Prophylaxis for Chronic Daily Headache and Chronic Migraine with Neuronal Stabilizing Agents

John Claude Krusz, PhD, MD

Introducțion

The similarities between chronic neuropathic pain states and the processes leading to migraine and tension-type headache have used similar nosologic descriptors such as central sensitization, wind-up, cortical spreading depression, and multiple orders of neuronal barrage of brainstem structures in the trigeminal vascular system from facial, sinus, and neck inputs [1–5]. Understanding that pain transmission and its modulation occurs in a two-way, dynamic interactive set of circuits throughout the central nervous system (CNS) is key a concept. The biochemical and physiologic mechanisms involved are understood incompletely [6].

I admit to a biased view that migraine may be a form of a neuropathic pain syndrome of cranial, cervical, and facial structures. Many headache specialists think that a migraine headache is a painful syndrome that inflicts itself on a brain that is easily overcome by many types of sensory stimulation (eg, sounds, lights, smells), hormonal fluctuations, foods, beverages, alterations in sleep patterns, barometric pressure changes, and many other environmental factors, including stress. It is a different brain from that in a person who does not experience headaches. Excellent summaries of these and other viewpoints regarding the pathogenesis are presented in this article.

Chronic daily headache (CDH) occurs in a population of patients that is much smaller numerically (approximately 4%) than the total number of people with tension-type headaches (TTH) in the population. One of the main nosologic problems is that there is no generally agreed on consensus regarding how frequent headaches, including daily headaches, should be classified. The International Headache Society has not classified these headache disorders in a formal way. Several tentative classification schemes have been proposed, including the idea that CDHs be divided into primary and secondary subtypes: the primary type should be considered an extension of chronic migraine that has evolved from an original form, which was episodic in nature. There is the additional element of transformation, which can result from the onset of simple analgesics, barbiturates, opiates, and other medication categories such as ergotamine and possibly shorter-acting triptans. The mechanisms that subserve or fuel analgesic overuse headaches, transformed migraine, chronic migraines, or CDHs are understood poorly. However, speculate regarding central sensitization, temporal and spatial overintegration of excessive barrage of peripheral stimuli, and other features (eg, chronic inflammation or wind-up phenomena in the spinal cord or brainstem) are at the core of thoughts regarding migraine and non-migraine headache pathophysiology [7].

Because neuronal stabilizing agents have been used increasingly in the acute and prophylactic treatment of migraines and other headaches, and because divalproex sodium has shown clinical efficacy in several studies [8–11] and has been approved by the Food and Drug Administration for the treatment of migraine, this article focuses primarily on newer neuronal stabilizing agents and other agents that can block pain transmission, which are being studied in a similar fashion (Table 1). The only exception is a brief discussion of current studies conducted with intravenous divalproex sodium in aborting acute and intractable migraines.

Intravenous Divalproex Sodium

The availability of an intravenous preparation of divalproex sodium (Depacon, Abbott Laboratories, Abbott Park, IL) to
Table 1. Proposed mechanisms of action of neuronal stabilizing agents

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Sodium Channel Blocker</th>
<th>Calcium Channel Blockade</th>
<th>Glutamate Receptor Antagonism</th>
<th>GABA Potentiation</th>
<th>Carbonic Anhydrase Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Topiramate</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

GABA—gamma-aminobutyric acid.

treat seizures has prompted the question of whether it may be effective in aborting or eradicating ongoing migraine headaches. Several recent reports of its successful use to treat intractable or acute migraines have appeared in the headache literature in abstract form [12, 13] and in larger studies [14–16]. Generally, results were similar and positive; however, dosages and the rates of administration varied. More aggressive intravenous (IV) therapy was associated with slightly higher rates of migraine reduction in terms of severity, with a high number of headaches not returning on the next day. High rates of nausea and reduction of agitation were observed with IV divalproex sodium [15•]. One study has addressed the use of IV valproate sodium for treating chronic daily headaches [17].

