Antipsychotics for Migraine Prophylaxis: An Initial Look at Quetiapine

Based on a poster presented by Brandes JL,* with Roberson SC,* Pearlman SH,† and S. Abu-Shakra‡

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The role of 5-hydroxytryptophan (5-HT) in neurological disorders of the brain has been increasingly appreciated in the past several decades, primarily due to the efficacy of 5-HT receptor agonists and antagonists in treating such disorders as depression, anxiety, obsessive-compulsive disorder, migraine, and schizophrenia. The use of antipsychotic drugs for migraine prophylaxis is still a novel idea, and perhaps not vigorously pursued because of the often unacceptable side effects associated with traditional antipsychotic medication. However, as recently reviewed by Barbanti and Fabbrini, both typical and atypical antipsychotic agents have been reported as effective acute treatment for migraine in emergency settings and for chronic daily headache, status migrainosus, or refractory migraine in routine care settings.1-7

Quetiapine is one of the newest agents in the class of atypical antipsychotic drugs. In general, this drug is associated with significantly fewer side effects, particularly extrapyramidal side effects, changes in QT interval, and weight gain. It acts on many neurotransmitter systems in the brain including 5-HT₁A and 5-HT₂, as well as dopamine, histamine, and alpha₁- and alpha₂-adrenergic receptors. To date, it has not yet been studied for the acute or prophylactic treatment of migraine.

This open-label retrospective study examined the safety and efficacy of quetiapine as adjunctive therapy in 20 International Headache Society-diagnosed migraineurs who had minimal or no response to at least 2 other prophylactic therapies. Doses of quetiapine began at 25 mg per day and were titrated up to 300 mg or down as tolerated. The study cohort was somewhat typical of other migraine treatment clinical trial cohorts: age range of 32 to 63 years, and 3 times as many women as men. The number of migraineurs with and without aura was equal: 10 and 10, respectively. The baseline disability scores, measured by the Migraine in Disability Assessment Scale (MIDAS), ranged from 0 to 215 with 95% of patients rated as a MIDAS grade IV (very severe disability).

Quetiapine was administered as prn only (n = 6), qhs only (n = 12), or both (n = 2). A total of 3 patients were excluded from the efficacy analyses because their treatment period (4 weeks) was too short to evaluate efficacy. The mean time of treatment was 5.4 months, ranging from 2 to 24 months. However, those excluded from efficacy analyses were included in tolerability analyses.

The results show that the dose ranges used for prn administration were substantially lower than for qhs administration (12.5 mg to 50 mg vs 12.5 mg to 300 mg). Headache frequency, duration, and severity improved in regard to efficacy in 11 of 20 patients, and improved MIDAS scores were observed in 11 patients, although 1 patient reported improvement in headache, but provided no MIDAS score. Conversely, 6 patients also discontinued therapy due to adverse events, most notably sedation. There were no reports of extrapyramidal side effects.

The investigators conclude that, given the results in this study suggesting some clinical benefit with acute and/or preventive quetiapine therapy, further study is necessary.
warranted to evaluate prophylaxis with quetiapine in severely affected migraineurs.

REFERENCES


EXAMINING fMRI CHANGES AND BRAIN ABNORMALITIES ON CONVENTIONAL MRI IN MIGRAINEURS

Based on a poster presented by Rocca MA with Colombo B, Codella M, Falini A, Scotti G, Comi G, and Filippi M, Neuroimaging Research Unit, Scientific Institute and University, Hospital San Raffaele, Milan, Italy

More than 10 years ago, Olesen et al showed differences in regional cerebral blood flow (rCBF) in the brain before and during headache attacks. During the aura and the early phase of headache rCBF is initially reduced. The decrease in rCBF travels across the brain at 3 mm/sec to 5 mm/sec, similar to the cortical spreading depression that occurs during seizure. Repeated reductions and increases in cerebral blood flow may cause permanent ischemic damage in the brain. In fact, magnetic resonance imaging (MRI) studies have already shown the presence of white matter abnormalities in brains of migraineurs.

Functional MRI (fMRI) is a relatively new technique which allows study of abnormal patterns of brain activation during various disease states. In fact, recent work has shown that neurons in the cortex respond adaptively to the presence of brain damage. In multiple sclerosis patients, this adaptive response is thought to contribute to maintenance of normal motor function, even in those with relatively few white matter lesions and minor clinical symptoms.

