An Update on the Management of Chronic Migraine

In 1672, Thomas Willis provided the first description of chronic migraine (CM) when he reported the case of the philosopher, Anne, Viscountess Conway, who was also treated by William Harvey and Robert Boyle without success.1-4 Has our treatment of chronic migraine since improved?

By Randolph W. Evans, MD

About 35 million people in the United States have migraines annually. CM, or transformed migraine, is a complication of intermittent migraine with 2.5 percent progressing yearly from episodic to CM. About 3.2 million adults have CM: 80 percent of women and 1.8 percent of adolescents. It may occur with or without medication overuse. The pain is often mild to moderate and not always associated with photophobia, phonophobia, nausea, or vomiting and may resemble a mixture of migraine and tension-type headaches with intermittent severe migraine type headaches. Depression is present in 80 percent. The International Classification of Headache Disorders 3 (beta) 2013 definition of CM is the following: headache occurring on 15 or more days per month for more than three months, which has the features of migraine headache on at least eight days per month. Patients meeting criteria for 1.3 Chronic migraine and for 8.2 Medication-overuse headache should be given both diagnoses.5

Risk factors for transformation include medication overuse (especially opiates and barbiturate combinations), high caffeine consumption, female gender, stressful life events, anxiety, depression, baseline high attack frequency, individuals with lower educational and socioeconomic levels, white patients, those previously married, lifetime injuries to the head or neck, obesity, snoring, and sleep apnea.6,7 Only 20 percent of patients with CM are diagnosed with the disorder; others instead are provided by healthcare providers or themselves with a variety of other diagnoses including sinus, stress, cervical spine, and allergies. Or they think their bad headaches are migraine and they have other diagnoses for the milder headaches.

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butalbital\textsuperscript{11} and opiates\textsuperscript{12} can lead to habituation and other side effects.

Use of non-steroidal anti-inflammatory drugs (NSAIDs) in migraineurs with less than 10 headaches per month is associated with dose-dependent reductions in the risk of CM onset, while in those with 10-14 headache days per month there is an increased risk of developing CM with increasing frequency of use.\textsuperscript{13} The combination use of NSAIDs and triptans was not protective against transition to CM but was not associated with increased risk of CM onset. However, might the risk of medication depend upon the NSAID as there is level B evidence for efficacy of naproxen and naproxen sodium for daily prevention.\textsuperscript{14}

**TREATING MEDICATION OVERUSE**

Withdrawal of the overused medication alone, which can be combined with a preventive medication, may result in a decrease in headache frequency in most patients. Caffeine use should be limited, as intake of as little as 200mg daily in susceptible individuals can lead to MOH,\textsuperscript{15,16} and some individuals have withdrawal symptoms with even low doses of 100mg daily.\textsuperscript{17} Overused medications can be tapered off. For those taking high-frequency butalbital combinations, phenobarbital 30mg twice a day (bid) can be substituted for two weeks followed by 15mg bid for two weeks (abrupt withdrawal can result in seizures). For those taking high doses of opioids, clonidine 0.1-0.2mg three times a day (tid) titrated up or down based on symptoms or clonidine patch 0.1-0.2mg/24 hours for one to two weeks.

There are several transitional therapy options. Naproxen 500mg bid for one to two weeks may be used alone or can be combined with tizanidine starting at 2mg at bedtime (hs) and titrating up. The evidence for efficacy for glucocorticoids is uncertain.\textsuperscript{18} The most recent study, a prospective double-blind, placebo-controlled trial of 96 consecutive German patients with MOH randomized to either 100mg of prednisone or placebo over five days, found that patients treated with prednisone requested less rescue medication within the first five days but did not decrease the severity and duration of withdrawal headache. However, these subjects with MOH were different than many United States patients, as only one was overusing opioids and none were overusing butalbital combinations.\textsuperscript{19} CM with medical overuse may also respond to the intravenous (IV) dihydroergotamine (DHE) regimen (see later). Greater occipital nerve blocks with local anesthetic only may be helpful.\textsuperscript{20} A small pilot study suggested some benefit of nabilone (a cannabinoid 1-receptor agonist) for intractable MOH.\textsuperscript{21} Larger scale studies will be of interest.