Gabapentin

Gabapentin (Neurontin, Pfizer, New York, NY) was introduced in 1993. There is significant literature on its use in treating many clinical disorders, including pain and headache. There was a time when the mechanism of action of this agent was unknown, although it had been shown that overall brain levels of gamma-aminobutyric acid (GABA) were elevated after administration. More recently, gabapentin has been shown to have a specific effect on an o2,3 substituent of a calcium channel. Whether this is its major mechanism of action remains unknown; however, the majority of prescriptions written for this drug are not for seizure disorders. In terms of migraine prophylaxis, it was shown in open-label studies that gabapentin could be used for migraine prophylaxis, although the studies used low doses and consisted of few patients [18, 19]. Recent, multi-center, placebo-controlled trials have extended these initial observations [20], and it appears that gabapentin can be used for migraine prophylaxis. No studies have specifically examined the effectiveness of gabapentin to reduce or alter chronic daily headaches.

Lamotrigine

Lamotrigine (Lamictal, GlaxoSmithKline, Research Triangle Park, NC) was introduced in 1995 in the United States as a broad spectrum anticonvulsant. Its pharmacologic mechanisms of action include blockade of voltage-gated sodium channels and subtypes of calcium channels. There are few studies of lamotrigine as an agent to treat headaches. An early study [21] did not show statistical efficacy in the treatment of migraine headaches. However, two studies were interesting because they showed that lamotrigine could affect the aura of migraine headache more selectively than it helped the migraine itself [22, 23]. Recent pilot studies show the effectiveness of lamotrigine as a prophylaxis for migraines and refractory headaches [24, 25]. These studies need well-designed, double-blind investigations to replicate their findings. Again, no studies have investigated lamotrigine specifically for its ability to reduce chronic daily headache.

Topiramate

Topiramate, an anticonvulsant that was introduced in 1996, has a number of unusual structural and pharmacologic features. It is a monosaccharide derivative (substituted sulfamate fructopyranose), the only medication in this category with this property. It acts by a number of pharmacologic mechanisms and has the broadest spectrum of effects in the CNS. It blocks voltage-gated Na+ channels and L-type, high-voltage-activated calcium channels. It also acts as an agonist at GABA-A receptors, which are distinct from sites in which barbiturates and benzodiazepines are known to modulate the GABA receptor complex. It acts further as an antagonist of the glutamate receptor system (non-N-methyl-D-aspartate at AMPA-type (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic-acid) receptor subtypes. Finally, it inhibits two types of carbonic anhydrase isozymes [26]. Specific activity at GABA-A receptors has been shown to be highly effective against intractable migraines. Recent studies with subanesthetic conscious sedation doses of propofol, a highly specific GABA-A receptor drug, has shown a high degree of efficacy and safety in aborting migraines [27•].

These diverse mechanisms have potential implications for the treatment of migraines, chronic headaches, pain, and other CNS disorders. It is not surprising that a spate of
open-label and double-blind studies of topiramate have been published in the past few years to treat migraines and other headache disorders [28–34]. None of the studies were specifically targeted towards topiramate’s activity against chronic daily headaches, although two studies [28,31] included migraines and other headache types in their evaluation.

A large, double-blind, placebo-controlled, multi-center trial is underway to test the efficacy of topiramate in migraine prophylaxis. If this agent truly is effective using stringent scientific criteria, it may add another approved agent to the list of migraine prophylaxis agents. More data regarding the ability of topiramate to positively impinge on CDH patterns should be studied because the potential exists for this agent to do so.

Tiagabine

Tiagabine (Gabitril, Cephalon, West Chester, PA) is an anticonvulsant with a single, but unique, mechanism of action. It is a presynaptic reuptake blocker for GABA in the CNS. It is a nicoletic acid derivative designed for penetration across the blood-brain barrier. It can be considered pharmacologically akin to the selective serotonin reuptake inhibitor medications for the serotonin system in the brain. Although it has not been studied formally for CDHs, there are two reports regarding the effectiveness of tiagabine in migraine and other headaches as an add-on medication [35,36]. One of these studies, a small series of case reports [35], did speak of the efficacy of this agent in treating refractory CDHs and migraines along with elements of neuropathic pain and myoclonus. More work with this agent is needed to explore any potential therapeutic implications for it in the treatment of CDHs and perhaps chronic pain disorders. Anecdotally, this author has had quite a number of positive patient experiences with this agent in suppressing chronic TTH and CDH.