This study was designed to investigate whether functional cortical changes are detectable in patients with migraine and subcortical white matter lesions as seen on conventional MRI scans, to quantify the extent of normal-appearing white matter (NAWM) damage in these patients using diffusion tensor MRI, and to assess whether fMRI changes might reflect a neuronal adaptation in patients with migraine.

A total of 15 righthanded patients with migraine were included (14 women, 1 man), with a mean of 26.4 attacks per year (ranging from 12 to 46 attacks). None of the migraineurs had a history of hypertension, hypercholesterolemia, diabetes mellitus, or vascular/heart diseases, and all of them had at least 4 brain abnormalities on previous MRI scans. The study also included 15 gender- and age-matched, righthanded, healthy volunteers.

The participants were assessed using conventional MRI to locate and quantify the lesions and damaged NAWM, and fMRI to measure areas of functional activation. During fMRI acquisition, participants were asked to perform a simple motor task: repetitive flexion-extension of the last 4 fingers of the right hand moving together at a fixed rate of approximately 1 Hz.

For conventional MRI, a dual-echo turbo spin echo and a pulsed-gradient spin-echo echo-planar sequence were acquired. Mean diffusivity and fractional anisotropy maps were produced. To study the mean diffusivity of NAWM, pixels lying inside lesion outlines were nulled out, and mean diffusivity histograms of the remaining NAWM were produced. All healthy volunteers had normal brain MRI dual-echo scans.

The peak height of the NAWM mean diffusivity histograms in migraine patients was reduced com-
pared with controls. Since the peak height of the mean diffusivity histogram is considered to be a measure of normal tissue, our results indicate that damage of white matter in migraine may extend beyond macroscopic brain lesions and include more subtle changes in NAWM. Also, compared with healthy volunteers, migraine patients had a significantly larger relative activation of the contralateral primary sensorimotor cortex (SMC), and a rostral displacement of the supplementary motor area (SMA).

Interestingly, the peak height of the NAWM mean diffusivity histogram was directly related to the extent of rostral displacement of the SMA. However, no correlations were found between fMRI changes and any of the structural MRI measures of intrinsic lesion damage, suggesting that migraine can be associated with interictal, local, functional reorganization of the cortex.

This study shows that the pattern of movement-related cortical activations is different between migraine patients with lesions on brain MRI scans and matched healthy volunteers (no lesions). The investigators note that previous event-related fMRI studies have shown that the rostral portion of SMA (pre-SMA) is preferentially activated in movement preparation. They also reference another study showing that rostral SMA activation precedes primary motor cortex activation by several seconds. Thus, the rostral displacement of the SMA in migraine patients might be due to widespread white matter damage, or to the fact that patients may perceive the task as relatively difficult. The increased pre-SMA activation might cause a greater SMC activation through fibers connecting these 2 cortical areas. To maintain normal functioning, corticospinal fibers projecting from the SMC may be recruited.

Because of the direct relationship between the extent of the shift of the SMA activation center and the peak height of the NAWM mean diffusivity histograms, the investigators suggest that changes in brain function may be induced by the extent of NAWM damage. This damage might impair communication between cortical areas involved in movement, and therefore might result in patients’ perception of the task as being more complex, thus requiring increased recruitment of neurons in the SMC and in the rostral part of the SMA.

The investigators propose 2 possible explanations, which are not mutually exclusive, for reduced peak height of the NAWM mean diffusivity histogram:

1. Diffusion tensor MRI changes in NAWM could result from ischemia caused by the blood flow reduction, which can persist for hours during a migraine attack.
2. Changes could reflect secondary Wallerian degeneration of axons projecting into the NAWM from damaged tissue.

There was no difference in the time course of the blood oxygen level-dependent signal intensity changes in the activated cortical areas, suggesting that the changes in cortical activation are more likely due to cortical reorganization in response to diffuse white matter damage rather than being a sign of migraine-related cortical perfusion abnormalities.

