EDITORIAL

Glen D. Solomon, MD
Professor and Chair, Department of Internal Medicine, Wright State University, Dayton, OH

Preventing migraine: The old and the new

Migraine is a highly prevalent and debilitating condition that significantly impairs quality of life. It affects people during their childbearing and most economically productive years.[1] Preventing migraine by pharmacologic means has long been a goal of both physicians and the pharmaceutical industry.

See related article, page 211

The ideal preventive (prophylactic) migraine treatment will be effective, safe, and well tolerated, will have few or no contraindications and few or no drug interactions, will not be teratogenic, and will be dosed in a manner to ease adherence. Our attempts to meet these goals have so far been unsuccessful.

The efficacy of preventive medications for migraine has been consistent across all drug classes. Roughly half of patients taking a preventive medication have a 50% reduction in migraine frequency. Whether in placebo-controlled trials or head-to-head studies, no medication has shown significant superiority in efficacy.

THE OLD

Methysergide was introduced into practice in the early 1960s.[2] Its use was limited by both contraindications and safety issues. Contraindications included pregnancy, peripheral vascular disorders, severe arteriosclerosis, coronary artery disease, severe hypertension, thrombophlebitis or cellulitis of the legs, peptic ulcer disease, fibrotic disorders, lung diseases, collagen disease, liver or renal function impairment, valvular heart disease, debilitation, and serious infection. Methysergide can induce retroperitoneal fibrosis and pleural and heart valve fibrosis, with an estimated incidence of 1 in 5,000 treated patients. Sale of methysergide in the United States was discontinued in 2002.[3]

Antidepressants have long been used for migraine prophylaxis. Monoamine oxidase inhibitors were studied in the late 1960s, but their use was limited by drug and food interactions that could lead to hypertensive crises. Amitriptyline was shown to reduce migraine frequency in the mid-1970s.[2] Side effects including weight gain and sedation limit its usefulness. While selective serotonin reuptake inhibitors have not been shown to be effective migraine preventives, serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine appear to provide benefit. Side effects include nausea, fatigue, and insomnia.

Roughly half of patients taking any preventive medication have a 50% reduction in migraine frequency

Antihypertensive medications have been a mainstay of migraine prophylaxis.

Beta-blockers such as propranolol and timolol are approved by the US Food and Drug Administration (FDA) for migraine prophylaxis. Propranolol was initially studied for migraine in the late 1960s after the discovery that a patient with cardiac disease treated with the drug had an improvement in his migraines.[2] The use of beta-blockers is limited by side effects including nausea, vomiting, diarrhea, decreased sex drive, impotence, difficulty having an orgasm, insomnia, and fatigue. Relative contraindications include asthma, heart failure, sinus bradycardia, Wolff-Parkinson-White syndrome, second- or third-degree atrioventricular block, hyperthyroidism, kidney disease, liver disease, Raynaud disease, pheochromocytoma, depression, and myasthenia gravis.

doi:10.3949/ccjm.87a.19147

Verapamil, a calcium channel blocker, was first studied for migraine in the early 1980s.[4] Its use is limited by drug interactions, constipation as a common side effect, and contraindications including second- or third-degree atrioventricular block, sick sinus syndrome, Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome, heart failure, muscular dystrophy, myasthenia gravis, liver disease, and kidney disease.

Antiepileptic agents including valproic acid and topiramate are FDA-approved for migraine prophylaxis. Valproic acid has been used for migraine since 1983 and topiramate since 2004. Use of these agents is limited by teratogenicity and adverse effects: cognitive impairment, weight loss, paresthesia, and nephrolithiasis with topiramate, and weight gain, alopecia, and hepatic dysfunction with valproic acid.

THE NEW: CGRP ANTAGONISTS

The newest options for migraine prophylaxis are the calcitonin gene-related peptide (CGRP) antagonists. The first 3 of these drugs entered the market in 2018 and are monoclonal antibodies to either the CGRP receptor (erenumab) or the CGRP ligand (galcanezumab, fremanezumab). They are given by subcutaneous injection. A fourth CGRP antagonist (eptinezumab), given by infusion, and several oral CGRP antagonists (gepants) are likely to be approved soon; ubrogepant was approved on December 23, 2019. Unlike the drugs discussed earlier, these drugs were specifically designed to treat migraine based on the currently proposed pathophysiology.