Oxcarbazepine

Oxcarbazepine is a 10-keto analogue of carbamazepine. Once absorbed, it is rapidly metabolized to form the 10-monohydroxy derivative, which presumably is the active agent in steady state. It has fewer drug-drug interactions and an overall better safety profile than carbamazepine (Tegretol, Novartis, Suffern, NY, and Carbatrol, Shire Richmond, Florence KY), with a similar, or better, efficacy. However, it can be associated with lowered sodium levels in the plasma [37].

The first data to show efficacy of oxcarbazepine in the treatment of refractory migraine headache and mixed headaches from two headache centers was presented as an abstract at the International Migraine Trust Meeting in September, 2000 [38]. This abstract was concerned with patients who had refractory migraine, but a few of the patients had daily headaches co-existent with their migraines. A larger series, which included 85 patients, has been accepted as a poster abstract and was presented at the Trust meeting in September, 2002. A double-blind, placebo-controlled, multicenter trial of this agent may take place to investigate its activity in migraine headaches.

Levetiracetam

Levetiracetam was introduced in 1999 as an anticonvulsant in the United States and in other countries. It is an S-enantiomer of a well-known and commonly used nootropic agent, piracetam. It has been used to improve cognitive functioning, memory, and myoclonus (particularly after traumatic brain injury) in Europe for 25 years. Unfortunately, it has never become available in the United States. It has been shown to have a pharmacologic effect on high-voltage (N-type) calcium channels, which certainly play a role in the reduction of pain transmission. The first data in the literature that used levetiracetam as prophylaxis for refractory migraines and other headaches were published as an abstract in 2000 by Krusz [39], and again in 2001 as an ongoing series [40]. Preliminary data on the reduction of neuropathic pain is also available and has been presented by the author [41]. No series of data exist that specifically study CDHs with this agent, although many of the patients in the previous series had mixed headache patterns, including chronic TTHs.

Concerning side effects, levetiracetam is a non-toxic medication. Preliminary observations will be presented that have demonstrated excellent efficacy of IV levetiracetam in aborting refractory headaches [42•]. Whether a similar profile of successful activity against CDH or chronic TTH will be shown using this novel agent remains unknown; further research efforts are needed.

Zonisamide

Zonisamide was introduced in 2000 in the United States as an anticonvulsant, although it had been used in Japan for more than 10 years. It had several unusual features, including a long half-life (50 to 60 h). This is a double-edged sword in treatment. For the purpose of treating migraines and headaches, the advantage of zonisamide is that it does not have to be dosed daily, at least initially. Therefore, dosing should suffice every third day, which tends to reduce any side effects. The disadvantage is that the time to steady-state is long. Once a steady-state blood level builds up, the dose can be advanced, which was shown in the first data presented on its use in headache and pain disorders [43]. As in the case with drugs similar to topiramate, there is a small increased risk of kidney stones thought to result from its mild carbonic anhydrase inhibiting activity. Zonisamide has major effects on the blockade of sodium and calcium channel subtypes, and modulates dopamine and serotonin metabolism, begetting an unusual pharmacologic profile. It needs to be studied further in the treatment of CDHs.
Tizanidine
Tizanidine, although not an anticonvulsant, qualifies as a neuronal stabilizing or modulating agent by virtue of its pharmacology. It was introduced in the United States for spasticity approximately 4 years ago and has been used in Japan and in Europe for more than 20 years. It has an unusual mechanism of action: it is an adrenergic α2 agonist. α2 receptors are present pre- and post-synaptically in the dorsal horn of the spinal cord; the effect of tizanidine may be to reduce excitatory amino acid release from spinal interneurons. Descending noradrenergic pathways in the spinal cord from the locus ceruleus also are inhibited by tizanidine. Data have shown abundant antinociceptive effects mediated by α2 receptors distinctly from opiate systems [44].

