Newer Antiepileptic Drugs: Possible Uses in the Treatment of Neuropathic Pain and Migraine

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ABSTRACT

Background: Both neuropathic pain and migraine are now being treated with a variety of newer antiepileptic drugs (AEDs). The proven efficacy of gabapentin in postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN), and of divalproex sodium in the prevention of migraine has led to increased clinical investigation of the newer AEDs for these conditions. While basic and clinical research are expanding the knowledge base concerning the fundamental mechanisms of neuropathic pain and migraine, growing recognition of the similarities in the pathophysiology of epilepsy, migraine, and various chronic pain disorders has further heightened interest in exploring the newer AEDs in the treatment of these conditions.

Objective: The goals of this article were to review the empiric basis and scientific rationale for the use of AEDs in the treatment of neuropathic pain and migraine; summarize available clinical research on the use of 5 newer AEDs (gabapentin, lamotrigine, oxcarbazepine, topiramate, and zonisamide) in these conditions; and provide a summary comparison of the dosing, tolerability, and drug-interaction potential of these agents.

Methods: Relevant English-language articles were identified through searches of MEDLINE (1990–March 2003), American Academy of Neurology abstracts (1999–2003), and American Epilepsy Society abstracts (2000–2002). The search terms were antiepileptic medication or drug, migraine headache, neuropathic pain, pathophysiology, treatment, mechanism of action, gabapentin, lamotrigine, oxcarbazepine, topiramate, and zonisamide.

Conclusions: The newer AEDs possess the potential advantages of better tolerability and fewer drug–drug interactions compared with standard treatments such as tricyclic antidepressants or established AEDs. However, with the excep-
tion of data supporting the efficacy of gabapentin in PHN and PDN, there is currently insufficient evidence to determine whether the newer AEDs have equal or superior efficacy relative to proven pharmacotherapies. (Clin Ther. 2003;25:2506–2538) Copyright © 2003 Excerpta Medica, Inc.

Key words: neuropathic pain, migraine headache, antiepileptic drugs, anticonvulsant drugs, pain treatment, novel analgesics.

INTRODUCTION
In the early 1990s, a new generation of antiepileptic drugs (AEDs) was introduced into clinical practice. As a class, these medications had a number of features that distinguished them from established AEDs; namely, greater tolerability, fewer drug–drug interactions (largely owing to substantially fewer effects on the cytochrome P450 [CYP] enzyme system), and new mechanisms of action.1 At the same time, basic scientific research was beginning to unravel the mystery of neuropathic pain and migraine pain,2–5 revealing a striking overlap between the pathophysiology of these 2 conditions and that of epilepsy. Furthermore, it was realized that many of the putative mechanisms of action that made the newer AEDs effective antiseizure medications might also allow them to function as analgesics.6–10

Gabapentin demonstrated efficacy in 2 randomized, controlled trials published in 1998—one in patients with postherpetic neuralgia11 (PHN) and the other in patients with painful diabetic neuropathy12 (PDN). At about the same time, many uncontrolled studies of the use of AEDs in the treatment of neuropathic pain, as well as a growing number of pilot studies and case series on the use of these agents in the prophylaxis of migraine, began to appear in the medical literature and in presentations at major national meetings.13,14 These developments were accompanied by a large increase in the prescribing of gabapentin (and of AEDs released subsequently) for patients whose pain was refractory to the standard approaches.

The goals of this article were to review the empiric basis and scientific rationale for the use of AEDs in the treatment of neuropathic pain and migraine; summarize available clinical research on the use of the newer AEDs in these conditions; and provide a summary comparison of the dosing, tolerability, and drug-interaction potential of these agents. The drugs discussed are the newer AEDs that have been most extensively studied and prescribed in the United States: gabapentin, lamotrigine, oxcarbazepine, topiramate, and zonisamide.

Relevant English-language articles were identified through searches of MEDLINE (1990–March 2003), American Academy of Neurology abstracts (1999–2003), and American Epilepsy Society abstracts (2000–2002). The search terms were
antiepileptic medication or drug, migraine headache, neuropathic pain, pathophysiology, treatment, mechanism of action, gabapentin, lamotrigine, oxcarbazepine, topiramate, and zonisamide. Only original clinical research was included in the clinical sections of this article; letters, case reports, and post hoc analyses of preexisting data were excluded. Articles used for the theoretical sections of the article were chosen as being timely, clearly written, and supported by experimental data.

It has been reported that physicians do not receive sufficient education on the topic of pain in medical school or during residency. Therefore, this article begins with a review of the definition, clinical characteristics, and common presentations of neuropathic pain, followed by a similar overview of migraine. The section closes with a discussion of the current understanding of the basic neurophysiology of pain perception and a brief summary of some current ideas concerning the pathophysiology of neuropathic pain and migraine.

NEUROPATHIC PAIN
There are 2 fundamental types of pain: nociceptive and neuropathic. In both cases, pain (from the Latin poena, a fine or penalty) arises from nociception (from the Latin noceo, to injure); in other words, pain is the price we pay for consciousness of something injurious happening to us. It can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Nociceptive pain, which can also be thought of as normal, or ordinary, pain, occurs when a pain signal originates in normally functioning tissue nociceptors—Aδ and C fibers—that have been activated by a mechanical, chemical, or thermal stimulus. Neuropathic pain, however, occurs when an algogenic (from the Greek algos, pain) signal originates within abnormally functioning peripheral or central neurons that have themselves been damaged or altered in some way. Therefore, although the clinical characteristics (intensity, quality, and course) of nociceptive pain are determined primarily by the physical injury causing the pain, the clinical characteristics of neuropathic pain are determined predominantly by the mechanisms, location, and severity of the neuropathologic process itself.

Neuropathic pain encompasses a heterogeneous group of disorders (Table I). Some of the more commonly seen syndromes include PHN, PDN, radiculopathy, and central poststroke pain. Trigeminal neuralgia and complex regional pain syndrome (CRPS) are less prevalent but highly debilitating diseases that account for a significant proportion of patients seen in specialty settings. With respect to their treatment, these illnesses share several critical clinical features: they follow a chronic course; they respond very poorly or not at all to standard analgesic therapies such as nonsteroidal anti-inflammatory drugs and acetaminophen; and they respond less predictably and less robustly to opioids than do nocicep-
It is for these reasons that neuropathic pain must be treated differently from nociceptive pain.

Unlike nociceptive pain, which—apart from the phenomenon of referred pain—patients can usually describe simply and clearly, neuropathic pain is characterized by a variety of dysesthetic sensations and is therefore reported with difficulty and less precision. Often the pain is hard to localize, is spread across a much larger area, and may not conform to any dermatomal distribution. Frequently encountered descriptors include burning, shooting, stabbing, hot, cold, itching, deep, or sensitive. In most cases, patients report that this type of pain is triggered by benign (nonpainful) stimuli such as light touch, mild heat, or minimal pressure. This characteristic of neuropathic pain is called allodynia. Equally distressing is the phenomenon of hyperalgesia, which is the experience of severe pain in response to stimuli that would ordinarily cause only mild pain. Patients may be troubled because their discomfort has no obvious source. As a consequence of these factors, patients with neuropathic pain endure much suffering and may become demoralized or clinically depressed. It is imperative that clinicians not minimize the seriousness of this pain or the “organicity” of its origins.

