AN UPDATE ON MIGRAINE TREATMENT*

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ABSTRACT

Although some pharmacologic treatments are used for both migraine and epilepsy, fundamental differences in treatment approaches and treatment goals exist. Migraine treatment requires acute and/or preventive therapy, whereas most epilepsy treatments are preventive (the exception being status epilepticus treatment). Some of the most commonly used preventive migraine therapies are antiepileptic drugs (AEDs). The mechanism of migraine activation is not yet completely understood, but it is associated with central and peripheral sensitization. Migraine-preventive drugs may raise the threshold for migraine activation or stabilize the excitable/sensitive nervous system. The biggest difference between the goals of migraine treatment and the goals of epilepsy treatment is the definition of treatment success—seizure free for epilepsy versus reduction in attack frequency, severity, and duration for migraine. This article discusses the principles of migraine-preventive therapy and the factors that affect drug choice, and compares them with the principles of epilepsy treatment. Only 2 AEDs (divalproex and topiramate) are approved by the US Food and Drug Administration for migraine prevention. All other preventive migraine drugs are used off-label.

MECHANISMS OF MIGRAINE PREVENTION

The drugs used for migraine prevention are listed in Table 1. Of the drugs, only 4 (divalproex and topiramate, which are AEDs, and propranolol and timolol, which are beta blockers) are approved by the US Food and Drug Administration for migraine prevention. All other preventive migraine drugs are used off-label.

MECHANISMS OF MIGRAINE

Although there is some overlap in the pharmacologic treatment of migraine and epilepsy, fundamental differences in treatment approaches and goals exist. One distinction is that migraine management involves acute and preventive therapy, whereas most epilepsy treatments are preventive (with the exception of status epilepticus, in which the individual attack is treated). Acute migraine treatment is used after the attack has begun, to relieve pain and disability and stop progression. Although many patients with migraine require only acute treatment for effective management, a subset of patients requires preventive therapy, which is used primarily to reduce the frequency, severity, and duration of headache attacks. Patients taking preventive medication still need acute medication for breakthrough headaches. Some of the most commonly used preventive migraine therapies are antiepileptic drugs (AEDs).
Hyperexcitability may be due to decreased magnesium levels or increased glutamate levels. If the activation continues long enough, the threshold for migraine is surpassed and a wave of neuronal activation is followed by a wave of neuronal depression, which moves slowly and steadily across the cortex (at about 3 mm/sec). This accounts for the aura of migraine. The spreading wave activates trigeminal afferents and the vascular structures they innervate. Headache probably results from the activation of meningeal and blood vessel nociceptors combined with a change in central pain modulation. Headache and its associated neurovascular changes are subserved by the trigeminal system. Activation results in vasoactive intestinal polypeptide release and vasodilation.

Trigeminal sensory neurons contain substance P (SP), calcitonin gene-related peptide (CGRP), and neurokinin A. Stimulation results in SP and CGRP release from sensory C-fiber terminals and neurogenic inflammation. The neuropeptides interact with the blood vessel wall, producing dilation, plasma protein extravasation, and platelet activation. Neurogenic

### Table 1. Drug Therapies for Migraine Prevention and Their Proposed Mechanisms of Action in Migraine

<table>
<thead>
<tr>
<th>Raise Threshold for Migraine Activation</th>
<th>Inhibit Migraine Generator</th>
<th>Enhance Antinociception</th>
<th>Inhibit CSD</th>
<th>Inhibit Sensitization</th>
<th>Block Neurogenic Inflammation</th>
<th>Stabilize Reactive Nervous System</th>
<th>Modulate Sympathetic or Serotonergic Tone</th>
</tr>
</thead>
</table>

