

CONFERENCE COVERAGE

Current Options in Migraine Prevention

The goals and principles of migraine prevention remain constant, regardless of which agent is chosen.

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STOWE, VT—The development of monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) has made migraine prevention a hot topic. Although FDA approval of these therapies could transform the field in the months ahead, the guiding principles and mainstays of preventive therapy remain unchanged. At the Headache Cooperative of New England's 28th Annual Stowe Headache Symposium, Robert E. Shapiro, MD, PhD, reviewed the goals, principles, and current options for preventive migraine therapy. Dr. Shapiro is Professor of Neurological Sciences at the Larner College of Medicine at the University of Vermont in Burlington.

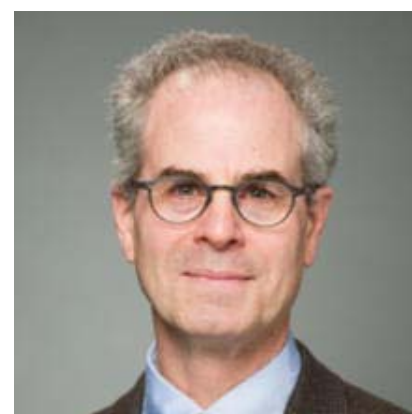
The goals of migraine prevention, Dr. Shapiro said, are to decrease attack frequency, severity, and duration; improve responsiveness to acute treatment; improve function and reduce disability; prevent acute analgesic overuse; and possibly reduce the total cost of treatment. "Achieving zero headaches and zero symptoms of migraine," he said, "is an emerging goal ... but we are not there yet."

First Things First

Before considering what to prescribe, a neurologist should keep certain guiding principles in mind. Using headache calendars to follow treatment compliance and effects is essential, said Dr.

Shapiro. To prevent patients from fixating on their symptoms, Dr. Shapiro advised that documentation be kept to a minimum. He asks his patients to record at the end of each day whether they had a headache and what the severity of the headache was at its worst.

Behavioral therapies also are essential. "Part of this [regimen] is simple cognitive restructuring," Dr. Shapiro said. He recommended stabilizing bedtime and waking hours, mealtime, and exercise time.



Robert E. Shapiro, MD, PhD

“Keep surprises to a minimum, in terms of daily schedule.” Avoiding exposures such as odors or food triggers can be helpful, as long as patients do not obsess over these exposures.

Cognitive behavioral therapy, yoga, and other types of behavioral therapies have demonstrated significant benefit. Likewise, sleep modification can be helpful. Incorporating these techniques into a prevention plan is important, Dr. Shapiro said. It also is important to treat relevant comorbid conditions. Dr. Shapiro also recommends tapering analgesics and caffeine.

Keeping Things in Perspective

There are several “inconvenient truths” about what can be achieved with preventive medications, Dr. Shapiro said. “Only four medications are FDA-approved for prevention of episodic migraine, and one for chronic migraine. None of them were developed for migraine. We are hopeful that later this year there will be FDA-approved medications that were developed for the prevention of migraine.” Additionally, the FDA cleared a few devices for migraine prevention. The caveat is that the standards for approval differ between drugs and devices. “Whenever a device is cleared ... it is important to go back and look with some level of higher scrutiny at what the evidence base is for efficacy,” Dr. Shapiro advised.

All available drugs have limited tolerability. There is no clear and obviously superior medication, from the standpoint of efficacy. “A 50% reduction in headache days in half the patients is considered a pretty good outcome,” Dr. Shapiro said. Treatment choice needs to take efficacy, comorbid conditions, cost, side effects, convenient formulations, patient preferences, and prior history into account.

Another basic principle is slow titration to the optimal dose. The dose–response curve for some medications reaches a plateau, Dr. Shapiro said. If the therapeutic window is exceeded, the efficacy begins to decrease. Analgesic overuse is another potential problem. “It is important to have a trial at the appropriate dose for at least two months before you can make a judgment as to whether the medication is helpful. Individual responses are hard to predict.” Finally, Dr. Shapiro suggested tapering a medication off after 12 months. “There is some sense that with a reduction in the frequency of events, there may be a stabilizing effect. That is not based on a lot of evidence. It is based, rather, on clinical experience. Successful preventive medications may be tapered off, and there may be a durable benefit after it has been there for a while,” he said.

The most sobering fact about preventive medications, Dr. Shapiro said, is that “83% of patients started on a preventive medication are not taking it one year later.”

Starting Preventive Treatment

The consensus among a panel of experts was that headache at six days or more per month should be

the threshold for offering a patient a preventive therapy, whereas it should be considered for patients experiencing four to five days with headache per month. “Based on this [principle], a 2007 study found that 13% of migraine patients were on preventive medications, while an additional 26% should be offered preventive medications, and in 13% preventives should be considered,” Dr. Shapiro said.