In many cases, a patient’s pain has both nociceptive and neuropathic mechanisms. Inflammatory states provide an excellent example. Although certain substances released during inflammation (eg, prostaglandins) are responsible for the sensitization and activation of the nociceptive Aδ and C fibers, some proinflammatory cytokines (eg, tumor necrosis factor–alpha, interleukin-1) can cause central and peripheral neurodegeneration and thereby induce neuropathic pain. The combination of inflammatory and neuropathic pain mechanisms is seen most commonly in patients with cancer. The important clinical message is that many patients present with a combination of pain mechanisms, which often requires a combination approach to treatment.

Table I. Neuropathic pain disorders.

<table>
<thead>
<tr>
<th>Neuropathic pain disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful diabetic neuropathy</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
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<tr>
<td>Radiculopathies</td>
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<tr>
<td>Painful HIV-associated neuropathy</td>
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<tr>
<td>Central poststroke pain</td>
</tr>
<tr>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>Deafferentation syndromes (eg, phantom limb pain)</td>
</tr>
<tr>
<td>Migraine headache</td>
</tr>
</tbody>
</table>
MIGRAINE
Migraine is a primary headache disorder with a number of syndromic subtypes; the 2 most common are migraine without aura and migraine with aura. The diagnosis of these subtypes is based on fulfillment of specific criteria concerning the duration, location, and severity of headache pain, and on the presence or absence of particular associated symptoms (Table II). Migraine is a common

<table>
<thead>
<tr>
<th>Table II. International Headache Society diagnostic criteria for migraine.</th>
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<tbody>
<tr>
<td><strong>1.1 Migraine without aura</strong></td>
</tr>
<tr>
<td>A. At least 5 attacks fulfilling conditions of B–D</td>
</tr>
<tr>
<td>B. Headache attacks lasting 4–72 hours</td>
</tr>
<tr>
<td>1. Untreated or unsuccessfully treated</td>
</tr>
<tr>
<td>2. If falling asleep with headache and awakening headache free, duration of attack includes sleep time</td>
</tr>
<tr>
<td>C. Headache has at least 2 of the following characteristics:</td>
</tr>
<tr>
<td>1. Unilateral location</td>
</tr>
<tr>
<td>2. Pulsating quality</td>
</tr>
<tr>
<td>3. Moderate or severe intensity (prohibits some daily activities)</td>
</tr>
<tr>
<td>4. Exacerbation by routine physical activity (e.g., climbing stairs)</td>
</tr>
<tr>
<td>D. During headache attack at least 1 of the following:</td>
</tr>
<tr>
<td>1. Nausea and/or vomiting</td>
</tr>
<tr>
<td>2. Photophobia and phonophobia</td>
</tr>
<tr>
<td>E. Any other disorder that causes headache is ruled out by history, physical and neurological examination, or appropriate investigation</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>The first headache attacks that fulfill the criteria for migraine in A–D do not occur in temporal proximity to such a disorder</td>
</tr>
</tbody>
</table>

| **1.2 Migraine with aura**                                    |
| A. At least 2 attacks fulfilling conditions of B              |
| B. At least 3 of the 4 following characteristics:             |
| 1. One or more fully reversible aura symptoms indicating focal cerebral, cortical, and/or brain-stem dysfunction |
| 2. At least 1 aura symptom develops gradually over >4 minutes, OR ≥2 aura symptoms occur in succession |
| 3. No aura symptom lasts >60 minutes; if >1 aura symptom is present, accepted duration is proportionately increased |
| 4. Headache follows aura with a free interval of <60 minutes (it may begin before or simultaneously with aura) |
| C. Any other disorder that causes headache is ruled out by history, physical and neurological examination, or appropriate investigation |
| OR                                                             |
| The first headaches that fulfill the criteria for migraine with aura in A–B do not occur in temporal proximity to such a disorder |
illness, affecting ~11% to 12% of the population of industrialized nations, with rates in women approximately 3-fold those in men.\textsuperscript{26–28} In the majority of patients with migraine, the frequency of attacks is low;\textsuperscript{29} the response to acute treatment is adequate,\textsuperscript{30–32} and the progression of disease over time is limited.\textsuperscript{33}

A subgroup of patients with migraine, however, experience a more debilitating illness.\textsuperscript{34} These patients may have a high frequency or greater severity of migraine attacks, or they may be unresponsive to or unable to tolerate acute therapies.\textsuperscript{33} It is thought that in some patients, overuse of analgesic (narcotic and nonnarcotic) or abortive medications (primarily triptans) contributes to development of a chronic form of the disease known as “transformed migraine.”\textsuperscript{35} Preventive treatment is indicated in these groups of patients.\textsuperscript{34} Although such treatment may include certain nonpharmacologic modalities, such as relaxation training or cognitive/behavioral therapy, medications can play a major role in the comprehensive treatment plan.\textsuperscript{36}

\textbf{PATHOPHYSIOLOGY OF NEUROPATHIC PAIN AND MIGRAINE}

\textit{Physiology of Nociception}

To appreciate the numerous possible etiologies of neuropathic pain, and, more importantly, understand the putative sites and mechanisms of action of AEDs and other agents in the treatment of neuropathic pain, it is helpful to review the structure and function of the pain neuraxis. Clinicians should be able to give patients short, simple explanations of the cause of their symptoms and how the proposed treatments work. These communications are an essential part of the physician–patient relationship and are of tremendous value in establishing trust and improving compliance with the prescribed treatment.\textsuperscript{37} This is particularly true for such conditions as neuropathic pain, in which the etiology is not obvious and treatment often takes weeks to begin working and rarely provides complete relief.

Nociception begins when $\alpha$ and $\delta$ fibers respond to noxious stimulation and transmit this information via the dorsal root ganglia to the dorsal horn of the spinal cord.\textsuperscript{38} These nerve fibers can be activated by a host of biochemical products of tissue damage and inflammation, including prostaglandins, cytokines, bradykinin, histamine, free radicals, protons, purines, neurotrophins, and others. The strength of the signal transmitted is proportional to the intensity of the noxious input. Critical membrane components of the dorsal horn nociceptor neurons (C fibers) are the sensory neuron–specific voltage-gated sodium channels, key ion channels responsible for the generation and maintenance of action potentials, and the N-type voltage-gated calcium channels, which, when activated, allow calcium to flow into the cell and promote excitation.\textsuperscript{38}

Nociceptive signals are processed at the spinal segmental level by the dorsal horn neurons. Both somatic and visceral afferents terminate on these neurons, which is probably the physiologic reason for typical pain referral. Interneurons
modulate both transmitter release presynaptically and signal intensity postsynaptically. This modulation is primarily inhibitory, and the predominant transmitter is \( \gamma \)-aminobutyric acid (GABA). Dorsal horn neurons have numerous receptors that respond to substance P and excitatory amino acids (glutamate and aspartate) as they are released at the terminals of the afferent inputs. These receptors include N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and neurokinin-1. The dorsal horn neurons project via ascending pathways to the thalamus, whereas supraspinal modulatory neurons originating in the brain stem reach the dorsal horn via descending pathways. These neurons are primarily noradrenergic and exert an inhibitory influence.

Afferent input from the cranial meninges is conducted through the trigeminal–vascular pathway, whose cell bodies are in the trigeminal ganglion, and through synapses on the trigeminal nucleus. Thus, the sensory fibers of the trigeminal nerve are analogous to the peripheral sensory fibers in the rest of the body, the trigeminal ganglion corresponding to the dorsal root ganglion and the trigeminal nucleus corresponding to the dorsal horn. The neurochemistry of these corresponding structures is essentially the same.

