Use of anticonvulsants for treatment of neuropathic pain

Misha-Miroslav Backonja, MD

Article abstract—Emerging evidence from animal models of neuropathic pain suggests that many pathophysiologic and biochemical changes occur in the peripheral and central nervous system. Similarities between the pathophysiologic phenomena observed in some epilepsy models and in neuropathic pain models justify the use of anticonvulsants in the symptomatic management of neuropathic pain. Positive results from laboratory and clinical trials further support such use. Carbamazepine was the first of this class of drugs to be studied in clinical trials and has been longest in use for treatment of neuropathic pain. Clinical trial data support its use in treating trigeminal neuralgia, but data for treatment of painful diabetic neuropathy are less convincing. Use of newer anticonvulsants has marked a new era in the treatment of neuropathic pain. Gabapentin has demonstrated efficacy, specifically in painful diabetic neuropathy and postherpetic neuralgia. Lamotrigine has been reported to be effective in relieving pain from trigeminal neuralgia refractory to other treatments, HIV neuropathy, and central post-stroke pain. Results from clinical trials of phenytoin are equivocal. Zonisamide's mechanisms of action suggest that it would be effective in controlling neuropathic pain symptoms. Other anticonvulsants, including lorazepam, valproate, topiramate, and tiagabine, have also been under investigation. Anecdotal experience provides support for studies with oxcarbazepine and levetiracetam for treating neuropathic pain. Evidence supporting the efficacy of anticonvulsants in treatment of such pain is evolving. Additional clinical trials should provide information that will better define their role in neuropathic pain.

NEUROLOGY 2002;59(Suppl 2):S14–S17

Neuropathic pain refers to a group of disorders characterized by pain caused by diseases of the central and peripheral nervous systems. Some examples of neuropathic pain syndromes include postherpetic neuralgia, painful diabetic neuropathy, posttraumatic neuralgia, and central post-stroke pain syndrome. Neuropathic pain is complex in its presentation, with many signs and symptoms that fluctuate in number and intensity over time. The complexity and heterogeneity of these pain syndromes still present challenges to basic and clinical research. Traditional views have held that neuropathic pain responds poorly to standard therapeutic approaches for pain and to standard doses of opioid analgesics.

There is a notable similarity between the pathophysiologic and biochemical mechanisms that are observed in epilepsy and in neuropathic pain. The pathophysiologic processes that underlie the wind-up phenomenon caused by nerve injury and in the kindling of hippocampal neurons in epilepsy are remarkably similar. Both wind-up and kindling appear to result, in part, from activation of N-methyl-D-aspartate (NMDA) receptors, among other mechanisms. The susceptibility of primary afferents and transmission neurons to the effects of sodium channel blockers in neuropathic pain models has been well recognized and is similar to that in models of epilepsy. In light of these mechanistic similarities, it is not surprising that anticonvulsant agents can be used to treat neuropathic pain.

The development of neuropathic pain models and the demonstration of neuroplasticity that occurs in neuropathic pain, including many components of peripheral and central sensitization mechanisms, have been the most significant advancements in pain research and therapy. Clinical signs and symptoms can now be explained on the basis of many mechanisms described in the literature, and the treatment strategies now have more specific targets. With improved assessment and specific diagnosis, therapy can be specifically oriented toward treatment of neuropathic pain based on its underlying mechanisms.

The introduction of newer anticonvulsants, with their wide range of pharmacologic effects on various ion channels and neurotransmitters and their safer side-effect profiles, has been a major advancement in the treatment of neuropathic pain. Carbamazepine, phenytoin, gabapentin, and lamotrigine have been studied in randomized clinical trials for neuropathic pain disorders, and other anticonvulsants are now under investigation.

Carbamazepine. Carbamazepine is an iminostilbene derivative chemically related to the tricyclic antidepressants. The effect of carbamazepine on pain suppression probably occurs via central and peripheral mechanisms. The ability of carbamazepine to...
block ion conductance appears to be frequency-dependent; this enables the drug to suppress spontaneously active Aδ- and C-fibers responsible for pain without affecting normal nerve conduction.