*FDA approved for migraine prevention.
CSD = cortical spreading depression; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme.
inflammation sensitizes nerve fibers (peripheral sensitization). Now innocuous stimuli, such as blood vessel pulsations, are interpreted as painful, causing, in part, the throbbing pain of migraine. Burstein et al have proposed that sensitization of trigeminovascular neurons may account for intracranial hypersensitivity, such as pain worsening during coughing, bending over, or rapid head movement, during migraine or the throbbing nature of the headache.\textsuperscript{3-6} Nerve impulses are also transmitted back into the trigeminal nucleus caudalis in the brain stem, which projects to the thalamus and cerebral cortex. Central sensitization (CS) can also occur. CS may account for extracranial sensitivity, such as cutaneous alldynia.\textsuperscript{1,2} As the migraine progresses, brain stem reflexes are thought to produce some of the migrainous symptoms, such as nausea, vomiting, photophobia, and phonophobia. Autonomic activation via the facial nerve causes nasal congestion, rhinorrhea, and lacrimation, which are experienced by nearly half of all migraineurs.

Each migraine-preventive drug listed in Table 1 appears to affect migraine by either raising the threshold for migraine activation or stabilizing the excitable/sensitive nervous system.\textsuperscript{3,6}

**Approaches to Migraine Treatment**

In the presence of epilepsy, every patient is treated with AEDs. In migraine, however, not all patients require preventive medication. Acute migraine medication overuse is a common and important concern, and its presence or absence helps to determine whether preventive medication will be used. Medication overuse occurs when acute medications are used so frequently that the migraine treatment itself increases migraine attack frequency and the drugs have to be withdrawn.

Preventive migraine medication should be considered when specific circumstances exist. For example, some patients receiving acute treatments may still experience migraines that interfere with their daily routine. When headache frequency is more than 2 per week, medication overuse is a risk. Preventive medications are also warranted when acute medications are ineffective, contraindicated, poorly tolerated, or overused. Patients at times prefer preventive medication, because the risk of a migraine is too great. Preventive medication is used in some less common types of migraine, such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction.\textsuperscript{7} Lipton et al have shown that although 58% of migraineurs meet disability and frequency criteria for preventive treatment (ie, 1-2 days of activity restriction per episode), only 5% are currently using preventive therapy, based on 2 large population-based surveys.\textsuperscript{8,9} Migraine prevention is an unmet need.

Preventive migraine therapy employs certain principles, independent of drug choice. The philosophy of "start low and go slow" is important, because migraine patients often need a lower dose of these medications than patients who take them for other indications. An adequate drug trial (2-3 months) is also important, because onset of action can take several weeks (as opposed to treatment for epilepsy, which usually controls the attack quickly, suggesting a difference in underlying pathophysiology and mechanism of action). Drug overuse with acute medications is a concern and should be avoided. Efficacy can be monitored and evaluated by having the patient keep a migraine diary or calendar, and drugs can sometimes be tapered (or discontinued) if the headaches are well controlled. Preventive medications often affect the cytochrome 450 enzyme system, so potential drug-drug interactions should be considered and pregnancy should be avoided if possible, especially when patients are using AEDs.\textsuperscript{7}

The goals of migraine-preventive treatment are 5-fold: (1) to reduce attack frequency, severity, and duration; (2) to improve responsiveness to acute treatment; (3) to improve function and reduce disability; (4) to prevent disease progression; and (5) to reduce costs.\textsuperscript{7} The first goal (ie, to reduce frequency, severity, and duration of headache) is an important departure from epilepsy treatment, wherein seizure-free status is the goal. Preventive migraine treatment can prevent disease progression wherein episodic migraine progresses to chronic migraine, defined as migraine on 15 or more days a month without medication overuse.\textsuperscript{10,11} The use of preventive migraine medication also reduces overall treatment costs. We performed a retrospective evaluation of a large claims database to determine resource utilization over an 18-month period among patients treated for migraine. Direct costs to patients who used only acute treatment were compared with direct costs to patients who added preventive treatments to their acute drug regimens. The results showed substantial cost decreases across several measures of resource utilization with concomitant preventive therapy: a 51% decrease in physician office visits, an 82% decrease in emergency department visits, a 75% decrease in computed tomography scans, an 88% decrease in
magnetic resonance imaging scans, and a $48 to $138 reduction in monthly medication costs per patient.