As antiemetics may cause sedation, inexpensive wrist bands, Sea-Band, which claim to apply acupressure on the P6 point were reported as effective for migraine associated nausea.\textsuperscript{22}

**THE IV DHE TRANSITIONAL THERAPY PROTOCOL**

The protocol was first proposed by Raskin in 1986\textsuperscript{23} and since has been modified with the following protocol recommended by Nagy, et al. for those without contraindications to use:\textsuperscript{24} Obtain a baseline electrocardiogram, complete blood count, comprehensive metabolic profile, prothrombin time, partial thromboplastin time, international normalized ratio, urinalysis, test for female, and toxicology screen. Pretreat with 4mg of ondansetron 30 minutes prior to DHE (beware of recent Food and Drug Administration [FDA] notification of risk of QT prolongation including the development of torsades de pointes with IV ondansetron use\textsuperscript{24} [some clinicians use metoclopramide 10mg IV instead]). Day 1: DHE 0.5mg in 100 mL of normal saline (NS) IV over one hour. If well tolerated, second dose eight hours later of 0.75mg in 250 mL of NS IV over one hour. Days 2-5: third and subsequent doses 1mg in 250 mL of NS over 1 hour IV every eight hours with the goal of a cumulative total dose of 11.25mg (+/-1mg) over five days (pediatric dose provided in article). Do not use triptans within 24 hours.

For moderate or severe nausea, the following are treatment options: additional dose of ondansetron 4mg IV every eight hours as necessary; addition of a second anti-emetic such as promethazine 12.5mg to 25mg IV every 12 hours; administration of DHE over two to three hours or not escalating the DHE dose or reducing the dose.

For muscle cramps or joint pain, consider naproxen 500mg every 12 hours as necessary (prn). In Nagy et al.’s study of 114 patients with medically refractory CM older than 16 years of age with a mean duration of migraine of 21 +/- 16 years with an average frequency four days per week, 74 percent had some benefit with this protocol and 50 percent had moderate or excellent benefit. During treatment, 67 percent had headache attack freedom and 75 percent had headache freedom within one month of completion with a duration of effect for an average of 28 days. Preventive medications were started one week after discharge. The attacks returned to the original frequency or intensity after a mean of 61 +/- 61 days. In the study’s cohort of 163 patients with primary headaches, the following percentages of patients reported these side effects: nausea, 58 percent (DHE stopped in 4 percent); leg cramps, 28 percent; diarrhea, 12 percent; abdominal cramps, 10 percent; and chest tightness, three percent. Some clinicians use IV valproate when DHE is contraindicated or in addition to DHE (loading dose of 15mg/
kg infused over 30 minutes followed by 5mg/kg infused over 15 minutes every eight hours). Some clinicians add ketorolac 30mg IV every 12 hours prn headache for three days.

**FDA-APPROVED TREATMENTS FOR CM**

There is one FDA-approved treatment for chronic migraine: onabotulinumtoxinA, although numerous other medications are used off label for CM (table). It was approved by the FDA in October, 2010, based upon the two Phase III research studies evaluating migraine prophylaxis therapy (PREEMPT) trials. The approved treatment is administration of 155 units in 31 fixed site fixed-dose injections of five units in each of the following muscles: the procerus and bilateral corrugators, frontalis, temporalis, occipitalis, cervical paraspinals, and superior trapezius muscles. At 24 weeks, 47.1 percent of onabotulinumtoxinA-treated patients had a 50 percent decrease from baseline in frequency of headache days (primary end point) compared with 35.1 percent of placebo-treated patients. OnabotulinumtoxinA was as effective in the 65.3 percent of the pooled patients from the two studies with medication overuse as the total PREEMPT population of 1384 adults with and without medication overuse. In the pooled population, the following percentages of nonresponders to the first injection became responders after additional treatment cycles: after treatment cycle 2, 11.3-14.5 percent; after treatment cycle 3, 7.4-10.3 percent. In this pooled population, discontinuation due to adverse events was 3.8 percent for onabotulinumtoxinA vs 1.2 percent for placebo.

Although onabotulinumtoxinA is an expensive treatment, the costs may be reduced by reduced triptan use. In addition, a retrospective study of 223 patients with CM who were treated with two injection cycles found a 39 percent offset of the estimated cost of the injections by a reduction in migraine-related emergency department visits, hospitalizations, and urgent care visits.

Two studies have compared onabotulinumtoxinA and topiramate for prevention of CM, finding similar efficacy. In a cohort of 60 subjects randomized to onabotulinumtoxinA up to 200 units vs topiramate up to 200mg daily, at month 9, 41 percent in the onabotulinumtoxinA group and 43 percent in the topiramate group had a 50 percent or greater reduction in headache days (with 2.7 percent of onabotulinumtoxinA patients stopping treatment due to adverse events vs 24.1 percent for topiramate). In the second study, 59 subjects were randomized to topiramate up to 200mg daily and placebo injections or onabotulinumtoxinA up to 200 units. At week 12, the mean number of headache days per month decreased by 12.4 days in the topiramate group and by 13.8 days in the onabotulinumtoxinA group.