The analgesic effects of carbamazepine on patients with trigeminal neuralgia were first reported in 1962. The analgesic efficacy of this agent has been most frequently documented in trigeminal neuralgia and painful diabetic neuropathy. Reports of analgesic effects of carbamazepine in postherpetic neuralgia, tabetic pain, and central pain are less well documented.

To date, 12 randomized clinical trials evaluating the efficacy of carbamazepine in neuropathic pain have been published. Three trials in patients with trigeminal neuralgia were double-blind, placebo-controlled crossover studies, in which carbamazepine was shown to be superior to placebo. One of these studies showed that, after 3 days of treatment, 80% of patients (16/20) had satisfactory pain control with carbamazepine, either alone or in combination with diphenylhydantoin. Another study showed that 73% of patients (27/37) showed an either “excellent” or “good” response after 14 days of carbamazepine treatment. A third study showed a 58% decrease in severity of pain and a 68% decrease in the number of pain episodes in 70 patients treated with carbamazepine.

The efficacy of carbamazepine in treating trigeminal neuralgia has been compared with that of active controls in three double-blind trials. Carbamazepine was found to be superior to tizanidine, an α2-adrenergic agonist, in a small (n = 12) 3-week trial. Carbamazepine produced similar pain relief compared with tocoainide, an antiarrhythmic agent, in a 4-week crossover study of 12 patients. In a larger study of 59 patients, carbamazepine was significantly less effective at relieving pain than pimozide (an antipsychotic agent), but pimozide was associated with a high frequency (83%) of adverse events. A third study showed a 58% decrease in severity of pain and a 68% decrease in the number of pain episodes in 70 patients treated with carbamazepine.

The efficacy of carbamazepine in treating trigeminal neuralgia has been compared with that of active controls in three double-blind trials. Carbamazepine was found to be superior to tizanidine, an α2-adrenergic agonist, in a small (n = 12) 3-week trial. Carbamazepine produced similar pain relief compared with tocoainide, an antiarrhythmic agent, in a 4-week crossover study of 12 patients. In a larger study of 59 patients, carbamazepine was significantly less effective at relieving pain than pimozide (an antipsychotic agent), but pimozide was associated with a high frequency (83%) of adverse events.

Three randomized trials evaluating carbamazepine in painful diabetic neuropathy used double-blind crossover techniques. Two had placebo controls, and one study used an active control arm with nortriptyline and fluphenazine. Both placebo-controlled trials showed carbamazepine to be more effective than placebo in the treatment of diabetic neuropathy. In the third study, when carbamazepine was compared with the tricyclic–neuroleptic combination, there were significant improvements from baseline associated with both therapies, but there was no significant difference between the treatment arms.

In one study of patients with central post-stroke pain, carbamazepine produced some pain relief in 5 of the 14 patients treated, but these results were not significantly different compared with placebo.

Of the two remaining studies of carbamazepine in neuropathic pain, one showed that a combination of carbamazepine and clomipramine was more effective than transcutaneous nerve stimulation in treating postherpetic neuralgia. The other study suggested efficacy of carbamazepine in treating a number of different types of neuralgia, including trigeminal neuralgia, postherpetic neuralgia, and tabetic neuralgia.

In summary, the efficacy of carbamazepine has been established in the treatment of neuropathic pain in patients with trigeminal neuralgia, with a number needed to treat (NNT) of 2.6 (range 2.2 to 3.3). Carbamazepine has also demonstrated efficacy in relieving pain in patients with painful diabetic neuropathy, with an NNT of 3.3 (range 2 to 9.4). Dosages used in these studies ranged from 300 to 1,000 mg/d, administered in divided doses. Withdrawal rates due to adverse events ranged from 0 to 7%, and many patients (up to 70%) experienced tolerable adverse events. The most common adverse events included somnolence, dizziness, and gait disturbance. Hematologic issues, such as agranulocytosis, were of concern during early experience with carbamazepine, and it is still advisable to monitor patients for this possible complication.

These positive results are overshadowed by limitations in study methodology, including study design that would not be acceptable for the modern clinical trials, lack of appropriate description of inclusion and exclusion criteria, and lack of adequate description of statistical analysis. In addition, carbamazepine has been very difficult to use in clinical practice, which demonstrates that the translation from clinical trials to clinical practice is complex.

