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Expert Opinion

A Rational Approach to the Management of Chronic Migraine

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About 2% of the adult population has chronic migraine with only 20% diagnosed with this disorder. Those with medication overuse may improve with withdrawal of overuse medications. The intravenous dihydroergotamine regimen usually produces short-term benefit for those with medically refractory chronic migraine. OnabotulinumtoxinA and topiramate have shown efficacy in large placebo-controlled randomized trials. Sodium valproate, gabapentin, tizanidine, amitriptyline, fluoxetine, zonisamide, and possibly memantine may be alternative or possibly combined treatment options but with lesser levels of evidence supporting their use. Preliminary evidence suggests that nerve blocks might be beneficial. Acupuncture, biofeedback, relaxation therapy, and cognitive behavioral therapy might be of benefit. Surgical treatments including bariatric and deactivation of trigger points are of growing interest but not appropriate for most sufferers. Occipital nerve stimulation is a promising treatment with ongoing studies defining its use.

Key words: chronic migraine, treatment, medication overuse, prevention

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In 1672,[1] 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.[2-4] (Lady Conway's disabling migraines inspired her concept that pain and suffering were purgative with the ultimate aim of restoring creatures to moral and metaphysical perfection.) Has our treatment of CM improved?

CLINICAL HISTORY

This 38-year-old woman has a 20-year history of migraine without aura, with headaches consistent with CMs occurring about 20 days per month or more for the last 3 years, which gradually increased from several times per month. She typically takes an acetaminophen, aspirin, and caffeine combination which may relieve the pain in a few hours, although some headaches last 1-2 days. Stress and her menses are triggers. She has never been on prescription headache medications. Past medical history is otherwise negative except for symptoms consistent with generalized anxiety disorder not on medication. Her body mass index is 30.5.

Questions.—What is the epidemiology of chronic migraine? How do you treat medication overuse? What is the intravenous dihydroergotamine transitional therapy protocol and is it effective? What is the evidence for prescription and complementary preventive treatments? Are surgical treatments effective? What is the prognosis?

EXPERT OPINION

How Common Is CM and What Are the Risk Factors?—About 35 million people in the United

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States have migraines annually. CM, or transformed migraine, is a complication of intermittent migraine with 2.5% progressing yearly from episodic to CM. About 3.2 million adults have CM. 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%. Risk factors for transformation include medication overuse (especially opiates and barbiturate combinations), high caffeine consumption, female gender, stressful life events, anxiety, 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, arthritis, and diabetes.[5,6]

Only 20% of patients with CM are diagnosed with the disorder[7] and 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. Only 33% of those with CM are using preventive medications.

Although the evidence should be taken with caution, medication overuse or rebound can occur with the use of opiates 8 or more days per month with the effect more pronounced in men, triptans in those with a high frequency of headache at baseline, or butalbital combinations 5 or more days per month with the effect more pronounced in women.[8] Triptans on 10 or more days a month or simple analgesics or any combination of triptans and analgesic opioids on 15 or more days per month on a regular basis for more than 3 months without overuse of any single class alone may result in medication-overuse headache (MOH).[9] Of course, in addition to causing medication overuse, chronic use of butalbital[10] and opiates[11] can lead to habituation and other side effects.

How Do You Treat 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 200 mg daily in susceptible individuals can lead to MOH,[12,13] and some individuals have withdrawal symptoms with even low doses of 100 mg daily.[14] Overused medications can be tapered off. For those taking high-frequency butalbital combinations, phenobarbitatal 30 mg twice a day (bid) can be substituted for 2 weeks followed by 15 mg bid for 2 weeks (abrupt withdrawal can result in seizures). For those taking high doses of opioids, clonidine 0.1-0.2 mg three times a day (tid) titrated up or down based on symptoms or clonidine patch 0.1-0.2 mg/24 hours for 1-2 weeks.

There are several transitional therapy options. Naproxen 500 mg bid for 1-2 weeks may be used alone or can be combined with tizanidine starting at 2 mg at bedtime (hs) and titrating up.

The evidence for efficacy for glucocorticoids is uncertain.[15] The most recent study, a prospective double-blind, placebo-controlled trial of 96 consecutive German patients with MOH randomized to either 100 mg of prednisone or placebo over 5 days, found that patients treated with prednisone requested less rescue medication within the first 5 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.[16]

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.[17]

A small pilot study suggested some benefit of nabilone (a cannabinoid 1-receptor agonist) for intractable MOH.[18] Larger scale studies will be of interest.