The actual perception of pain is initiated only when the nociceptive signal is transmitted through the thalamus and neighboring nuclei to the somatosensory cortex, anterior cingular cortex, and amygdala. Whereas the somatosensory cortex is responsible for pain sensation, it is the other centers that underlie the affective experience associated with pain. This cortical–limbic–thalamic circuitry is quite complex and highly individualized, mirroring the dramatic variation in the human experience of pain.

**Etiologies and Mechanisms of Neuropathic Pain**

Anything that causes a structural lesion or a functional change in the peripheral or central neurons of the pain neuraxis can result in neuropathic pain. Hereditary abnormalities (eg, Fabry’s disease), traumatic injury, vascular insufficiency, viral infection, toxic/metabolic insult, disk disease, spondylosis, and unremitting nociceptive input are common examples of the etiologies of neuropathic pain disorders (Table III).

It is not yet clear which specific neuronal changes are responsible for the aberrant pain sensations associated with neuropathic diseases, but basic science research is unraveling a host of potential neuropathic pain mechanisms. In particular, abnormalities in ion channel conductivity and receptor function probably play some role in the majority of these perplexing illnesses. For example, one of the consequences of peripheral nerve injury is an alteration in the expression of adrenergic receptors, resulting in pathologic activation of these nociceptive neurons by noradrenaline. This puzzling process is called sympathetically maintained pain, and it plays a pathogenic role in some cases of CRPS. Several animal models of periph-
eral neuropathy have shown an increase in both the number and conductivity of sodium ion channels, which in turn increases the strength of the inward sodium current and causes persistent aberrant firing of these neurons.\textsuperscript{2,45}

Central neuropathic pain, or central pain, encompasses the entire neuraxis. It is heuristically useful to separate central pain into 2 processes: (1) the pain-signaling process, which involves the dorsal horn neurons (the segmental level) and the descending modulatory pathways originating in the brain stem; and (2) the pain-perception process, which takes place exclusively in the brain. It is only the latter that generates the subjective experience of pain, whereas the former is responsible for the intensity of the nociceptive signal.\textsuperscript{46} It has been amply demonstrated that central sensitization, a process somewhat like kindling, is an important component of the neuropathology of central pain. In kindling, the seizure threshold of the postsynaptic neuron progressively decreases, whereas in central sensitization the magnitude of response of the postsynaptic neuron progressively increases. This process is mediated, at least in part, by the NMDA-receptor complex.\textsuperscript{47} (Table IV lists the potential targets of neuropathic pain treatments.\textsuperscript{2–5,23,42–48})

**Etiologies and Mechanisms of Migraine**

It is now widely recognized that migraine, as well as other primary headache disorders such as cluster headache and chronic daily headache, may share several of the mechanisms known to play a role in neuropathic pain, including peripheral and central sensitization,\textsuperscript{49} channelopathies,\textsuperscript{50} and neurogenic inflammation of the meninges.\textsuperscript{51} Although the origin of pain in migraine is still a fiercely debated topic, there is general agreement that involvement of the trigeminal nerve is crucial and that there is an interplay between central and peripheral processes.\textsuperscript{52}
One theory posits that abnormal activation of the trigeminal nucleus is the primary mechanism in migraine. In this theory, trigeminal nucleus dysfunction is possibly initiated by hyperactivity in neighboring midbrain structures and is complicated by an antidromic conduction of impulses toward the periphery, promoting both neurogenic inflammation and central sensitization. Another theory proposes a central role for nitric oxide, which is found in the perivascular sensory nerve endings as well as in key brain stem structures known to be involved in nociceptive processing. According to this theory, nitric oxide may function as either the trigger for spontaneous migraine attacks, a critical component

<table>
<thead>
<tr>
<th>Target</th>
<th>Receptors</th>
<th>Ion Channels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral</strong></td>
<td>Vanilloid</td>
<td>Sensory neuron–specific</td>
</tr>
<tr>
<td></td>
<td>Tyrosine kinase</td>
<td>voltage-gated sodium channels</td>
</tr>
<tr>
<td></td>
<td>Purinergic (ATP)</td>
<td>Other types of sodium channels</td>
</tr>
<tr>
<td></td>
<td>Adrenergic</td>
<td>Acid-sensing ion channels</td>
</tr>
<tr>
<td></td>
<td>Serotonergic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Opioid</td>
<td>Nitric oxide synthase*</td>
</tr>
<tr>
<td></td>
<td>Cannabinoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interleukin</td>
<td></td>
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<tr>
<td></td>
<td>Glutamate</td>
<td></td>
</tr>
<tr>
<td><strong>Segmental</strong></td>
<td>NMDA</td>
<td>N-type voltage-gated calcium</td>
</tr>
<tr>
<td></td>
<td>AMPA</td>
<td>channels</td>
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<tr>
<td></td>
<td>GABA</td>
<td>Other types of calcium channels</td>
</tr>
<tr>
<td></td>
<td>Opioid</td>
<td>Sensory neuron–specific</td>
</tr>
<tr>
<td></td>
<td>Alpha₂-adrenergic</td>
<td>voltage-gated sodium channels</td>
</tr>
<tr>
<td></td>
<td>Neurokinin-1</td>
<td>Other types of sodium channels</td>
</tr>
<tr>
<td></td>
<td>Adenosine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycine</td>
<td>Nitric oxide synthase*</td>
</tr>
<tr>
<td></td>
<td>N-nicotinic acetylcholine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabotropic glutamate</td>
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<tr>
<td></td>
<td>Cannabinoid</td>
<td></td>
</tr>
<tr>
<td><strong>Central</strong></td>
<td>Forebrain-specific NMDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha₂-adrenergic</td>
<td></td>
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<tr>
<td></td>
<td>Serotonergic</td>
<td></td>
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<tr>
<td></td>
<td>N-nicotinic acetylcholine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannabinoid</td>
<td></td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; NMDA = N-methyl-D-aspartate; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA = γ-aminobutyric acid.

*Nitric oxide synthase is the key enzyme required for nitric oxide formation.*
of peripheral and central sensitization, or both. There are many other theories of the origin of migraine pain, but a neuropathic etiology is assigned a substantial role in all of them.

RATIONALE FOR THE USE OF AEDs IN NEUROPATHIC PAIN AND MIGRAINE

Use of AEDs for the treatment of neuropathic pain is an attractive option, not least because of the similar pathophysiologies of neuropathic pain and epilepsy. One example of these similarities is provided by the mechanisms of kindling and central sensitization noted in the previous section, and another is provided by the processes of ectopic neuronal firing common to both epilepsy and neuropathic pain. In addition to these closely related pathophysiologic mechanisms, both disorders can be caused by a central nervous system injury, such as head trauma.

The clinical connection between epilepsy and migraine is also becoming increasingly clear. Several studies have reported that epilepsy and migraine occur as comorbid conditions with greater than random frequency. The median prevalence of epilepsy in patients with migraine is 5.9% (range, 1%–17%), compared with <1.0% in the general population. Similarly, patients with epilepsy have a higher lifetime prevalence of migraine. The Epilepsy Family Study found that those with epilepsy had a 2.4 times greater rate of migraine than family members without epilepsy. The possible explanations for this comorbidity include a shared etiology (eg, head trauma), a shared genetic vulnerability to neuronal hyperexcitability (eg, channelopathies), or some as yet unproved common etiologic factor (eg, particular types of serotonergic dysfunction).