REFERENCES


MRI Study of Lesions in Migraineurs: The CAMERA Project

Based on a poster presented by Kruit MC,* with Buchem MA,* Hofman PA,† Bakkers JR,*, Ferrari MD,† and Launer LJ†

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The possible relationship between the clinical phenomenon of migraine and the pathophysiologic phenomenon of brain infarcts is of recent interest to medical researchers. In particular, the neurovascular contribution to migraine etiology is increasingly recognized, but not yet well understood.

The Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA) study used magnetic resonance imaging (MRI) to evaluate a large population to determine if there is any relationship between the presence of clinical and subclinical brain infarcts and white matter lesions and migraine. Participants for the CAMERA project were randomly selected from the Genetic Epidemiology of Migraine (GEM) Study, which included 6000 adults, aged 20 to 65 years, selected randomly from 2 county population registries in the Netherlands.1 Of those, 863 were migraineurs. For the CAMERA study, those aged 30 to 60 years participated, including 134 migraineurs without aura (MO), 161 migraineurs with aura (MA), and 140 controls (matched to the cases by gender, 5-year age strata, and region of residence). Brain MRI images were evaluated by 1 neuroradiologist, who was blinded to clinical status.

Previously, results from the CAMERA study reported that migraineurs are at significantly increased risk of infarcts in the posterior circulation (PC). The risk was highest for MA with >1 attack per month. In their latest report, the authors focused on the characteristics (ie, size, number) and the anatomical and vascular distribution of the identified infarcts in the PC territory.

The authors found that in MA, MO, and controls, infarcts were located in the anterior (carotid) circulation, PC, basal ganglia, and the corona radiata or semioval center; however, there were significant differences only in the PC. In fact, more than half of all identified infarcts were located within the PC in 16 migraineurs (5.4%) and 1 control (0.7%; P=.02). The prevalence was 4 times higher in MA vs MO. The vast majority of infarcts in migraineurs were cerebellar, whereas 1 control had 1 cerebellar infarct. The PC infarcts had a mean diameter of 7.4 mm, and almost three fourths were located on the right side. A total of 88% of the 34 PC territory infarcts were involved the cerebellar arterial border zones, which are vulnerable to hypoperfusion seen in migraine or ischemia. Overall, structural brain changes in the PC, including hyperintense lesions in the pons, were 6 times more prevalent in migraineurs compared with controls. Migraineurs with aura had more than twice the frequency of lesions in MO.
Not surprisingly, those with lesions were significantly older. After controlling for cardiovascular risk factors, migraineurs were still at significantly increased risk (OR = 5.7; P = .02) compared with controls. As with previous findings, risk was greatest in MA with >1 attack per month. None of the subjects with lesions reported a history of stroke or transient ischemic attack.

Because most of the lesions were located in areas (border zones) vulnerable to hypoperfusion or ischemia, further study of these lesions may provide information on the pathophysiological mechanisms involved in migraine.

REFERENCES


HEADACHE PREVENTIVES: WEIGHT LOSS OR WEIGHT GAIN?

Based on a poster presentation by Loewinger LE, with Young WB.

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Some of the leading classes of drugs used for migraine prevention are notorious for causing weight gain, including antiepileptic drugs and selective serotonin reuptake inhibitors (SSRIs). Overweight and obesity have reached epidemic rates in the United States and the health problems that they cause or contribute to are now becoming well known including increased risk for arthritis, heart disease, diabetes, and certain types of cancer. As a result of the increasing incidence of weight gain and its associated health problems, drugs that induce weight gain have been associated with poor patient compliance.

This study was a retrospective review of the medical records of patients seen in a headache clinic. All of the study participants were adults with at least 1 type of the following headaches: chronic (transformed migraine), episodic migraine, chronic and episodic tension-type headache, and new daily persistent headache. They were taking 1 of the following headache preventives as monotherapy for more than 90 days: divalproex sodium, topiramate, fluoxetine, nortriptyline, or riboflavin. However, riboflavin cotherapy was allowed and a minimum of other daily medications were permitted (eg, cholesterol-lowering agents, multivitamins). Generally, no more than 1 such medication was permitted and none of the medications were widely recognized as causing weight gain.

Patients who were pregnant or who had other major medical conditions that could alter weight, as well as those taking any other daily medication thought to influence weight, were excluded. Weight was measured at 90 days, 180 days, and 270 days after treatment initiation. Weight was assumed to increase or decrease at a linear rate between time points, accordingly.