Based on the 2012 American Headache Society/American Academy of Neurology guideline for episodic migraine preventive drugs, there is Level A (established as effective) evidence for divalproex sodium ER (1,000 mg daily), topiramate (50 mg bid), propranolol (120 mg to 160 mg daily), timolol (10 mg to 15 mg bid), metoprolol (100 mg bid), and petasites (ie, butterbur). The first four medicines are FDA-approved for migraine, and metoprolol is included based on the evidence available, even though it is not FDA-approved for this indication. “Butterbur is effective, but there is an almost universal sense that we should not be offering this to patients because of the concern about potential liver toxicity and insufficient assurance from manufacturers that the agents that might cause that toxicity have been removed,” Dr. Shapiro said.

Several studies comparing efficacy, defined as the 50% responder rate, have indicated that valproate, topiramate, and propranolol all have approximately the same level of efficacy. Approximately 45% of patients receiving these therapies had 50% reduction in attack frequency or severity.

Level B (probably effective) evidence exists for several agents that are in common use, such as amitriptyline, candesartan, lisinopril, amlodipine and zonisamide. Other agents with Level B evidence include nutraceuticals and vitamin agents, such as megadoses of riboflavin and magnesium.

As previously mentioned, selection of a preventive agent may be guided by comorbidity. If a patient has hypertension, for example, angiotensin receptor blockers, ACE inhibitors, beta blockers, or calcium channel blockers are worth considering. In its evaluation of medications for migraine prevention, the Agency for Healthcare Research and Quality issued its own evaluation of medications for migraine prevention and suggested that even though angiotensin receptor blockers such as candesartan, or angiotensin converting enzyme inhibitors such as lisinopril, are not FDA-approved to treat migraine, their relative tolerability suggests that they could be first-line agents for this purpose. For depression, venlafaxine could be an appropriate choice. If a patient is obese, topiramate or zonisamide should be considered. If epilepsy is comorbid with migraine, obvious choices would be topiramate, divalproate, or zonisamide. For neuropathic pain or insomnia, tricyclic antidepressants are appropriate.

Game Changer?

“We are all excited about the new developments” related to the CGRP agents in clinical trials, Dr. Shapiro said, “but how much these drugs may improve clinical outcomes remains to be seen.”

Independent lines of evidence suggest that CGRP is involved during migraine attacks and that blocking the effects of CGRP can have therapeutic benefit.

The four medications in late-stage clinical development are erenumab, fremanezumab, galcanezumab, and eptinezumab. Three of them have been submitted to the FDA for review. They are all either fully human or humanized antibodies. All of them have been studied in clinical trials for episodic and chronic migraine. Galcanezumab and fremanezumab are being studied for episodic and chronic cluster headache. Erenumab is an antibody directed against the CGRP receptor, whereas the other three treatments target CGRP itself. Erenumab, fremanezumab, and galcanezumab are delivered by monthly or quarterly subcutaneous injections. Eptinezumab has been studied as a quarterly IV infusion. The dosage and frequency of administration will remain uncertain until the FDA approves specific regimens for these therapies, Dr. Shapiro said.

Regulatory news is pending. The PDUFA date for FDA reporting on erenumab is May 17, 2018. Unexpected problems at the manufacturing plant in South Korea have raised questions about the timing of fremanezumab availability, but the FDA is still expected to render a judgment on its approvability by this summer. For galcanezumab, an FDA decision is expected by late September 2018. Eptinezumab has not yet been submitted for approval.

Other Options

Botox is approved for prevention of chronic migraine. Neurologists administer 155 units to 31 injection sites. In clinical trials, baseline monthly headache frequency of 20 days was reduced to 11.5 days among patients receiving onabotulinumtoxinA and to 13 days among controls. The therapeutic gain was about 9%, or about 1.7 days, during the 28-day trial period. At least 78% of the improvement associated with Botox was attributed to the placebo effect, Dr. Shapiro noted. “But that does not mean that this is not a helpful thing to do.... This helps a lot of people, even though the placebo effect is substantial.”

The Cefaly transcutaneous electrical nerve stimulation (TENS) device has been cleared for marketing by the FDA. In clinical trials, the device did not significantly reduce the number of headache days at three months, compared with sham treatment, but the FDA cleared the device nevertheless. “This [treatment] is of variable benefit,” Dr. Shapiro said. “Evidence of that is that only about half of the patients who tried it were willing to buy the device after two months.”

The sTMS mini transcranial magnetic stimulation device was cleared for marketing in the summer of 2017. In clinical trials, this device reduced headache frequency by two to three days per month when used for prevention of episodic or chronic migraine. The clinical trial, however, was open-label and used a “performance goal” comparator that was estimated from placebo responses in several other clinical trials, rather than a sham control; this design raises concerns about the validity of the efficacy claims. “This [device] is another potential option, but again, the evidence that the FDA accepted for clearing this device was not what we would prefer,” Dr. Shapiro said.

—Glenn S. Williams

Suggested Reading

Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults. *J Gen Intern Med* <<https://www.ncbi.nlm.nih.gov/pubmed/23592242>>. 2013;28(9):1225-1237.

Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* <<https://www.ncbi.nlm.nih.gov/pubmed/22529202>>. 2012;78(17):1337-1345.

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