**ARE THERE OTHER RANDOMIZED PLACEBO-CONTROLLED TRIALS SHOWING BENEFIT FOR CM?**

Yes. Trials have been performed with topiramate, sodium valproate, gabapentin, tizanidine, amitriptyline, candesartan, and propranolol. A randomized, double-blind, placebo-controlled European trial (RCT) of 59 subjects with a 16-week treatment phase with CM found efficacy for topiramate titrated to a target dose of 100mg per day (including for those with medication overuse which was a surprising and controversial finding) with 22 percent having a 50 percent or greater reduction in headache days per month vs. 0 percent for placebo (P = .012) and a reduction in mean monthly migraine days was -3.5 ± 6.3 days compared with placebo (0.2 ± 4.7 days; P = .02). Patients with medication overuse (mainly triptans) had a significant reduction in the mean number of migraine days with topiramate vs placebo (P < .03). A second similar but larger United States trial of 306 subjects also found efficacy with a target dose of 100mg per day with a significant reduction in the mean monthly rate of migraine/migrainous days (6.4 ± 5.8 days), compared with placebo (4.7 ± 6.1 days; P = .01). A post-hoc analysis in patients with medication overuse (mainly triptans) showed a strong trend in favor of topiramate (P < .05). Seventy subjects with chronic daily headache (including 29 with CM)
were randomized to sodium valproate 500mg twice daily or placebo for three months. There was significant improvement in pain levels and frequency in the CM subgroup. An RCT cross-over study of 133 subjects with chronic daily headache (two thirds with migraine features) randomized to gabapentin 2400mg daily or placebo found significantly higher headache free rates in those on gabapentin.

An RCT study of 134 subjects with chronic daily headache (77 percent with CM) randomized to tizanidine (slowly titrated to a target dose of 24mg per day as tolerated) or placebo found significantly fewer headache days per week in those on tizanidine. In a reanalysis of an RCT study published in 1979, subjects titrated to 100mg daily of amitriptyline as tolerated had a significantly superior reduction in headache frequency at 16 weeks. An RCT trial of fluoxetine titrated to 40mg daily depending upon patient response for chronic daily headache (n = 64) found significant improvement in overall headache status at three months. A small triple-blind double crossover study found efficacy for candesartan 16mg daily and propranolol slow release 160 mg daily as compared to placebo in episodic and chronic migraine.

ARE THERE MEDICATIONS WHICH MAY BE EFFECTIVE BASED UPON OPEN-LABEL TRIALS?

There are some other options for CM with open-label studies suggesting efficacy for pregabalin titrated to 150mg twice a day, zonisamide titrated as high as 400mg daily (in those with no response or intolerant to topiramate), atenolol 50mg daily, olanzapine 2.5 to 35mg daily, methylergonovine maleate .2-.4mg three times daily with drug holidays, and possibly memantine titrated to 10-20mg daily. Anecdotally, I have found venlafaxine extended release titrated to 150mg daily to be effective which has evidence for efficacy for episodic migraine with better tolerability than amitriptyline.

TAPERING “OVERUSED” MEDICATION BEFORE STARTING PREVENTIVE TREATMENT

The onabotulinumtoxinA and topiramate trials suggest benefit even for those overusing medications primarily triptans, although there is inadequate evidence whether other preventive medications might be effective. Other authorities would like to see additional studies and believe better results may be achieved with withdrawal first and then preventive medication use. The medication being overused may also be quite significant as triptan overuse may be easier to treat than butalbital and opioid overuse.

COMBINATION THERAPY

A RCT of 191 subjects with CM inadequately controlled with topiramate (50-100mg/day) to either propranolol long acting (LA) 240mg/day or placebo found no evidence of benefit from the addition of propranolol. However, this may not be the end of combination therapy as there were methodological issues with this study and other agents in combination might be effective.

THE ROLE OF NERVE BLOCKS

In an open-label single treatment arm study of 150 chronic migraineurs with a prominent cervicogenic element (at least 50 percent of their most severe headaches arose from one side of the occipital skull base or both) who received unilateral or bilateral occipital nerve blocks with local anesthetic and steroid, 52 percent experienced a 50 percent or greater reduction in headache days over the month following the procedure compared with the pretreatment baseline month. In a randomized study of 37 patients with transformed migraine, greater occipital nerve blocks and trigger point injections were equally effective with local anesthetic with steroid as local anesthetic alone. An open label study of 35 pediatric chronic migraineurs found benefit in 62 percent with a mean duration of 5.4 weeks from greater occipital nerve blocks with Depo-medrol and lidocaine. A prospective open-label trial was performed of 218 patients with intractable CM without butalbital or opioid medication overuse who received a fixed-dose (0.1cc of 0.25 percent bupivacaine) and fixed-site (10 at greater and lesser occipital nerves, five at auriculotemporal and zygomaticotemporal, two at supraorbital and supra trochlear areas bilaterally) pericranial injections every three months. After 12 months, 53.2 percent of patients had a more than 50 percent reduction in mean frequency of headache days. Further confirmation of the efficacy of nerve blocks will be of interest.