Drug choice for preventive treatment depends on several factors: headache type, efficacy and adverse event profile of the drug, comorbid or coexisting conditions (ie, other present conditions that are not associated with headache), and patient preference. As discussed by Dr Lipton in this monograph, comorbid and/or coexisting conditions can present therapeutic opportunities as well as therapeutic limitations, depending on the preventive therapy and the patient’s current medical status.

**AEDs for Migraine Prevention**

Several currently available AEDs have been studied for migraine prevention, but the data to support their use vary widely among individual drugs. Divalproex and topiramate both have strong scientific evidence (ie, placebo-controlled, double-blind trials) to support their use as migraine-preventive therapy. The data for gabapentin, carbamazepine, and zonisamide are limited and sometimes conflicting. Levetiracetam has not been shown to be effective in migraine. Data for phenytoin and pregabalin are not available.

**Divalproex**

Divalproex sodium is an oligomeric complex of sodium valproate and valproic acid in a 1:1 molar ratio. Along with its indications for epilepsy and mania in bipolar disorder, it was approved by the US Food and Drug Administration for migraine treatment. A total of 5 placebo-controlled, double-blind trials have established the efficacy of divalproex in migraine prevention, and other groups have studied its use in cluster and chronic daily headache with mixed results.12-17 A brief review of the evidence is described here but is discussed more extensively elsewhere.18-20

Two of the 3 US trials used the standard formulation of divalproex. The results (ie, responder rate, or percentage of patients achieving at least 50% improvement in outcome) from these trials are shown in Figure 1.21-23 Of note, results from the Freitag study are not consistent with other studies. Overall, responder rates were between 44% and 48%.21-23

We performed a long-term (up to 3 years) open-label study of patients who completed 1 of 2 multicenter, double-blind, randomized, placebo-controlled studies of divalproex for migraine prevention. A total of 163 patients from 24 centers were followed to evaluate the long-term safety of divalproex. The most frequently used dose (ie, in 26% of patients) for headache was 1000 mg/day, ranging from 500 to 2500 mg/day. The efficacy results confirmed results from other studies of divalproex and showed that improvements are maintained long-term (excluding those who dropped out of the study), as shown in Figure 2. The other main outcome measures were number and proportion of patients reporting treatment-emergent adverse...
events, prevalence and incidence for each treatment-emergent adverse event, vital signs, and body weight. Nausea (in 37%) occurred early in the treatment course and declined 3% to 6% by 6 months. Tremor (in 35%) and weight gain (in 24%) tended to occur later, at 6 months. Alopecia declined after 12 months; and discontinuations due to adverse events were primarily caused by these 4 adverse events (alopecia 6%, nausea 4%, weight gain 2%, and tremor 2%).

In clinical practice, the most common adverse events associated with divalproex use are gastrointestinal disturbance (anorexia, nausea, vomiting, dyspepsia, and diarrhea), asymptomatic serum hepatic transaminase elevations, tremor, sedation, increased appetite, weight gain, and alopecia. Less common are rashes and hematologic dysfunction; ataxia is rare. Hepatitis and pancreatitis are rare; their incidence depends on the number of concomitant medications, the patient’s age, the presence of genetic metabolic disorders (although migraine in mentally disabled persons is not common), and the patient’s general health.

The extended-release (ER) formulation of divalproex minimizes adverse events. Starting doses are 250 mg twice daily for the delayed-release (DR) version and 500 mg qhs for the ER version. Doses are started low and titrated up to 500 mg/day to 1000 mg/day (DR, twice daily, qhs). A dose-response curve has not been observed in clinical studies. Unlike in epilepsy, rapid titration is not necessary. However, higher doses are needed for patients with comorbid epilepsy.