Given the interconnection of these disorders, it is reasonable to speculate that the mechanisms of action that may be responsible for the therapeutic efficacy of the newer AEDs in the treatment of epilepsy may also prove beneficial in the treatment of neuropathic pain and migraine. Seven mechanisms of action are shared by ≥1 of the newer AEDs that relate directly to the pathophysiology of neuropathic pain and migraine, any or all of which may account for the effectiveness of the medications discussed in this article: (1) sodium channel blockade; (2) calcium channel blockade; (3) enhancement of GABAergic transmission; (4) inhibition of glutamatergic transmission; (5) free radical scavenging; (6) inhibition of nitric oxide formation; and (7) enhancement of serotonergic transmission (Table V).

EARLY CLINICAL EXPERIENCE WITH AEDs IN NEUROPATHIC PAIN AND MIGRAINE

Carbamazepine for Neuropathic Pain

In addition to the foregoing rationale for their use, the AEDs showed some early clinical promise in the treatment of neuropathic pain. Carbamazepine emerged as a treatment for trigeminal neuralgia before the discovery of much of
what we now know about the neurophysiology of nociception and the neuropathology of neuropathic pain. It first began to be used for trigeminal neuralgia after the publication in *Lancet* in 1962 of a report by Blom describing its successful use in a series of patients with this condition.68 Because previous pharmacotherapies for this condition had been almost uniformly unsuccessful, the fact that carbamazepine worked at all was remarkable. Two double-blind, placebo-controlled, crossover studies69,70 subsequently provided definitive scientific evidence for the efficacy of carbamazepine in the treatment of trigeminal neuralgia. In these studies, which involved 151 patients, improvement in pain was 2- to 3-fold greater with carbamazepine compared with placebo. The dosing was identical to that used for the treatment of epilepsy, ranging from 400 to 1000 mg/d PO, corresponding to serum levels of 6 to 10 mg/L. Thus, carbamazepine was established as the treatment of choice for trigeminal neuralgia.

The success of carbamazepine in trigeminal neuralgia led to its investigation in other neuropathic conditions. A small randomized, double-blind, crossover trial of carbamazepine conducted in the late 1960s in 30 patients with PDN suggested some benefit, although the outcome measures were not well designed—for example, a standardized pain rating scale was not used.71 Sixty-seven percent of the patients noted “moderate or significant” pain relief with carbamazepine, compared with 20% with placebo. A subsequent comparison of carbamazepine with the combination of nortriptyline and fluphenazine in patients with PDN found that carbamazepine was equivalent in efficacy to the tricyclic antidepressant (TCA)–neuroleptic combination.72 The clinical experience with carbamazepine in PDN

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Gabapentin</th>
<th>Lamotrigine</th>
<th>Oxcarbazepine</th>
<th>Topiramate</th>
<th>Zonisamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance GABAergic transmission</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-, N-, or T-type calcium channel blockade</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibit glutamatergic transmission</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium channel blockade</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Free radical scavenger</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Enhance serotonergic transmission</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inhibit formation of nitric oxide</td>
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</table>

GABA = γ-aminobutyric acid.
has not been satisfactory, however, and trigeminal neuralgia is the only neuropathic pain state for which carbamazepine is considered a first-line agent. One small study in patients with central pain failed to show efficacy,73 and the results of another small study in patients with PHN or other neuralgias were inconclusive.74 Clinical studies examining the efficacy of phenytoin in PDN yielded equivocal results.75,76 With the exception of sodium valproate for the prophylaxis of migraine (discussed in the following section) and carbamazepine for the treatment of trigeminal neuralgia, none of the other older AEDs were ever demonstrated to be effective in the treatment of any neuropathic pain syndrome or headache disorder.

Thus, little progress has been made in the development of medications for neuropathic pain in the >30 years since the discovery that carbamazepine was efficacious in the treatment of trigeminal neuralgia. TCAs have remained the treatment of choice for most neuropathic pain disorders (except trigeminal neuralgia),77 and beta-blockers and TCAs have continued to be used as first-line treatments for the prevention of migraine.13 Over the past decade, however, this situation has been changing, in part because of the introduction of the next generation of AEDs.

**Valproic Acid for the Prophylaxis of Migraine**

It was not until the early 1990s that valproic acid was studied as an antimigraine agent. In 2 randomized, controlled trials in patients with migraine,78,79 sodium valproate was found to significantly decrease the frequency of headache compared with placebo ($P = 0.002$78 and $P < 0.001$79). Divalproex sodium, a slightly different preparation of this agent, was studied in 2 controlled trials and found to have similar efficacy to sodium valproate.80,81 In the most recent of these 2 trials,81 divalproex given at 500, 1000, and 1500 mg/d reduced the mean frequency of headaches by between 1.7 and 2.0 per month from a baseline value of 4.5 to 4.7 per month. Among patients who received divalproex, 44% had a $\geq 50\%$ decrease in migraine occurrence, compared with 21% in the placebo group ($P < 0.05$). In clinical practice, however, high rates of adverse events (AEs) (eg, nausea, weight gain, tremor); the need for regular monitoring of drug levels, liver enzymes, and blood counts; and the lack of its clear superiority over conventional treatments have limited the usefulness of this AED as a prophylactic treatment for migraine. Despite these problems, these studies of sodium valproate indicated the potential utility of AEDs in the prevention of migraine.

Many migraine patients are candidates for prophylactic therapy, particularly those with transformed migraine, whose headaches occur on a daily or almost-daily basis.13 Furthermore, excessive use of triptans or other abortive agents (≥3 times per week) can compound the problem by causing medication-overuse, or rebound, headaches.82 In addition, a sizeable minority of patients do not respond well to triptans or other abortive agents, and there are those whose headaches are
so disabling they prefer to treat them prophylactically, even if this means taking medication on a daily basis. The International Headache Society recognizes all of these circumstances as medical indications for the use of prophylactic therapy. The possibility that AEDs might be effective for this purpose, as suggested by the experience with sodium valproate, has led to interest in the newer AEDs.

**CLINICAL TRIALS OF THE NEWER AEDs IN NEUROPATHIC PAIN AND MIGRAINE**

Gabapentin is the only AED empirically shown to be beneficial in the treatment of some forms of neuropathic pain. Limited numbers of randomized, placebo-controlled, double-blind trials have evaluated lamotrigine and topiramate in various neuropathic pain states, and gabapentin and topiramate in the prophylaxis of migraine. Much of the clinical research concerning the use of the newer AEDs for neuropathic pain and migraine has been in the form of open-label, uncontrolled studies in small, nonrandomized samples.

Many of these studies have been presented at the national meetings of professional societies and have been published in abstract form only. Although the majority of these open-label, uncontrolled studies have reported positive results, further randomized, controlled trials are necessary to determine the safety and efficacy of the newer AEDs in the treatment of neuropathic pain and migraine. The following sections summarize the available literature on the 5 most commonly prescribed newer AEDs.