**Phenytoin.** Three randomized clinical trials of phenytoin for the treatment of neuropathic pain have been published, two for diabetic neuropathy and one for various neuropathies. The two painful diabetic neuropathy studies showed conflicting results. Based on the data from these studies, the NNT was calculated to be 2.1 (range 1.5 to 3.6). The third study reported that IV phenytoin at doses of 15 mg/kg demonstrated analgesic efficacy when administered as a bolus 2-hour infusion, suggesting its usefulness in an acute setting for the treatment of neuropathic pain flare-ups. Although these studies provide some evidence for the efficacy of phenytoin in neuropathic pain, data on its utility are still lacking.

**Gabapentin.** Developed as a structural γ-aminobutyric acid (GABA) analogue, gabapentin does not have any direct GABAergic action, nor does it affect GABA uptake or metabolism. Preliminary evidence points to the possible effect of gabapentin on α2-δ calcium channels as an explanation for its role in pain relief.

Two large, randomized clinical trials have established the efficacy of gabapentin in treating neuropathic pain. One study included patients with painful diabetic neuropathy, and the other studied patients with postherpetic neuralgia. A total of 165 patients were randomized to gabapentin or placebo in a double-blind, placebo-controlled design. The primary outcome measure was the change in pain intensity from baseline to end of treatment. A statistically significant reduction in pain score was observed in the gabapentin group compared with placebo. The study also reported reductions in pain-related disability and improvements in quality of life.
patients (n = 84 gabapentin; n = 81 placebo) were included in the diabetic neuropathy study. At the study end point, the gabapentin group had a significant improvement in mean daily pain scores compared with the placebo group. Pain relief was observed during the second week of treatment after the gabapentin dosage reached 1,800 mg/d, and was maintained after further dosage increases and for the duration of study (8 weeks). In the postherpetic neuralgia study, patients receiving gabapentin (n = 113) had a significant reduction in average daily pain score compared with patients receiving placebo (n = 116). In both of these studies, symptoms frequently associated with chronic pain were also assessed; sleep, mood, and quality of life were improved with gabapentin therapy.

One randomized, double-blind crossover trial compared the use of gabapentin and amitriptyline for peripheral diabetic neuropathy (n = 21).26 No significant difference in the analgesic efficacy of gabapentin (900 to 1,800 mg/d) and amitriptyline (25 to 75 mg/d) was noted. The two drugs had similar adverse events profiles, with the exception that more amitriptyline-treated patients (six versus zero for gabapentin) experienced weight gain.

In summary, gabapentin has demonstrated efficacy in relieving pain and associated symptoms for patients with painful diabetic neuropathy and postherpetic neuralgia, with an NNT of 3.8 (range 2.4 to 5.0) for postherpetic neuralgia. 25 Dosages used in these studies ranged from 900 to 3,600 mg/d, administered in three divided doses, but for most patients, pain relief was achieved beyond the dosage of 1,800 mg/d. Gabapentin was well tolerated and was similar to placebo with regard to overall occurrence of adverse events. However, one study of patients with postherpetic neuralgia did show a slightly higher rate of withdrawal due to adverse events in patients treated with gabapentin (13.3%) than those receiving placebo (9.5%).25 Dizziness and somnolence were the most commonly reported adverse events, but these were well tolerated. Studies are warranted to investigate the use of gabapentin in other painful neuropathic disorders, such as central pain syndromes secondary to cerebrovascular disease, spinal cord injury, and phantom limb pain.

Lamotrigine. Lamotrigine, one of the newer antiepileptic agents, is a phenyltriazine derivative that blocks voltage-dependent sodium channels and inhibits glutamate release.3 One study of patients with trigeminal neuralgia resistant to other therapies found that lamotrigine was superior to placebo, based on a composite efficacy index.27 In addition, a small study of patients with HIV-associated painful neuropathy found that the mean reduction in pain score from baseline to week 14 was significantly greater in the lamotrigine group than in the placebo group.28 In a rare randomized crossover trial of lamotrigine in patients with central post-stroke pain, 44% of patients had their pain symptoms respond to 200 mg/d of lamotrigine.29 In contrast to the positive results of these studies, a randomized, double-blind, placebo-controlled 8-week trial of lamotrigine at dosages up to 200 mg/d showed that lamotrigine was not more effective than placebo in 100 patients with a variety of neuropathic pain conditions.30