**TOPIRAMATE**

Topiramate, an AED, was recently approved for migraine prophylaxis. It is a sulfamate-substituted monosaccharide (a fructose-1,6-diphosphate analog) that inhibits carbonic anhydrase and modulates kinase phosphorylation on neuronal ion channels. Shank et al proposed that topiramate binds to presynaptic ion channel proteins and blocks their phosphorylation, thus allosterically modulating channel conductance. It also blocks postsynaptic gamma-aminobutyric acid and kainate receptors. The exact mechanisms by which it prevents migraine are not yet known, although blocking phosphorylation of protein kinase A on these various proteins appears to be the common factor. Topiramate has been studied as preventive treatment for migraine, cluster headache, and chronic migraine.

Four phase 3 clinical trials have been completed in the United States and their results are published. Table 2 outlines the study doses and comparator groups in the 3 published studies. MIGR-001, -002, and -003 were large studies, and the primary efficacy end point in all 3 studies was a reduction in mean 28-day rate of migraine periods compared with baseline rates. The migraine period was defined as the length of time between onset and cessation of painful migraine symptoms; it could last up to but not more than 24 hours (eg, a headache lasting 25 hours would extend into a second period).

**Table 2. Phase 3 Clinical Trials with Topiramate for Migraine Prevention**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose of topiramate (mg/day)</th>
<th>Comparator(s)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIGR-001</td>
<td>200</td>
<td>Placebo, Propranolol (180 mg/day)</td>
<td>United States</td>
</tr>
<tr>
<td>MIGR-002</td>
<td>100</td>
<td>Placebo</td>
<td>United States</td>
</tr>
<tr>
<td>MIGR-003</td>
<td>100</td>
<td>Placebo</td>
<td>Canada</td>
</tr>
<tr>
<td>MIGR-003</td>
<td>50</td>
<td>Placebo</td>
<td>United States</td>
</tr>
</tbody>
</table>

*Number of countries.

Figure 3. Topiramate Responder Rate in US and Canadian Trials

Data from Silberstein et al; Brandes et al.
Responder rates for the American and Canadian studies (MIGR-001 and -002) showed a dose response up to 100 mg, with the highest responder rates at about 50% (Figure 3). Pooled data from MIGR-001, -002, and -003 also show a dose response up to 100 mg (Figure 4), with a maximum reduction in the primary end point of 50.7% (an absolute reduction of 30%), and approximately half of the responders had at least a 75% decrease in migraine frequency.26-29 Onset of action appears to be early, significantly more than placebo at 4 weeks and continuing up to 26 weeks.30 Approximately 6% of patients have a greater than 95% reduction in mean monthly migraine periods (Figure 5).26-28

Treatment-emergent side effects with topiramate include weight loss, loss of appetite, nausea, taste perversion, kidney stones, paresthesias, fatigue, memory difficulty, and diarrhea.26 Those considered to be most treatment-limiting are paresthesias, fatigue, memory difficulty, and insomnia.31 Topiramate is a unique AED in that it is associated with modest weight loss (up to 5% change in body weight), which may be a benefit rather than an adverse event for some patients. Pooled data from all 3 major studies show a dose response in weight loss (Figure 6).26-29

Overall, topiramate significantly reduces mean monthly migraine periods at dosages of 100 mg and 200 mg/day (some patients may require doses as high as 600 mg/day-800 mg/day). As with all migraine-preventive treatment, it should be titrated up slowly. If adverse events become intolerable, the dose should be titrated more slowly or reduced. Topiramate has a rapid onset of action (within the first month of treatment) and a high responder rate.

**Gabapentin, Carbamazepine, and Lamotrigine**

Two US studies have evaluated the use of gabapentin as preventive therapy for migraine. A
small, double-blind, placebo-controlled study of 45 patients indicated that gabapentin had no effect on migraine frequency. In a second double-blind, placebo-controlled study of 145 patients, the response rate was 36% versus 16%, gabapentin versus placebo, respectively, in the intent-to-treat population. The most common drug-associated adverse events were somnolence, dizziness, and asthenia; however only somnolence occurred significantly more frequently with gabapentin compared with placebo. Gabapentin is dosed between 900 and 2400 mg 3 times daily with a maximum dosage of 3600 mg/day.