**Gabapentin**

**Neuropathic Pain**

Clinical interest in the potential role of the newer AEDs in the treatment of neuropathic pain reawakened in 1998 with publication of the results of 2 multicenter, randomized, double-blind, placebo-controlled trials of gabapentin in patients with PHN and PDN in the same issue of the *Journal of the American Medical Association*. In the PHN study, 229 patients were randomized to receive gabapentin or placebo. Gabapentin was titrated over 4 weeks to a maximum of 3600 mg/d, followed by a 4-week maintenance phase. Patients were allowed to continue stable doses of TCAs and/or opioids. The primary outcome measure was the mean daily pain score (11-point scale), which decreased from 6.3 to 4.2 in the active-treatment group and from 6.5 to 6.0 in the placebo group (P < 0.001). There was no significant difference in the rate of withdrawals in the gabapentin group (13.3%) and the placebo group (9.5%).

In the PDN study, 165 patients with a ≥1-year history of pain of at least moderate severity were randomized to receive gabapentin or placebo. This study also employed a 4-week titration phase and a 4-week maintenance phase. In this study, however, all other medications that could affect the symptoms of PDN were pro-
hibited from 30 days before randomization throughout the study period. (The only exceptions were stable doses of a serotonin reuptake inhibitor, low-dose acetylsalicylic acid [up to 325 mg/d], and acetaminophen [up to 3 g/d].) One hundred thirty-five patients completed the study, with no significant between-group difference in dropout rates (17% gabapentin, 20% placebo). The mean daily pain score (10-point visual analog scale [VAS]) in the gabapentin group decreased from 6.4 at baseline to 3.9 by the end of the 8-week study, compared with a decrease from 6.5 to 5.1 in the placebo group (P < 0.001). Somnolence, dizziness, ataxia, and confusion were the most commonly occurring AEs with gabapentin.

A randomized, controlled study directly compared gabapentin with amitriptyline in patients with PDN, as did another study employing an open-label design. Neither study found a significant difference between the 2 agents in terms of efficacy or total AE burden. The second study reported numerically greater reductions in pain and paresthesias with gabapentin and less gain in body weight, although the differences were not statistically significant. Although each study included only 25 patients, the data suggested that gabapentin was at least as efficacious and as well tolerated as the TCA.

A randomized, double-blind, placebo-controlled study of gabapentin in the treatment of PHN confirmed the positive results of the earlier PHN trial. This 7-week study in 334 adults evaluated 2 gabapentin regimens—1800 and 2400 mg TID. The active-treatment groups had a 34% decrease in mean daily pain ratings from baseline to the final week of the study, whereas the placebo group had a 16% decrease (P < 0.01). Subsequent to this confirmation of the drug’s efficacy in PHN, the US Food and Drug Administration (FDA) added PHN to the indications for gabapentin. This is the only approved indication for a neuropathic pain disorder for any of the newer AEDs.

The actual improvement in pain scores in those who received gabapentin in the preceding studies was not dramatic. The magnitude of response to other AEDs has also been limited—this is partly a reflection of the wide range of responses in the treatment groups, with some patients experiencing a benefit (≥50% reduction in pain) and others receiving no benefit at all. It must be remembered, however, that there are few effective treatments for neuropathic pain, and even a modest benefit is meaningful.

There are published reports suggesting therapeutic benefit for gabapentin in trigeminal neuralgia, multiple sclerosis pain, and neuropathic head and neck pain. Because none of these studies were prospective or controlled, the results can be considered only preliminary.

**Migraine**

Gabapentin was efficacious for the prophylaxis of migraine in a multicenter, randomized, double-blind, placebo-controlled trial. Ninety-eight patients re-
ceived gabapentin and 45 received placebo. Among those who were able to tolerate a stable dosage of 2400 mg/d, 46.4% had a ≥50% reduction in the frequency of migraine, compared with 16.1% in the placebo group ("P = 0.02). This group had a reduction in the frequency of headaches from 4.2 during the 4-week baseline period to 2.7 during the final 4 weeks of the study (mean reduction, 1.5; "P = 0.006), whereas the placebo group had a reduction from 4.1 to 3.6 (mean reduction, 0.5). Sixteen patients (16.3%) in the gabapentin group dropped out of the study because of AEs, compared with 4 (8.9%) in the placebo group. These results have yet to be confirmed by other trials.

**Lamotrigine**

**Neuropathic Pain**

Lamotrigine is the only other newer AED to have been evaluated in randomized, controlled trials involving patients with neuropathic pain. In a multicenter, 14-week, randomized, double-blind, placebo-controlled trial in 42 patients with painful HIV-associated neuropathy, lamotrigine 300 mg reduced pain significantly compared with placebo ("P = 0.03). In descriptive terms, the pain decreased from moderate to very mild. Interpretation of the results is limited by the small sample size and the high dropout rate (11/20 lamotrigine, 2/22 placebo). Five patients in the lamotrigine group developed a rash that caused them to discontinue treatment, although there were no serious medical consequences in any of these cases. Nonetheless, the results of this study are intriguing, as most other treatments for HIV-associated neuropathy, including amitriptyline, have shown no benefit over placebo.

In a subsequent randomized, double-blind, placebo-controlled trial in 247 patients with painful HIV-associated neuropathies, patients were stratified according to whether or not they were currently receiving neurotoxic antiretroviral therapy. Only those who were receiving antiretroviral therapy had a statistically significant decrease in scores on a VAS for pain, with a 27.1% reduction in the lamotrigine group and a 9.0% reduction in the placebo group ("P < 0.02).

An 8-week, randomized, double-blind, placebo-controlled trial evaluated lamotrigine monotherapy in 59 patients with PDN. Medication was titrated slowly to a final dosage of 400 mg/d in the eighth week. The primary outcome variable was the mean daily pain score (0–10 scale), which decreased from 6.4 to 4.2 in the active-treatment group (lamotrigine 200, 300, and 400 mg/d) and from 6.5 to 5.3 in the placebo group ("P < 0.001). There was no difference in rates of attrition, with 83% of lamotrigine recipients and 73% of placebo recipients completing the study. Twelve of 24 patients (50%) in the lamotrigine group who completed the study reported a ≥50% decrease in pain, compared with 5 of 22 patients (23%) in the placebo group. The efficacy and tolerability results of this study were comparable to those of the studies of gabapentin in PDN.
In a small randomized, double-blind, placebo-controlled, crossover study in 30 patients with central poststroke pain, lamotrigine was titrated to 200 mg/d over 6 weeks and continued at that dosage for the final 2 weeks of treatment. This was followed by a 2-week washout period and another 8 weeks of double-blind treatment. Lamotrigine reduced the final median weekly pain score compared with placebo \((P = 0.01)\), as well as the patient’s global assessment of pain (11-point Likert scale) from strong (4) at baseline to moderate (3) at the end of the study \((P = 0.02)\). Three patients who received lamotrigine withdrew from the study because of AEs, compared with no placebo recipients. The results were not dramatic, although they suggested potential benefit for lamotrigine. Conversely, an 8-week, randomized, double-blind, placebo-controlled trial of lamotrigine monotherapy in 100 patients with a variety of neuropathic pain conditions found no benefit for lamotrigine; however, the drug was titrated very slowly and the maximum dosage reached was only 200 mg/d.

**Migraine**

Lamotrigine has been evaluated as part of combination therapy for the prevention of migraine in a prospective, open-label trial enrolling 65 patients, most of whom had transformed migraine. Only 35 patients were included in the final analysis; 12 dropped out because of AEs. The primary end point was reduction in the frequency of severe headaches. By this measure, 17 patients (48.6%) were responders at a mean dosage of 55 mg/d. Those who had migraine with aura had a better response rate (12/18 [66.7%]); among these responders were 4 of 8 patients whose headaches were chronic. This finding was supported by the results of an interesting pilot study that assessed the impact of lamotrigine on aura itself and reported that the drug significantly reduced both the frequency and duration of aura (both, \(P < 0.001\)).