A total of 169 patients were initially enrolled; 108 patients completed the study at day 270. The mean ages of the patients ranged from approximately late 30s (topiramate group) to 50 years (divalproex sodium). The female-to-male ratio ranged from 3:1 to 11:1, as expected based on demographic data of migraineurs. The mean initial weight for each treatment group was approximately 146 pounds to 154 pounds, with the exception of the topiramate-treated patients, whose mean initial weight was 167 pounds.

The results show steady weight gain at each time period with nortriptyline, fluoxetine, and divalproex, with a maximum weight gain of 7 pounds by day 270 in the fluoxetine group. There was no change in weight in those receiving riboflavin, and a weight loss of more than 10 pounds in those receiving topiramate by day 270. The weight decline in the topiramate group was observed at each time point, decreased in an almost linear fashion, and was significant compared with each of the other study drugs at all time points, up to P < .001 (Fisher's exact test).

By day 270, 35% of the fluoxetine-treated patients gained more than 5% of their body weight, while 32% of the divalproex group, 20% of the nor-
triptyline group, 14% of the riboflavin group, and 8% of the topiramate group had gained more than 5% of their initial body weight. Conversely, by day 270, 58% of topiramate patients had lost more than 5% of their body weight, compared with less than 10% in each of the other treatment groups.

Of particular note, initial weight, duration of treatment, preventive medication, and dose within each category were significantly correlated with final weight (P ≤ .05). The mean dose for each drug during the study and the typical doses used for migraine prophylaxis are shown in the Table. Clearly, all of the drugs were used well within their normal ranges. Age and use of another SSRI did not correlate significantly with final weight, and sex was only marginally significant (ie, women were more prone to gain weight).

Although other studies have examined the effects on weight of various migraine preventive drugs, those populations were controlled and, therefore, different from the typical patient population seen by most neurologists and headache specialists. Because this group was from a headache clinic and was not controlled, it offers a better representation of the weight issues many patients and their treating neurologists will encounter in everyday practice. It would be interesting to evaluate the weight of patients who were not taking preventive medications over 270 days as a control, and compare the results with those in this study.

Given the detrimental effects of weight gain, headache specialists should consider the potential for weight gain and ways to avoid it when choosing a preventive therapy.

REFERENCES


ALTERNATIVES TO PROPHYLAXIS: FURTHER RESULTS ON THE EFFICACY AND SAFETY OF PETASITES

Based on a poster presented by Lipton RB; with Gobel H; Wilks K; Muskop A

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Migraineurs have frequently turned to alternative or complementary medicine for their headaches, most notably feverfew and riboflavin. More recently, complementary medicines for migraine prophylaxis are gaining interest. Petasites hybridus (known as “butterbur”) has been used for medicinal purposes for more than 2000 years and has been used as a migraine prophylactic agent in Germany for about 10 years. A perennial shrub, the migraine treatment is extracted from the roots of the plant. The active components of the extract are thought to be smooth muscle vasodilators (petasin and isopetasin), which also have anti-muscarinic and anti-inflammatory effects through inhibition of leukotriene synthesis.1-6

Previously, 50 mg Petasites (Petadolex®, W eber and W eber, G mg H & Co, Kiel, Germany) was compared with placebo in 60 migraineurs. After 12 weeks of treatment, patients receiving Petasites extract had significantly fewer migraine attacks compared with those receiving placebo (P < .05) from week 4 throughout treatment, and the study drug was well tolerated.6 Patients treated with Petasites also had significantly fewer migraine days per 4 weeks...
compared with the placebo patients. Other benefits included fewer accompanying symptoms, reduced intensity of the migraine attacks, and decreased analgesic use.6

This study builds on the information learned from the first study by comparing 50 mg and 75 mg Petasites with placebo in another 12-week study period in 202 participants (Petasites 50 mg, n = 71; Petasites 75 mg, n = 68; placebo, n = 63). This was a double-blind, randomized, parallel-group study in patients with established migraine diagnosis (based on International Headache Society criteria) who were treated in an outpatient setting. Their average frequency of attacks was 3 per month for the previous 3 months, with a minimum of 2 attacks during the 4-week baseline phase (in which the frequency and severity of attacks were recorded).