In summary, lamotrigine at dosages of 50 to 400 mg/d has demonstrated efficacy in relieving pain in patients with trigeminal neuralgia refractory to other treatments [with an NNT of 2.1 (range 1.3 to 6.1)],3,27 in addition to patients with HIV-associated neuropathy and central post-stroke pain. However, adverse events, such as dizziness, ataxia, constipation, nausea, somnolence, and diplopia could be significant limiting factors in the use of lamotrigine, as was revealed in the HIV neuropathy study.28

Zonisamide. Zonisamide is a newer anticonvulsant agent that is believed to exert its effects by blocking sodium and T-type calcium channels and by increasing GABA release, suggesting possible efficacy in neuropathic pain. The use of zonisamide for neuropathic pain was studied in an open-label, dose-titration pilot study (Elan Pharmaceuticals, Inc.; unpublished data, 2001). The study began with an 8-week dose-titration period, followed by a 2-week maintenance period. Efficacy was assessed using the daily pain scores (from patient diaries; 0 = no pain and 10 = worst pain imaginable), Wisconsin Brief Pain Inventory (WBPI), Pain Relief Scale, Neuropathic Pain Scale (higher numbers indicating worse pain), and Investigator Global Assessment. Safety was assessed via monitoring of vital signs, laboratory values, and adverse events. Thirty-five patients were enrolled in the study (19 males, 16 females) and diagnoses included a wide variety of neuropathic pain types, such as diabetic neuropathy, peripheral neuropathy, reflex sympathetic dystrophy, post-laminectomy syndrome, radiculopathy, and others. Most of these patients were treated with many medications in the past and failed to obtain any relief. Mean patient age was 51.5 years (range 24.5 to 88 years). Seventeen patients (49%) completed the study and 18 patients withdrew from the study (1 for insufficient efficacy, 10 for adverse events, 4 for study noncompliance, and 3 for other reasons).

Mean daily pain scores improved marginally from 6.82 at baseline to 6.72 after 8 weeks of zonisamide treatment. Mean WBPI scores showed slight improvements in several categories of pain assessment during the 10 weeks of zonisamide treatment. Pain Relief Scale scores indicated that, after 10 weeks of zonisamide treatment, 3 patients felt worse, 21 patients had no change, 7 patients were improved/much improved, and 1 patient experienced complete pain relief. Mean Neuropathic Pain Scale scores showed little improvement, rising from 49.71 at baseline to 51.1 at week 8, but then declining (i.e., improving) to 49.41 at week 10. Mean Investigator Global Assessment scores showed little change over
the course of the study. What was not captured in these results was the observation that a few patients who did not respond to any treatments in the past finally obtained noticeable pain relief.

Patients in the study showed no change in blood pressure, heart rate, or body weight while taking zonisamide. Adverse events were similar to those seen in zonisamide-treated epilepsy patients and most commonly included pain, abnormal thinking, asthenia, dizziness, nausea, headache, somnolence, dyspepsia, constipation, and paresthesia.

Given the results of this pilot study, zonisamide is now under further investigation for use in various types of neuropathic pain to elucidate its potential benefits and to determine how it might best be employed.

**Other anticonvulsants.** Because of the mechanistic similarities underlying neuropathic pain and epilepsy, other anticonvulsants may prove useful in treating neuropathic pain syndromes. Other such agents currently under investigation for neuropathic pain include lorazepam, valproate, topiramate, and tiagabine. Anecdotal experience provides support for studies with oxcarbazepine and levetiracetam for treatment of neuropathic pain.

**Conclusion.** Anticonvulsants are becoming increasingly important in the management of neuropathic pain syndromes. Studies to date, along with some positive clinical experience, have indicated that several anticonvulsants, including gabapentin, carbamazepine, lamotrigine, and zonisamide, show promise in the treatment of several different types of neuropathic pain. It is hoped that data from ongoing and future clinical trials will better establish the role of other anticonvulsants in the management of neuropathic pain.

**References**