There are case reports in which lamotrigine is mentioned as having potential benefit in the treatment of a type of headache known as SUNCT—short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing. Although the relationship of SUNCT to migraine is uncertain, the condition is thought to be primarily neuropathic in origin.

**Oxcarbazepine**

**Neuropathic Pain**

The literature search identified no published randomized, controlled trials of oxcarbazepine, the 10-keto homologue of carbamazepine, in the treatment of any neuropathic pain disorder. Reports of several open-label trials of oxcarbazepine in patients with trigeminal neuralgia that was refractory to carbamazepine suggested that this agent was useful and well tolerated. Twelve of 15 patients responded in one trial, 13 of 15 in another, and 14 of 14 in the third. The titration of oxcarbazepine was rapid (over 7–10 days), and effective dosages
ranged from 900 to 2400 mg/d. The AE profile of oxcarbazepine was favorable relative to carbamazepine in all 3 trials.

An open-label study of adjunctive oxcarbazepine in 36 consecutive patients with various neuropathic pain disorders that had not responded to treatment with gabapentin found that the addition of oxcarbazepine 600 to 1200 mg/d was helpful in almost two thirds of patients.\textsuperscript{112} Excellent results (>70\% improvement in neuropathic symptoms, based on VAS pain score, the Short-Form McGill Pain Questionnaire, the physician’s global assessment, and physical examination) were reported in 22.2\% of patients, good results (51\%–70\% improvement) in 41.7\%, and fair or poor results (≤50\% improvement) in 38.9\%. In the subset of patients who presented with radiculopathy (n = 18), the proportion of those with excellent or good results was greater than in the sample as a whole (84\% vs 64\%, respectively). Discontinuation of treatment was more frequently attributed to poor response than to AEs.

**Migraine**

The literature search identified no studies examining the use of oxcarbazepine in the prophylactic treatment of any headache disorder.

**Topiramate**

**Neuropathic Pain**

The structurally unique AED topiramate has shown possible efficacy as monotherapy in 1 small randomized, controlled study in patients with PDN.\textsuperscript{90} Twenty-six adult patients were randomized to receive placebo or topiramate titrated over 10 weeks to 400 mg/d or the highest tolerated dose. At the conclusion of the study, the topiramate group had a 35\% mean decrease in VAS pain scores, compared with a 4\% mean increase in the placebo group.

Four larger randomized, double-blind, placebo-controlled trials were later conducted, only 1 of which has been published.\textsuperscript{89} The latter, also the only 1 of the 4 trials to report a significant benefit for topiramate, was a 12-week trial in which 192 patients with PDN received topiramate 400 mg/d (or the maximum tolerated dose) or placebo. The topiramate group had a mean reduction in pain score of 21.8 mm on a 100-mm VAS, compared with a reduction of 15.1 mm in the placebo group (P = 0.038). A higher proportion of patients in the topiramate group reported ≥50\% reduction in pain scores compared with the placebo group (36\% vs 21\%, respectively; P = 0.005). The authors hypothesized that higher baseline pain scores or certain design differences may have explained the discrepancy between the results of this study and the other 3.

Use of topiramate for other types of neuropathic pain has been investigated to a limited extent. One case report of a patient with intercostal neuralgia cited some benefit,\textsuperscript{113} and a small case series (N = 6) reported dramatic benefit in patients
with trigeminal neuralgia. However, a later placebo-controlled, crossover study in 3 patients with trigeminal neuralgia failed to show an advantage for topiramate relative to placebo.

Migraine

Two randomized, double-blind, placebo-controlled studies of topiramate monotherapy in the preventive treatment of migraine have been published. One study enrolled 40 adults with migraine with or without aura (35 completed the study). After a 4-week baseline period, patients were randomized in a 1:1 ratio to receive topiramate or placebo. Topiramate therapy was titrated to 200 mg/d over 8 weeks and was maintained at the highest tolerated dose for 8 weeks. The mean dosage was 125 mg/d. The mean frequency of headaches per 28 days was reduced from 5.14 at baseline to 3.31 during the maintenance period in the topiramate group, compared with a reduction from 4.37 to 3.83 in the placebo group (P = 0.003). The second study had essentially the same design, with 30 patients randomized in a 1:1 ratio to receive topiramate or placebo, and a similar timetable for the baseline, titration, and maintenance phases. There was a limited group effect, but 7 of 15 patients receiving topiramate had ≥50% reduction in headaches, compared with only 1 of 15 receiving placebo. This benefit was counterbalanced by 7 of 15 patients in the topiramate group dropping out of the study, as a result of AEs.

The results of 2 multicenter, randomized, double-blind, placebo-controlled studies of topiramate for the prophylactic treatment of migraine were presented at a national meeting in 2003. In the first study, patients were randomized to receive topiramate 50 mg/d (n = 125), 100 mg/d (n = 128), or 200 mg/d (n = 117), or placebo (n = 117). The primary outcome measure was change in headache frequency from baseline to the end of the double-blind phase. Patients in all 3 treatment groups had significantly greater response rates (defined as a ≥50% reduction in headache frequency) relative to placebo (50 mg: 36%, P = 0.039; 100 mg: 54%, P < 0.001; 200 mg: 52%, P < 0.001; placebo: 23%). Similarly, patients in the topiramate 100- and 200-mg groups had significantly greater reductions in the mean monthly frequency of headaches compared with placebo (P < 0.001).

The second study was methodologically identical, with 483 patients randomized to the same 4 treatment groups as in the first study. The results again showed a statistically significant benefit for topiramate, whether measured in terms of response rates (P < 0.001, topiramate 100 and 200 mg vs placebo) or reduction in mean monthly frequency of headache (100 mg, P = 0.008; 200 mg, P = 0.001). There was no difference in completion rates between the 4 groups (50 mg, 49%; 100 mg, 52%; 200 mg, 58%; placebo, 52%). A greater proportion of topiramate recipients dropped out of the study because of AEs compared with the placebo group (200 mg, 26%; placebo, 12%), whereas a greater proportion
of placebo recipients dropped out because of lack of efficacy (100 and 200 mg, both 10%; placebo, 18%).

Zonisamide
Neuropathic Pain

Zonisamide has not been evaluated in any randomized, controlled trials in patients with neuropathic pain, but a number of open-label case series and anecdotal reports have been published. In the largest open-label study, zonisamide was added to existing therapy in 50 patients with treatment-refractory neuropathic pain that was primarily associated with cervical or lumbar radiculopathies. Ten patients had not completed dose titration at the time of publication, so the analysis included data from 40 patients. At a mean daily dosage of 260 mg/d, daily pain scores were decreased by >60% in 10 patients (25%) and by 30% to 60% in 8 patients (20%). Only 2 of 40 patients (5%) discontinued therapy because of an AE (drowsiness). Eighteen of 40 patients (45%) were able to discontinue the AED they had been taking at the time of study entry. The initial AED was gabapentin in 12 of 18 patients, and topiramate in 3 (J.C. Krusz, MD, Anodyne PainCare, Dallas, Texas, written communication, November 26, 2002).