The results showed both doses of Petasites produced a significant reduction in migraine attack count over 3 months of treatment from the baseline attack count. Interestingly, there was a 26% reduction in placebo-treated patients, but the Petasites groups had reductions of 34% and 48% with the 50-mg and 75-mg doses, respectively. Similar results were seen with the reduction in migraine frequency during the 4-month treatment period. Again, there was a notable placebo response, but the reduction in migraine frequency at 4 months was significant for the 75-mg dose of Petasites, but not for the 50-mg dose. The difference was significant only at 4 months, but the trend was observed throughout the treatment period.

For patients with a ≥50% reduction in attack count, the difference from placebo was significant throughout the treatment period up to 4 months for the 75-mg Petasites group only, but the trend was also noted for the 50-mg group. The placebo response was also observed.

Decreases in the use of acute medications were observed in all 3 treatment groups during the study period; the difference was significant only for the 75-mg Petasites group at 3 months: 55% vs 34% (50 mg) vs 33% (placebo), P <.02 vs placebo.

Other results showed significant reductions in the mean attack intensity score and the mean attack days per month at 3 months for the 75-mg group only.

Adverse events were minimal, the most frequent being gastrointestinal disorders such as burping, nausea, vomiting, lower abdominal pain, heartburn, diarrhea, and bad taste in the mouth (22.4% in patients taking 75 mg Petasites; 25.6% of those taking 50 mg Petasites; and 6.7% of those taking placebo). Other adverse events occurred at very low frequencies in all 3 treatment groups (1% - 5%). Neurological disorders occurred slightly more frequently in the 50-mg group than the other 2 treatment groups (5.1% vs 1.3%) and included tension-type headache, cluster headache, increased intensity of migraine attack, bitter taste, increased headache frequency, and sleep interruption.

The Petasites extract was well tolerated with no changes in blood pressure, heart rate, or liver enzymes.

The results suggest that 75 mg appears to be the more efficacious dose of Petasites, and the positive effects on migraine attack frequency and intensity warrant further investigation, particularly given the recent interest in complementary medicine for headache treatment.

REFERENCES
FIRST RESULTS OF THE SAFETY AND EFFICACY OF TOPIRAMATE IN PEDIATRIC MIGRAINEURS

Based on a poster presented by Ferreira J , with Garcia N, Pedreira L*

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Antiepileptic drugs (AEDs) are well established as effective prophylactic medications for migraine, and topiramate is the most recent AED to enter the market. Studies in adults have shown it to be safe and effective in the prevention of migraine. Its use in children is not well established, however, and migraine headaches occur in up to 11% of children younger than 15 years. This relatively high frequency is thought to account for up to 1 million missed school days per year in the United States.1,2

Some AEDs are associated with weight gain in both migraine and epilepsy patients; however, topiramate has been associated with weight loss in a subset of adult migraine and epilepsy patients. Given the more than 60% incidence of overweight and obesity in the United States, the potential for weight loss makes it an attractive option for migraine prevention, particularly among women.

This study was a retrospective chart review of pediatric patients who had been treated with topiramate for migraine. A total of 34 patients were identified (10 boys, 24 girls) with an average age of 14 ± 4 years. Almost one half received a diagnosis of migraine (n = 16) and one half received a diagnosis of chronic daily headache (n =17). One child received a diagnosis of headaches associated with hydrocephalus. Patients were asked to keep a headache diary (supervised by parents) to record the frequency and severity of headaches, based on a 1-5 scale.

Most patients started with a topiramate dose of 25 mg per day and increased the dose each week by 25 mg per day until relief was obtained or they reached the maximal tolerated dose. The mean dose of topiramate was 138 mg ± 85 mg per day, ranging from 15 to 325 mg per day. Patients were treated for a minimum of 3 months and a maximum of 2 years.

The results show substantial reductions in mean monthly migraine frequency, mean migraine severity, and mean migraine disability with topiramate treatment compared with baseline measurements (Table).

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<th>Baseline</th>
<th>Topiramate</th>
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<td>Mean monthly migraine frequency</td>
<td>19.4</td>
<td>4.5</td>
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<tr>
<td>Mean migraine severity</td>
<td>2.66</td>
<td>0.85</td>
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<td>Mean migraine disability</td>
<td>2.09</td>
<td>0.61</td>
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The use of concurrent medications was also tracked, and the results show that prior to topiramate therapy, most patients took an average of 3.2 medications (acute and prophylactic), most commonly acetaminophen (n = 15), ibuprofen (n = 14), isometheptene/ dichloralphenazone/ acetaminophen (n = 12), sumatriptan (n = 6), sertraline (n = 5), and naproxen (n = 2). Almost one third of the children in the study (n = 10) were able to stop concurrent medications after topiramate therapy.

