine also has been studied in certain subgroups of these pain patients.<sup>26,27</sup> A double-blind, randomized, placebo-controlled trial looked at the combination of morphine and memantine in patients with complex regional pain syndrome (CRPS) and neuropathic pain.<sup>26</sup> Only the combination therapy reduced pain at rest and during movement. A preliminary report of six CRPS cases had similar results and showed a significant decrease in pain levels in all patients after 6 months of therapy with memantine.<sup>27</sup>

Also worthy of mention are the NMDA antagonists dextromethorphan and ketamine. Both of these medications are considered less frequently in treating neuropathic pain but have been studied extensively. A recent review article included 28 studies of different subgroups of neuropathic pain patients, with the majority of interventions being either ketamine or dextromethorphan.<sup>28</sup> In many of the trials, high-dose dextromethorphan or ketamine used in postherpetic neuralgia, diabetic neuropathy, and post-amputation patients showed significant reductions in pain.<sup>28</sup> It is

**Available literature at this time appears to support the hypotheses that certain opioids could be more efficacious than others in treating neuropathic pain.**

important to note that several studies contradictorily resulted in no significant pain reductions, especially for dextromethorphan. Lack of efficacy in the dextromethorphan group was, in part, due to subtherapeutic dosing.<sup>28</sup> Because many varying types of neuropathic pain were studied, it was difficult for any comprehensive conclusions to be drawn on the efficacy of either medication.

### Opioids That Inhibit Norepinephrine Reuptake

Several unique opioids have norepinephrine reuptake inhibition as a mechanism of action. Before focusing on the newer opioid therapies, it is helpful to review the non-opioid therapies with norepinephrine reuptake-inhibiting properties that have demonstrated efficacy and are commonly

employed to treat neuropathic pain.<sup>12,29</sup> In two concomitant crossover studies, desipramine was compared with amitriptyline (TCA), while fluoxetine was compared with placebo. Desipramine and amitriptyline yielded similar positive responses to pain; fluoxetine and placebo both yielded inferior results. Because both amitriptyline and desipramine work by blockade of norepinephrine reuptake, the investigators concluded that antidepressants mediate their analgesic effect in neuropathic pain via this mechanism.<sup>30</sup>

Considering that these commonly used medications inhibit the reuptake of norepinephrine in patients with neuropathic pain, an opioid that shares this similar mechanism would logically be an effective treatment as well. Tramadol likely has usefulness in neuropathic pain for this reason. Although tramadol has an affinity for opioid receptors 6,000 times less than morphine, it also acts as a norepinephrine and serotonin reuptake inhibitor.<sup>31</sup> A review of four placebo-controlled studies evaluating the efficacy of tramadol in neuropathic pain was published in 2006.<sup>32</sup> The authors concluded that tramadol was effective in treating patients with diabetic neuropathy, painful polyneuropathy, and postherpetic neuralgia.

A newer medication, tapentadol (Nucynta), which has a mechanism of action that is similar to that of tramadol, has been approved for moderate to severe pain. It blocks reuptake of

norepinephrine and has a high binding affinity for the mu receptor that is only 18 times less than that of morphine.<sup>33</sup> In a recent randomized-withdrawal, placebo-controlled trial of patients with diabetic peripheral neuropathy, tapentadol was evaluated using the change in average pain intensity as a primary efficacy outcome.<sup>34</sup> A total of 588 patients were included and of the patients randomized to receive tapentadol, 53.6% reported at least a 30% improvement in pain intensity versus 42.2% of the placebo group. A 50% or greater improvement was observed in 37.8% of patients receiving tapentadol, versus 27.6% of placebo patients. Tapentadol's ability to provide a statistically significant improvement in pain intensity compared with placebo suggests that this novel medication may be particularly useful in treating pain with neuropathic constituents.

### Conclusion

It is thought that neuropathic pain is largely caused by excessive activation of NMDA receptors in the central nervous system by glutamate. By blocking glutamate's actions at this receptor, a medication should, theoretically, reduce pain.<sup>18</sup> Additionally, the inhibition of norepinephrine reuptake is thought to play a significant role in the alleviation of neuropathic pain stemming from the descending nerve pathway. If antidepressants that block norepinephrine reuptake are considered effective in

treating this type of pain, then opioids that work similarly should, likewise, be particularly useful. Available literature at this time appears to support the hypotheses that certain opioids could be more efficacious than others in treating neuropathic pain. Despite the promising data that exists, more research directly comparing various opioids is needed. Specifically, more randomized controlled trials are necessary to demonstrate the value of mechanistically unique opioids in the treatment of neuropathic pain. ■

**Authors' Bios:** *At the time of writing, Kristen E. Zorn, PharmD, was a student at the Albany College of Pharmacy & Health Sciences in Albany, NY.*

*Dr. Jeffrey Fudin is Adjunct Associate Professor of Pharmacy Practice at Albany College of Pharmacy & Health Sciences and Clinical Pharmacy Specialist in Pain Management at the Samuel Stratton VA Medical Center in Albany, NY.*

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**Continued on Page 119 >>**

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**Author's Bio:** Joan M. Stachnik, PharmD, BCPS, is a Clinical Assistant Professor and board-certified Pharmacotherapy Specialist in the Department of Pharmacy Practice at the University of Illinois at Chicago (UIC) College of Pharmacy. Dr. Stachnik is a Drug Information Specialist within the UIC Drug Information Group. Dr. Stachnik has no financial information to disclose.

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## Treatment of Neuropathic Pain, continued from Page 33 >>

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