A retrospective review of 300 consecutive cases of chronic pain treated at an outpatient pain clinic included 142 patients with neuropathic pain who received a prescription for zonisamide. Eighty-six of these patients had a diagnosis of cervical or lumbar radiculopathy, 30 PDN, 19 fibromyalgia, and 7 pelvic pain. Zonisamide was initiated at 100 mg/d and titrated monthly to the maximal tolerated dose. (Use of concomitant pharmacotherapy was not reported.) Follow-up data on patients’ subjective assessment of pain were available for 132 of 142 patients. Only 10 patients (7%) discontinued zonisamide because of AEs. At a mean daily dose of 252 mg, 100 of 142 patients (70%) reported at least moderate reduction in pain; only 9 (6%) felt they received no benefit. Although not the chief complaint in this population, headache was present in 23 patients, of whom 16 (70%) reported at least moderate improvement in head pain.

In a retrospective case series involving 11 adult patients with various neuropathic pain diagnoses who received adjunctive zonisamide therapy, all 11 reported at least some benefit from the drug. The mean daily dosage was 275 mg/d. The response was categorized as excellent in 5 patients (45%). No patients discontinued zonisamide as a result of AEs. In a similar review including 12 adult patients with neuropathic pain conditions in which the investigator’s assessment was the primary end point, 2 patients (17%) were reported to have an excellent result and 5 (42%) a good result. Two patients dropped out because of AEs (palpitations and decreased response to opioids), neither of which appeared to be related to zonisamide therapy.

A recent report described the case of a 53-year-old woman with idiopathic polyneuropathy and severe pain that had responded poorly to several nerve-
blocking procedures, gabapentin, 2 TCAs, and carbamazepine. Addition of to-piramate at a dosage of up to 100 mg QID resulted in some diminution of pain. Addition of alpha2-agonists, first clonidine and then tizanidine, was not helpful. Zonisamide was then started at 100 mg/d and increased every other week to a maximum of 400 mg/d, with a reduction in mean daily pain score from 9 at baseline to 5 (on a scale from 0 to 10). This benefit was sustained when the topiramate dosage was decreased to 50 mg BID after the patient experienced shortness of breath. Another report described the cases of 2 patients with type 1 CRPS who received low dosages of zonisamide (75 and 125 mg/d) for 10 weeks. Pain reduction, as measured on the Neuropathic Pain Scale and the Wisconsin Brief Pain Scale Inventory, was minimal.

Migraine
Results of 2 retrospective, open-label studies of zonisamide in the preventive treatment of episodic migraine have been published. In one study, 34 patients with treatment-refractory migraine with or without aura received adjunctive treatment with zonisamide at dosages up to 400 mg/d. Headache data were obtained from patients’ headache diaries and by telephone report. A 40% reduction from baseline in headache severity, 50% reduction in headache duration, and 25% decrease in headache frequency were reported at 3 months. Four patients (12%) discontinued zonisamide because of AEs, and 9 (26%) discontinued the drug because they believed it was not working. The other study showed improvement in 14 of 33 patients (42%), with 4 patients dropping out as a result of AEs.

Zonisamide was examined as prophylactic monotherapy in a prospective, open-label study in 9 patients with episodic migraine with or without aura. The drug was titrated to a mean dosage of 244 mg/d, and investigator efficacy ratings were made after therapy had remained at a stable dose for 6 weeks. By this subjective and imprecise standard, the drug was deemed effective or very effective in 6 patients (67%).

Zonisamide was assessed in a population with chronic daily headache, almost all of them with transformed migraine. Patients in this study had failed to respond to ≥2 trials of prophylactic agents (mean no. of agents, 5.9). Sixteen patients received zonisamide, 10 taking 100 mg/d and 6 taking 200 mg/d. After 3 months of treatment, total headache time (frequency × duration) was reduced by 50% in the group as a whole, with the mean number of headache days per month reduced from 22.0 to 14.5 (34% reduction). These results in a highly treatment refractory population receiving a relatively low dose of medication suggest benefit for zonisamide.

CLINICAL PROFILE OF THE NEWER AEDs
The first consideration in the decision to use a particular treatment must always be the evidence base. Most of the published data on the use of the newer AEDs
in the treatment of neuropathic pain and migraine suggest that each agent may be helpful in some patients. With the exception of gabapentin in PHN, however, the evidence base is insufficient to warrant use of these agents in any pain disorder; this lack of evidence is reflected in the fact that none of the other agents have obtained FDA approval for the treatment of any neuropathic pain disorder or for the prophylaxis of any type of migraine. Therefore, the decision to prescribe an AED for any of these conditions must depend on assessment of the potential risks and benefits in the individual patient. The following sections summarize what is known about the AE and drug-interaction profiles of each of the 5 newer AEDs, and the article concludes with a review of their dosing and titration.

AE Profiles

All medications in the current generation of AEDs have better tolerability than the established AEDs.1 Table VI summarizes the AEs that have been associated with use of the 5 AEDs discussed in this article. All of these agents have 2 common AEs: dizziness and somnolence. These AEs are clearly dose related, and most patients develop some degree of tolerance to them over time. Most other AEs in the clinical trials and case series were also dose related, did not lead to discontinuation of treatment, and improved once steady-state levels were achieved and dosing remained constant.124 Investigators and clinicians consistently noted that low initial doses followed by slow titration reduced the incidence and severity of AEs for most of these drugs. Gabapentin can be initiated at a higher dose and titrated more quickly than the other 4 AEDs

Table VI. Adverse effects of the 5 newer antiepileptic drugs,* based on data presented in the double-blind trials reviewed in this article11,12,21,83–97,128 or discussed in the cited review articles.124,129,138,142

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Gabapentin</th>
<th>Lamotrigine</th>
<th>Oxcarbazepine</th>
<th>Topiramate</th>
<th>Zonisamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness/ataxia</td>
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<td>3</td>
<td>3</td>
<td>2</td>
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<td>1</td>
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<tr>
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</table>

*The grading system used in this table is as follows: 0 = same as placebo; 1 = 2%–5% more than placebo; 2 = 6%–10% more than placebo or >2 times placebo; 3 = >10% more than placebo or >3 times placebo.
†<1% Incidence of serious rash.
‡<0.1% Incidence of serious rash.
(see Dosing and Titration section). Rates of particular AEs varied depending on whether the drug was used as monotherapy or as adjunctive therapy, and on whether patients were naive to AEDs or had received these drugs previously. In general, the incidence of AEs was lower with monotherapy and in AED-naive patients.

**Gabapentin**

Gabapentin has gained rapid acceptance among physicians, in part because of its excellent tolerability. Common AEs (occurring in >10% of patients when used adjunctively) are limited to somnolence, dizziness, ataxia, and fatigue. In the randomized, controlled trial in patients with PDN discussed previously, the only AEs that occurred significantly more frequently with gabapentin than with placebo were somnolence ($P = 0.004$) and dizziness ($P < 0.001$), and only 8% of patients in the gabapentin group withdrew because of AEs. In the PHN study, in which gabapentin was used adjunctively in most cases, 13.3% of patients in the gabapentin group dropped out as a result of AEs. Somnolence, dizziness, ataxia, infection, and peripheral edema occurred more frequently in the gabapentin group than in the placebo group.