A total of 12% of the children experienced weight loss, and those with the heaviest initial weight experienced most of the weight loss (a mean of 12 lbs). The remaining patients lost an average of 1 lb. Other common adverse events were paresthesias (9%), loss of appetite (9%), and cognitive slowing (6%), as expected based on studies in adults.

These initial results suggest that topiramate is a safe and effective prophylactic migraine medication in children. The benefits of weight loss appear to carry over into this younger patient population, which may be an advantage in more overweight children—a growing proportion of the children in the United States. These results warrant further studies in randomized, controlled trials.

REFERENCES

PREVALENCE OF MORNING MIGRAINE AND THE THERAPEUTIC IMPLICATIONS

Based on a poster presented by Diamond M,* with Richardson MS; O'Quinn S; McNeal S;
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The development of the triptans in the 1990s revolutionized the acute treatment of migraine. They are now considered the standard of care for aborting a migraine attack and most of them are able to significantly reduce pain within 2 hours of administration. However, there is a subset of patients who remain refractory to triptans or whose migraine is so frequent that preventive medication is warranted. Similarly, the timing of migraines can significantly impair quality of life (eg, missed work or school), so the migraines must be prevented rather than treated once they occur.

Morning migraine is defined as migraines occurring between 4:00 am and 9:00 am.1 Fox and Davis studied more than 3500 migraineurs and found that almost one half (48%) are morning migraines according to this definition.1 The pain intensity of morning migraines can be so severe, the sufferer wakes from sleep.

Migraine intensity can affect the likelihood of response to abortive therapy. Cady et al showed that severe headaches are less responsive to oral abortive treatments compared with milder headaches. The pain-free response is higher and there is a reduced need for redosing with milder headaches.2

The American Migraine Study II (AMS II) examined prevalence and burden, diagnosis, and treatment of migraine in 4000 migraineurs from the United States.3,4 In a follow-up survey to the AMS II, participants were asked about their migraine symptoms, comorbid conditions, headache impact on quality of life, treatment choices, and types of health care providers consulted for treatment. All participants met criteria for migraine, but patients self-reported various headache diagnoses from physicians. Based on the reported physician diagnoses, patients were divided into groups: migraine only, sinus headache only, tension-type headache (TTH) only, sinus + TTH, migraine + sinus headache, migraine + TTH, migraine + TTH + sinus headaches.

Fifty-four percent of the 4000 surveys sent were returned; and 74% (1607) of the returned surveys were evaluable. As with other migraine studies, 80% of the respondents were women, with a mean age of 43 years. The vast majority were Caucasian, and all suffered from migraines for a mean of 19 years.

When asked about the frequency of headaches occurring during the night, respondents could choose: several times per week, several times per month, once per month, less than once per month, or never. Those with sinus + migraine and TTH + migraine most often answered “several times per week” and those with sinus + migraine and TTH only most often answered “several times per month”; those with migraine only most often answered “never.”

When asked how often nighttime headaches woke the sufferer, respondents could choose: always, often, sometimes, rarely, or never. Those with sinus only, TTH only, and migraine + sinus + TTH most often answered “always,” with the highest incidence at 30%. Those with migraine + sinus, sinus + TTH, and migraine + sinus + TTH most often answered “often.” Those with TTH only most often answered “never” and 67% of those with TTH only were wakened “often” or “always” by their headaches, followed by migraine + sinus + TTH and migraine + sinus headache. These results show that morning migraine is common and can be found in patients with many different types of migrainous headaches.

Treating morning migraine is a challenge because the goal is to avoid the wakening altogether. Use of oral triptans, while very effective, may take too long to abort the headache, thus disturbing sleep patterns. Nonoral rescue medications (eg, injectable triptans) are one therapeutic option. Clearly, however, these patients would benefit from preventive therapy. Recognition of morning migraine can help optimize therapy and reduce the impact on quality of life.

REFERENCES