The data for carbamazepine experience in migraine are scarce and poorly described. Only 2 small double-blind, placebo-controlled studies with lamotrigine have been published, and the results indicate that lamotrigine is ineffective in migraine prevention but may have some benefit in treating aura symptoms. There are no published data for the other AEDs (ie, zonisamide, levetiracetam, oxcarbazepine, vigabatrin, and tiagabine).

Table 3 summarizes the responder rates in large clinical trials with the 3 main AEDs for migraine prophylaxis—divalproex, topiramate, and gabapentin.

<table>
<thead>
<tr>
<th>AED</th>
<th>Responder Rate</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex</td>
<td>44%</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Mathew</td>
<td>48%</td>
<td>14%</td>
<td>34%</td>
</tr>
<tr>
<td>Freitag</td>
<td>30%</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>Jensen</td>
<td>50%</td>
<td>16%</td>
<td>34%</td>
</tr>
<tr>
<td>Topiramate</td>
<td>54%</td>
<td>23%</td>
<td>31%</td>
</tr>
<tr>
<td>Silberstein</td>
<td>49%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>36%</td>
<td>16%</td>
<td>20%</td>
</tr>
</tbody>
</table>

AED = antiepileptic drug.

Managing patients with comorbid migraine and epilepsy presents challenges—not only in diagnosis but also in treatment options. The possibility of using a single drug to treat both disorders is a “therapeutic opportunity.” However, given the differing and sometimes conflicting treatment principles and treatment goals between migraine and epilepsy, the entire patient profile should be considered in determining not only optimal drug choice but also dosing and definition of treatment success.

**DISCUSSION**

**Dr Haut:** I am always fascinated by the use of valproate and topiramate in migraine in contrast to our experience in epilepsy. Many adult patients with epilepsy have trouble tolerating topiramate, and valproate has many troubling side effects. Is there a difference in tolerance between migraine and epilepsy patients?

**Dr Silberstein:** In my experience, migraine patients respond differently than patients with epilepsy. Also, I think the doses are different. What dose, for example, of divalproex or topiramate would you give for epilepsy?

**Dr Haut:** The doses are higher, but with topiramate I often cannot get to the higher doses. I generally give 200 mg and above.

**Dr Silberstein:** For migraine, the general dose is 25 mg to 50 mg and we go very slow. If it takes us 8 weeks to titrate to 100 mg, we do not have to worry about it. Since we know it takes a couple of months to get the benefit, I am perfectly willing to go up 15 mg or 25 mg every other week. Whereas in epilepsy, you cannot wait 2 months to get a patient with epilepsy under control. I think that is the fundamental difference. With gabapentin, however, we need high doses, and we often have a lot more side effects at higher doses, which we need for migraine. With lamotrigine, if we go slow, we do not seem to have a problem with rash, but it seems to only be effective for migraine with aura, less effective for patients with migraine without aura. Most of the other AEDs do not seem to be effective. Zonisamide may be, but the side-effect profile is very similar to topiramate. Phenytoin and phenobarbital do not seem to have a benefit. Oxcarbazepine does not seem to have a benefit proven in placebo-controlled trials. We use that more often for trigeminal neuralgia.

**Dr Gidal:** I have had similar experience with topiramate. I think it is a wonderful drug for headache in our population, but like epilepsy, and presumably with migraine, you get patients who are refractory.
Dr Silberstein: We use lots of combination therapy. We learned about combination therapy by accident. If you had somebody on valproate who had a lot of side effects, you decreased their dose and started him/her, for example, on topiramate and his/her headaches got better; on combination therapy the patient did better than on monotherapy. I think that the combination of topiramate and valproate is reasonable, as is the combination of AEDs with drugs of an entirely different class. Nobody has thoroughly studied these at all. In epilepsy, many of the new trials are using add-on therapy. So, you study a drug as add-on first and then as monotherapy. In migraine it is studied as monotherapy; nobody ever studies add-on therapy. That is something that desperately needs to be done in a refractory population to see if add-on therapy makes a difference. We have never done it. Juliet Pascual has open-label data for combination therapy, but nobody has ever studied it scientifically.