**Lamotrigine**

Lamotrigine is the only drug in this group whose prescribing information contains a “black box” warning, indicating an incidence of severe rash of 3 per 1000 adult patients exposed. The total incidence of rash with lamotrigine is ~10%, and because there is no way of distinguishing clinically between benign and potentially malignant rashes, discontinuation of medication is necessary in all patients who develop a new rash while taking this drug. Clinical trials in epilepsy and bipolar depression have found that the incidence of rash is reduced when lamotrigine is begun at a low dose and titrated very slowly. In the clinical trials summarized in the present article, rash was more common in patients with HIV-associated neuropathy (5/20) than in those with central poststroke pain (2/30) or PDN (2/29). In a meta-analysis of controlled trials of add-on lamotrigine therapy in patients with partial epilepsy, the 5 most frequently reported AEs were nausea, dizziness, ataxia, diplopia, and blurred vision.

**Oxcarbazepine**

Despite its greater tolerability relative to carbamazepine, oxcarbazepine has been associated with the highest rates of reported AEs among the newer AEDs discussed in this article. Oxcarbazepine does not appear to present any risk of serious hepatic or hematologic reaction, and serum monitoring is not required. Rashes were rarely noted. However, the following AEs were reported at least twice as often—or with an additional 10 percentage points—in those who received oxcarbazepine compared with control groups: dizziness, somnolence, ataxia, nystagmus, diplopia, visual abnormality, vertigo, nausea, vomiting, and fatigue.
As noted, the rates of AEs are lower with monotherapy than with adjunctive therapy. Hyponatremia (serum sodium level <125 mmol/L) has been documented in 2.7% of patients who received oxcarbazepine in 14 studies.129

**Topiramate**

Of the newer AEDs discussed, topiramate has been associated with the highest rate of cognitive AEs (up to 10%), including psychomotor slowing, confusion, memory difficulties, and speech- and language-related problems.124 These are predominantly dose related and may occur less frequently if the drug is started at a low dose and titrated very slowly.125 Other common AEs associated with the use of topiramate are dizziness, somnolence, and fatigue. Kidney stones were reported in 1.5% of adults taking part in clinical trials of topiramate.124

Weight loss has been noted with this medication. The most recently reported study of topiramate in epilepsy included 38 patients who received topiramate as an adjunct to their existing regimens for the control of refractory partial seizures and who continued the drug for 1 year.130 Weight loss was noted in 83% of patients at 3 months (mean weight loss, 3.0 kg) and 86% of patients at 1 year (mean weight loss, 5.9 kg). Interestingly, patients who were obese at baseline lost almost twice as much weight as the overall sample (mean weight loss, 10.9 kg).

**Zonisamide**

As a member of the sulfonamides, zonisamide poses a risk for serious dermatologic or hematologic reactions. However, the incidence of such AEs has been extremely small (46 cases of toxic dermatologic events per million patient-years of exposure; 3 cases of serious hematologic events), and the background rate of rash is 2%.129 Zonisamide is structurally different from sulfonamide antibiotics, and there is no evidence of cross-reactivity between them.131 It has been used with caution in patients who report allergy to sulfonamide antibiotics with no occurrence of rash or other allergic reaction.131 Somnolence and dizziness are the only other AEs occurring with a frequency >10%. Kidney stones were suspected clinically in 4.0% of patients receiving zonisamide in epilepsy clinical trials and were symptomatic in 1.4%.129

Weight loss is an unexplained AE that has been associated with the use of zonisamide. In 3 randomized, placebo-controlled trials of adjunctive zonisamide therapy for the treatment of partial seizures,132 reliable weight data were available for 314 of the 493 enrolled patients. In a comparison between the end of the baseline period and the end of double-blind treatment (3–5 months), 76 zonisamide recipients (28.9%) and 18 placebo recipients (8.4%) lost >5 lb (P = 0.001), and a respective 17 (6.5%) and 40 (18.6%) gained >5 lb (P = 0.001).
Dosing and Titration

The starting dose, titration schedule, and target dosage range for each of the 5 AEDs are summarized in Table VII. The initial dosing and titration schedules are the same for neuropathic pain and migraine prophylaxis, although the effective dose is generally in the middle of the dosing range for migraine, whereas higher doses are often necessary in neuropathic pain.88,97

Therapeutic and/or toxic levels of the newer AEDs have not yet been rigorously defined as they have for standard AEDs, and serum monitoring of plasma levels is not currently performed on a routine basis.133 However, several studies have investigated the relationship between serum levels and therapeutic effects for some of these agents.133–136 Large interindividual and intraindividual differences were observed, and definitive therapeutic ranges could not be established for any of the newer AEDs.133–135 Therefore, monitoring of serum drug levels is recommended to assess compliance, determine target levels for individual patients, or guide dosing in the presence of changes in concomitantly administered medications that could affect serum levels of the AED.134,136

Drug Interactions

The newer AEDs present fewer problems of drug interactions than older AEDs.137,138 When coadministered, none of the newer AEDs have an effect on lev-

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Table VII. Dosing and titration of the 5 newer antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Titration Schedule</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>300 mg/d–300 mg TID</td>
<td>Increase by 300 mg/d, maintaining TID dosing</td>
<td>1800–3600 mg/d given TID</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25 mg/d</td>
<td>Increase to 25 mg BID for 2 wk, then to 50 mg BID for 2 wk, then by 100 mg/wk</td>
<td>200–500 mg/d given BID</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>150–300 mg at bedtime</td>
<td>Increase by 150–300 mg every 3–5 days</td>
<td>900–1800 mg/d given BID</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25–50 mg/d</td>
<td>Increase by 25–50 mg/wk</td>
<td>50–500 mg/d given BID</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100 mg at bedtime</td>
<td>Increase to 200 mg/d after 2 wk, then to 300 mg/d for 2 wk, then by 100 mg/wk</td>
<td>100–500 mg/d given BID or at bedtime</td>
</tr>
</tbody>
</table>

*References: 11, 12, 84, 88, 89, 97, 112, 115, 121.
els of any of the others. The newer AEDs also have much less effect on the CYP family of enzymes than the standard AEDs. Only topiramate and oxcarbazepine have been documented as having a clinically significant effect on any of these isozymes. Both agents induce CYP3A4, which causes more rapid metabolism of most of the steroid hormones used in oral contraceptives and can lead to failure of birth control. For that reason, it is recommended that patients taking either of these AEDs not use oral contraceptives. Oxcarbazepine also inhibits CYP2C19, which alters levels of commonly used calcium channel antagonists.

Phenytoin, phenobarbital, and carbamazepine are all potent inducers of CYP isozymes and will lower serum levels of all AEDs mentioned in this article (except for gabapentin). Valproic acid produces clinically significant decreases in the clearance of lamotrigine and thus raises lamotrigine levels. Therefore, the dose of lamotrigine must be reduced in patients taking these medications concomitantly.

Both zonisamide and topiramate are weak carbonic anhydrase inhibitors, and combining them may increase the risk for kidney stones. In clinical practice, however, these 2 agents have generally been combined safely.

CONCLUSIONS

The study of the pathophysiology of neuropathic pain and migraine is developing rapidly and is beginning to shed light on the underlying disease processes. This research should help direct the development of increasingly specific therapies—for example, sensory neuron–specific sodium channel blockers or more selective NMDA antagonists. Scientific study of the clinical effectiveness of the newer AEDs in the treatment of these diseases is beginning to provide the evidence needed to determine how well each may work.

The primary clinical advantages of newer AEDs relative to the established AEDs are their greater tolerability, potential for fewer drug–drug interactions, and, in some instances, greater pain relief. Randomized, double-blind, placebo-controlled trials of the newer AEDs in neuropathic pain and migraine are needed to yield a broader evidence base.

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