ALTERNATIVE OR COMPLEMENTARY TREATMENTS AND SURGERY

Acupuncture may be effective for CM with additional benefit when added to medical management. Another study found safflower seed acupuncture point injection more effective than NS in subjects with chronic daily headache. In a study of 66 CM patients randomized to treatment with acupuncture administered in 24 sessions over 12 weeks or topiramate titrated to a maximum of 100mg daily, the mean monthly number of moderate/severe headache days was reduced from 20.2 to 9.8 in the acupuncture group compared with 19.8 to 12.0 in the topiramate group with benefit also seen in those with medication overuse.

Behavioral sleep modification may be effective for transformed migraine. Although biofeedback, relaxation therapy, and cognitive behavioral therapy have demonstrated efficacy for prevention of episodic migraine, there are
limited data for treatment of CM. In a study of 91 subjects with episodic migraine randomized to treatment groups, physical exercise, relaxation therapy, and topiramate were equally effective for prevention. Biofeedback-assisted relaxation may supplement pharmacologic therapy based upon a three-year follow-up study of chronic daily headache associated with medication overuse. Although exercise has not been prospectively studied for treatment of CM, regular physical exercise might be of benefit (see next section). Alternative supplements have been studied in episodic but not CM.

The risk of migraine frequency and severity increases with increasing degrees of obesity. Two small observational studies have found a significant reduction in episodic migraine frequency after bariatric surgery. However, larger bariatric surgery and dietary weight loss studies to include subjects with CM are needed to determine if there is benefit of weight loss for episodic and CM.

Surgical deactivation of trigger points has been reported as having a 5-year benefit in patients with episodic migraine. The confirmation of trigger sites using onabotulinumtoxinA does not significantly improve the outcome of migraine surgery. A high sham surgery response rate and patient selection criteria remain problematic. In theview of the American Headache Society, “Surgery for migraine is a last-resort option and is probably not appropriate for most sufferers. To date, there are no convincing or definitive data that show its long-term value.”

The benefit of occipital nerve stimulation for CM is still being assessed. In a study of 110 subjects with CM with occipital nerve stimulation, 75/110 subjects were assigned to a treatment group and responders to an occipital nerve block were randomized to adjustable stimulation (AS), preset stimulation (PS), or medical management (MM) groups. After three months, a 50 percent or greater reduction in headaches was reported as follows: 39 percent, AS; six percent, PS; 0 percent, MM. In the first published study of subjects (n = 125) with CM assigned to sham stimulation or active intermittent occipital nerve stimulation for 12 weeks, there was no significant difference in the decrease of the number of headache days per month. Significant benefit was found in a study of 30 randomized patients (29 completers) who responded to a stimulation trial and were then randomized to “stimulation on” and “stimulation off” arms, crossed over after 1 month or when their headaches worsened, and then switched on for all patients. The second study of patients with CM randomized 2:1 to active (n = 105) or sham (n = 52) stimulation found no significant difference in the percentage of responders in the active compared with the control group who received sham stimulation at 12 weeks in the primary end point of achieving a 50 percent or greater reduction in mean daily visual analog scale scores. However, there was a significant difference in the percentage of active stimulation patients that achieved a 30 percent reduction, headache days, and migraine-related disability. Dual occipital and supraorbital nerve stimulation may produce better efficacy. Adverse events include lead migration, infections, unpleasant traction on the connecting cables, paresthesias, and battery depletion. There is limited long-term evidence of efficacy.

**THE PROGNOSIS OF CM**

In a mailed questionnaire study of 383 patients with self-reported CM, 26 percent had remitted CM over two years (defined as fewer than 10 headache days per month). Predictors of remission included a lower baseline headache frequency (less days per month) and the absence of alldynia. In a study of 136 patients with transformed migraine presenting to a specialty headache clinic followed for one year, 70 percent reverted to episodic migraine. Predictions of reversion included complete withdrawal of overused medications, compliance with preventive medication treatments, and regular physical exercise.

Some 350 years after Willis had nothing but compassion to offer chronic migraineurs, many (no population-based data available) are still refractory to treatment. As our best treatments have only become available in the last decade, hopefully the pace of development will continue to accelerate for this disabling, poorly understood, underrecognized, undertreated, and underfunded disorder.
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