CGRP antagonists have some clear advantages over existing therapies, but also present some new challenges

That these drugs were specifically designed to treat migraine may be a valuable marketing slogan, but it has no clinical meaning. Drugs such as aspirin, a critical drug for acute coronary syndromes, was developed as an anti-inflammatory agent for arthritis, and sildenafil, the drug that revolutionized erectile dysfunction treatment, was initially developed as an antihypertensive drug. Designing a drug specifically for migraine has not improved the efficacy of this class of drugs compared with our older agents.

The CGRP antagonists have some clear advantages over existing therapies but also present new challenges for the prescribing clinician. These drugs have many of the characteristics of an ideal prophylactic migraine treatment. While they are only as effective as our current drugs, they are well tolerated, have few contraindications, have no drug interactions, and can be dosed either monthly or quarterly to improve adherence.

Concerns about safety, especially in pregnancy

The safety of blocking CGRP remains a concern. CGRP and its receptor are present throughout the vasculature and in the peripheral and central nervous system. In addition to its role in cranial nociception, CGRP is a potent arterial vasodilator. Potential safety concerns include loss of vasodilation during ischemic events, difficulties with wound healing, problems with gastrointestinal motility and mucosal integrity, and dysregulation of pituitary function.[5] While these issues have not been demonstrated in clinical trials, long-term use of these drugs and use in patients with significant medical comorbidities have not yet been studied.

There are no data on the safety of CGRP blockade in pregnancy. In pregnancy, levels of CGRP increase. CGRP levels are lower in women with preeclampsia than in women with normotensive pregnancies, suggesting that CGRP blockade during pregnancy might be harmful.[6] This is a concern for a therapy aimed at a disease most prevalent in women during childbearing years. With many pregnancies unplanned, the long half-life of these drugs may prove to be a disadvantage. Preclinical data[7] have not shown fetal abnormalities or problems with organogenesis when CGRP antagonists were given during pregnancy in animal models. Data on humans are not yet available.

With these concerns, clinicians will need to determine the appropriate place for CGRP antagonists in practice. These medications should be avoided in pregnant women or in women of childbearing potential not using contraception. They should be used with caution in patients with significant risk of ischemic cardiovascular or cerebrovascular disease. Patients should be advised of the potential risks of CGRP block-

ade if they have gastrointestinal disease or are planning surgery.

The CGRP antagonists are a welcome addition, having many of the properties that we desire for migraine prophylaxis. But as with any new class of medication, we need to be mindful of the potential safety risks and risks to the developing fetus.

REFERENCES

1. **Solomon GD, Santanello N**. Impact of migraine and migraine therapy on productivity and quality of life. Neurology 2000; 55(9 suppl 2):S29–S35. pmid:11089517
2. **Diamond ML, Solomon GD, eds**. Diamond and Dalessio's the Practicing Physician's Approach to Headache. 6th ed. Philadelphia, PA; WB Saunders; 1999.
3. **Silberstein SD**. Methysergide. Cephalalgia 1998; 18(7):421–435. doi:10.1046/j.1468-2982.1998.1807421.x
4. **Solomon GD, Steel JG, Spaccavento LJ**. Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. JAMA 1983; 250(18):2500–2502. pmid:6355533
5. **Deen M, Correnti E, Kamm K, et al; European Headache Federation School of Advanced Studies (EHF-SAS)**. Blocking CGRP in migraine patients – a review of pros and cons. J Headache Pain 2017; 18(1):96. doi:10.1186/s10194-017-0807-1
6. **Loder EW, Burch RC**. Who should try new antibody treatments for migraine? JAMA Neurol 2018; 75(9):1039–1040. doi:10.1001/jamaneurol.2018.1268
7. **Eli Lilly and Company, Indianapolis, IN**. Emgality (galcanezumab-gnlm) prescribing information. https://pi.lilly.com/us/emgality-uspi.pdf. Accessed December 2, 2019.

***Address**: Glen D. Solomon, MD, Department of Internal Medicine, Wright State University, P.O. Box 927, Dayton, OH 45401-0927; glen.solomon@wright.edu; solomongd@aol.com*