What Is the IV DHE Transitional Therapy Protocol and Is It Effective?—The protocol was first proposed by Raskin in 1986[19] and has been modified since with the following protocol recommended by Nagy et al for those without contraindications to use:[20] Obtain a baseline electrocardiogram, complete blood count, comprehensive metabolic profile, prothrombin time, partial thromboplastin time, international normalized ratio, urinary pregnancy test if female, and toxicology screen. Pretreat with 4 mg 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[21] [some clinicians use metoclopramide 10 mg IV instead]). Day 1: DHE 0.5 mg in 100 mL of normal saline (NS) IV over 1 hour. If well tolerated, second dose 8 hours later of 0.75 mg in 250 mL of NS IV over 1 hour. Days 2-5: third and subsequent doses 1 mg in 250 mL of NS over 1 hour IV every 8 hours with the goal of a cumulative total dose of 11.25 mg (±1 mg) over 5 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 4 mg IV every 8 hours as necessary; addition of a second anti-emetic such as promethazine 12.5 mg to 25 mg IV every 12 hours; administration of DHE over 2-3 hours or not escalating the DHE dose or reducing the dose. For muscle cramps or joint pain, consider naproxen 500 mg 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 4 days per week, 74% had some benefit with this protocol and 50% had moderate or excellent benefit. During treatment, 67% had headache attack freedom and 75% had headache freedom within 1 month of completion with a duration of effect for an average of 28 days. Preventive medications were started 1 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% (DHE stopped in 4%); leg cramps, 28%; diarrhea, 12%; abdominal cramps, 10%; and chest tightness, 3%.

Some clinicians use IV valproate when DHE is contraindicated or in addition to DHE (loading dose of 15 mg/kg infused over 30 minutes followed by 5 mg/kg infused over 15 minutes every 8 hours).[22] Some clinicians add ketorolac 30 mg IV every 12 hours prn headache for 3 days.

Are There Any FDA-Approved Treatments for CM?—Yes, one, onabotulinumtoxinA, which was approved by the FDA in October, 2010, based upon the 2 phase 3 research evaluating migraine prophylaxis therapy (PREEMPT) trials.[23,24] The approved treatment is administration of 155 units in 31 fixed-site fixed-dose injections of 5 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% of onabotulinumtoxinA-treated patients had a ≥50% decrease from baseline in frequency of headache days (primary end point) compared with 35.1% of placebo-treated patients.[25] OnabotulinumtoxinA was as effective in the 65.3% of the pooled patients from the 2 studies with medication overuse as the total PREEMPT population of 1384 adults with and without medication overuse.[26,27] 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%; after treatment cycle 3, 7.4-10.3%.[28] In this pooled population, discontinuation due to adverse events was 3.8% for onabotulinumtoxinA vs 1.2% for placebo.

Although onabotulinumtoxinA is an expensive treatment, the costs may be reduced by less triptan use.[29] In addition, a retrospective study of 223 patients with CM who were treated with 2 injection cycles found a 39% offset of the estimated cost of the injections by a reduction in migraine-related emergency department visits, hospitalizations, and urgent care visits.[30]

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 200 mg daily,[31] at month 9, 41% in the onabotulinumtoxinA group and 43% in the topiramate group had a 50% or greater reduction in headache days (with 2.7% of onabotulinumtoxinA patients stopping treatment due to adverse events vs 24.1% for topiramate). In the second study, 59 subjects were randomized to topiramate up to 200 mg daily and placebo injections or onabotulinumtoxinA up to 200 units.[32] 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, andamitriptyline.

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 100 mg per day (including for those with medication overuse which was a surprising and controversial finding) with 22% having a 50% or greater reduction in headache days per month vs 0% 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; $P = .02$).[33] 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 100 mg 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; $P = .010$).[34] A post-hoc analysis in patients with medication overuse (mainly triptans) showed a strong trend in favor of topiramate ($P < .059$).[35]

Seventy subjects with chronic daily headache (including 29 with CM) were randomized to sodium valproate 500 mg twice daily or placebo for 3 months. There was significant improvement in pain levels and frequency in the CM subgroup.[36]

An RCT cross-over study of 133 subjects with chronic daily headache (two thirds with migraine features) randomized to gabapentin 2400 mg daily or placebo found significantly higher headache free rates in those on gabapentin.[37]