Dr Lipton: It is considered unethical to treat a migraine sufferer with placebo, so you cannot do placebo-controlled trials.

Dr Silberstein: Dr Lipton: To study topiramate as add-on therapy in nonresponders might be interesting.

Dr Silberstein: It will take time to do that. There are ongoing migraine trials now comparing topiramate and amitriptyline. There are no good modern trials on amitriptyline. The second ongoing trial is studying chronic migraine. The ideal situation would be to add-on therapy in a patient who is not stable on topiramate. It is going to be very difficult to get a pharmaceutical company to do that, and it is difficult so far to get federal funding to do what needs to be done for headache studies.

Dr Lipton: When you do add-on therapy, would you tend to do combinations within a class, such as 2 neuromodulators, or would you be more inclined to do combinations across classes?

Dr Silberstein: Both. It depends on what they are. For example, I would not combine zonisamide with topiramate, or topiramate with gabapentin, but I would combine topiramate with valproate simply because I discovered that by accident. If I have somebody on monotherapy, I am more likely, in general, to add drugs of another class, but occasionally I will use topiramate. Patients often will do well on something like valproate, but they cannot take the side-effect profile of weight gain or tremor. So, we often find that low doses of 2 drugs work together just as for epilepsy. But that is, I think, a refractory strategy. In less difficult patients, I might simply add a small amount of an antidepressant to a small amount of a neuromodulator, taking cues from a large amount of experience from psychiatry in treating bipolar disorder.

Dr Krumholz: In epilepsy treatment, we often look at blood levels to guide therapy. Do you do that in migraine patients?

Dr Silberstein: Blood levels are mainly a truth detector. The major value is if I have a patient who is on a lot of medicine, and he/she is not doing well, and he/she has no side effects, you would be amazed that when you get a level back he/she finally tells you the truth—that he/she was not taking the drugs but did not want to tell me because he/she did not want to hurt my feelings. I have a few reliable patients who have no benefit and no side effects. Most often, I just follow the side-effect profile and the patient’s response.

Dr Lipton: The exception may be nortriptyline in high doses.

Dr Silberstein: The exception to my rule is when I start using drugs like nortriptyline and amitriptyline at levels used to treat depression, because of the potential cardiac adverse events. But it is more a safety concern than a therapeutic concern.

Dr Lewis: One difference from the pediatric perspective is the use of another antiepileptic drug, levetiracetam. There is one retrospective report, which included 19 children, mean age of 12, who were treated with 125 to 250 mg twice daily for 4 months to reduce the frequency of their migraines. The mean frequency of headache attacks before treatment was 6.3/month and after treatment, fell to 1.7/month (P<.0001). More than half of them experienced “elimination” of migraine and there were no side effects in the 80% of the children, but 10% discontinued the drug due to side effects.39

Dr Silberstein: It is hard to tell what mechanism of an AED will work for both diseases. For example, valproate and topiramate both work for migraine and epilepsy. Why don’t some of the other medicines work? I understand that pregabalin has been approved by the FDA [US Food and Drug Administration], but is being held up by the DEA [Drug Enforcement Administration]. Did you know that?

Dr Gidal: There are 2 lines of evidence. One, there is some preclinical evidence suggesting euphoria, and
the agencies decided that could lead to some drug-seeking behavior in patients. So, my guess is the DEA is going to make it a schedule IV drug. I have looked on the FDA's Web site; I can only find the approvable letters for the pain indication, and there are no action items on epilepsy.

**Dr Gidal:** I want to turn the headache story around, to ask about exacerbation of headaches. I have had a reasonable amount of anecdotal experience with carbamazepine. It appears that it worsens their complaints of headache. How about exacerbation with AEDs?