Earlier published data using tizanidine to treat TTH [45,46] suggested good, clinical efficacy, although these studies were limited. One study was double-blind and placebo-controlled [47], but consisted of few patients. Another study alluded to the efficacy of tizanidine for the treatment of cluster headaches [48]. It was not until tizanidine was used in the United States that larger series began to appear in the literature, using it to treat chronic TTH and CDH.

The largest series, treating more than 350 patients with chronic TTH, CDH, and with co-existent migraine headache showed good efficacy and tolerability with tizanidine. Results were reported on 222 responders and the frequency of daily and chronic TTH was reduced by 72%; the frequency of co-existent migraines was reduced by 78% [49]. The average dose of tizanidine was 26 mg daily, with the bulk of the dosing reserved for creating a sound sleep platform because 93% of patients with a poor sleep pattern reported much improved sleep with tizanidine. A smaller study, using much lower doses of tizanidine, subsequently was published showing that pericranial muscle tenderness was improved by this agent, although no clear data were presented regarding reductions in headache frequency and severity [50].

A more recent double-blind, placebo-controlled, multicenter outcome study of patients with CDH (predominantly chronic migraine) showed efficacy for tizanidine under controlled conditions. When compared with a single-blind placebo baseline, the mean percentage improvement in the overall headache index during the last 4 weeks of a 12-week treatment period was 54% for tizanidine versus 19% for double-blind placebo. In this study, dosing was titrated slowly over 4 weeks to as high as 24 mg divided equally into three dose intervals daily (mean, 18 mg. SD = 6.4; range 2–24), depending on patient tolerance [51]. Results were in accord with a previous open-label study of tizanidine for CDH using a similar medication protocol [52].

Tizanidine has been useful to treat chronic headaches and migraines, to promote sleep, to improve cramps, myoclonus, restless legs, dysesthetic posturing, joint and vertebral axis pain, neuropathic pain, and anxiety disorders. The author has treated more than 1000 patients, conservatively, with this agent. Double-blind studies that consider tizanidine for the treatment of chronic TTH definitely are warranted, based on open-label data. There are no agents that have an indication for TTH.

Venlafaxine
Although originally introduced as an antidepressant with a dual mode of action (ie, blockade of reuptake of serotonin and norepinephrine), there is some anecdotal evidence (unpublished by the author) that venlafaxine (Effexor, Wyeth, Madison, NJ) can reduce headaches and pain. Its pharmacologic actions resemble that of the older tricyclic antidepressants, without any of the negative side effects (eg, weight gain, constipation, sedation, cognitive effects). The older agents have been used to treat migraines and neuropathic pain disorders, but have no official indication for these disorders [53].

Conclusions
The future direction of the treatment of chronic headaches, migraine, and pain disorders may lie in the direction of modulating neuronal excitability by stabilizing various pain pathways. Success may lie in cutaneous afferents and in the various interconnections in the dorsal horn of the spinal cord, in enhancing descending inhibitory pain pathways, in promoting inhibition of ascending pain transmission mechanisms, and in successful gating of supraspinal and thalamic connections to inhibit cortical and limbic perception of painful stimuli. Neuronal stabilization, by many pharmacologic mechanisms, will be a mainstay of treatment for many years to come.

References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


Because potentially millions of visits to emergency departments for migraine occur yearly, we are in need of new intravenous treatments for intractable migraines. This study indicates new directions using neuronal stabilizing agents.


Recent study indicates new directions using neuronal stabilizing agents.


38. Kusse JC: Levetiracetam (Keppra TM) as prophylaxis for resistant headaches. Headache Q 2000, 12:5A.


Indicates new directions using neuronal stabilizing agents.