An RCT study of 134 subjects with chronic daily headache (77% with CM) randomized to tizanidine (slowly titrated to a target dose of 24 mg per day as tolerated) or placebo found significantly fewer headache days per week in those on tizanidine.[38]

In a reanalysis of an RCT study published in 1979, subjects titrated to 100 mg daily of amitriptyline as tolerated had a significantly superior reduction in headache frequency at 16 weeks.[39] An RCT trial of fluoxetine titrated to 40 mg daily depending upon patient response for chronic daily headache (n = 64) found significant improvement in overall headache status at 3 months.[40]

Surprisingly, despite the established use of propranolol for episodic migraine, there is no RCT evidence supporting its efficacy for CM, although β-blockers are commonly used and recommended in therapy reviews.

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 150 mg twice a day,[41] zonisamide titrated as high as 400 mg daily (in those with no response or intolerant to topiramate),[42,43] and possibly memantine titrated to 10-20 mg daily.[44]

Should Patients With Medication Overuse Be Tapered Off the 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.[45] Other authorities would like to see additional studies and believe better results may be achieved with withdrawal first and then preventive medication use.[46] The medication being overused may also be quite significant as triptan overuse may be easier to treat than butalbital and opiate overuse.[33]

Is Combination Therapy Effective?—An RCT of 191 subjects with CM inadequately controlled with topiramate (50-100 mg/day) to either propranolol long acting (LA) 240 mg/day or placebo found no evidence of benefit from the addition of propranolol.[47] 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.[48]

Might Nerve Blocks Be Effective?—In an open-label single treatment arm study of 150 chronic migraineurs with a prominent cervicogenic element (at least 50% of their most severe headaches arose from 1 side of the occipital skull base or both) who received unilateral or bilateral occipital nerve blocks with local anesthetic and steroid, 52% experienced a 50% or greater reduction in headache days over the

month following the procedure compared with the pretreatment baseline month.[49]

A prospective open-label trial was performed of 218 patients with intractable CM without butalbital or opioid medication overuse who received a fixed-dose (0.1 cc of 0.25% bupivacaine) and fixed-site (10 at greater and lesser occipital nerves, 5 at auriculotemporal and zygomaticotemporal, 2 at supraorbital and supratrochlear areas bilaterally) pericranial injections every 3 months.[50] After 12 months, 53.2% of patients had a more than 50% reduction in mean frequency of headache days. Further confirmation of the efficacy of nerve blocks will be of interest.

Are Alternative or Complementary Treatments Effective for CM?—Acupuncture may be effective for CM[51] with additional benefit when added to medical management.[52] Another study found safflower seed acupuncture point injection more effective than NS in subjects with chronic daily headache.[53] 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 100 mg 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.[54]

Behavioral sleep modification may be effective for transformed migraine.[55] 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.[56] Biofeedback-assisted relaxation may supplement pharmacologic therapy based upon a 3-year follow-up study of chronic daily headache associated with medication overuse.[57] 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.[58]

Are Surgical Treatments Effective for CM?—The risk of migraine frequency and severity increases with increasing degrees of obesity.[59] Two small observational studies have found a significant reduction in episodic migraine frequency after bariatric surgery.[60,61] 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.[62] The confirmation of trigger sites using onabotulinumtoxinA does not significantly improve the outcome of migraine surgery.[63] A high sham surgery response rate and patient selection criteria remain problematic. In the view 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."[64]

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.[65] After 3 months, a 50% or greater reduction in headaches was reported as follows: 39%, AS; 6%, PS; 0%, 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.[66] 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.[67] 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% or greater reduction in mean daily visual analog scale scores.[68] However, there was a significant difference in the percentage of active

stimulation patients that achieved a 30% reduction, headache days, and migraine-related disability.

What is the Prognosis of CM?—In a mailed questionnaire study of 383 patients with self-reported CM, 26% had remitted CM over 2 years (defined as few than 10 headache days per month).[69] Predictors of remission included a lower baseline headache frequency (less days per month) and the absence of allodynia.

In a study of 136 patients with transformed migraine presenting to a specialty headache clinic followed for 1 year, 70% reverted to episodic migraine.[70] Predictions of reversion included complete withdrawal of overused medications, compliance with preventive medication treatments, and regular physical exercise.

CONCLUSION

Some 350 years after Willis had nothing but compassion to offer chronic migraineurs, many[71] (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.[72]

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