**Dr Silberstein:** I look at migraine like a roller coaster. Often patients will come to you when their headaches are getting worse, and they get better, and they get worse again, and it is difficult to tell whether it is the drug. It could be just coincidental, or it could be an adverse event from the drug. It can aggravate the migraine, so it is hard to tell. Certain drugs, I am convinced, make people worse, but I have not seen this with carbamazepine. I think it is neutral, to be honest with you. But if you give a patient a drug and he/she gets a constant side effect, that can make people migrainous.

**Dr Lewis:** What is the usual duration of treatment for prevention of migraine?

**Dr Silberstein:** We don't know. That is the bottom line, and you get a bunch of people in the room, you force them to stay there, they all come up with 6 months. Nobody has yet done discontinuation trials. Nobody has done well-controlled trials.

In the 001 and 002 topiramate trials, we have long-term data, but it is open-label. In the European 003 trial, it is placebo-controlled, so eventually we may have some data on what happens to patients who have been discontinued. We do not know the answer to that question. It has not been done. Nobody has shown whether, if a patient is on a drug for 6 months and well controlled, he or she needs to continue on the drug. Very practically, I say if the headache is controlled for 6 months, that is the magic number, and we try to taper and discontinue the medication.

**Dr Lewis:** In kids, we use September until June, during the school year.

**Dr Silberstein:** Everybody knows headaches get better in the summertime.

**Dr Kossoff:** For some of the epilepsy drugs when we are treating epilepsy, the half-life is important. So, twice-daily and 3-times-daily dosing for some of these drugs matters, but it seems like in migraine it is not as important.

**Dr Silberstein:** We are lucky because we give the extended-release formulation of valproate at bedtime, and topiramate has close to a 24-hour half-life. So, we can if we need to give topiramate at bedtime. I start it twice daily mainly because its $T_{\text{max}}$ is 1 hour, and when you are titrating up the dose, I think there are fewer side effects by splitting the dose to begin with. When you get steady-state levels, you can go to once-a-day dosing.

**Dr Lipton:** Once-a-day dosing is certainly a huge advantage.

**Dr Haut:** But for epilepsy, once-daily dosing for valproate ER formulation is not recommended because of the reliance on steady-state levels.

**Dr Silberstein:** Yes, but in migraine we do not have to worry about that. It is very interesting. In epilepsy, the drug level is associated with seizure control. It is not in migraine, and my guess is that epilepsy is probably a neuronal disease, migraine is a glial disease, and there is increasing evidence now that a lot of the problems in both migraine and chronic neuropathic pain states are probably related to abnormalities in glia. In familial hemiplegic migraine Type II, the ATPase fundamental abnormality is in the alpha 2 subunit of the Na/K pump, involved in glia transport of glutamate. So I think that is the fundamental difference. It may be the way epilepsy produces migraine, with secondary changes in the surrounding tissue.

**Dr Lipton:** Do you want to comment on whether preventive therapy alters the efficacy of the key treatment?

**Dr Silberstein:** There is a trial now being designed to prove that. David Dodick did a subset analysis in topiramate trials and showed it did. It is our experience over and over again that a patient will come in, take an acute drug and it does not work, but they go on a preventive drug and it works. There are a lot of ideas about why that happens. Rami Burstein has shown in patients who develop central sensitization (which is manifested as allodynia, in which painful stimuli hurt), a lot of the acute drugs do not work or do not work as well. We have some evidence in our laboratory that preventive drugs may inhibit central sensitization. If that is the case, it may explain the synergism between acute and preventive medication. Our experience has been that acute drugs work better in the pres-
ence of preventive medication. The mechanism may be decreased central sensitization, but there still needs to be a lot more work. A trial now going on will look at a triptan (almotriptan) alone and in conjunction with a preventive medication (topiramate) in unblinded conditions, to see if that makes a difference. We believe it, and finally somebody is testing it.

REFERENCES