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CME ACTIVITY

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The Changing Landscape  
of Chronic Migraine:  
**Insights on Patient  
Assessment and  
Integration of Newer  
Treatment Strategies**

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Release Date: December 2015  
Expiration Date: December 2016

Jointly provided by Dannemiller and Bryn Mawr Communications, LLC  
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## INTENDED AUDIENCE

This certified CME activity is designed for neurologists involved in the diagnosis and management of chronic headache.

## LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

1. Distinguish between various forms of chronic headache, including migraine.
2. Identify the challenges of chronic headache management, including the impact of the disease on affected individuals.
3. Describe principles of acute and preventive therapy for chronic headache and their limitations.
4. Recognize the indications for prophylactic migraine therapy and effectively initiate prophylactic treatment.
5. Utilize optimal preventive and palliative approaches for chronic headache based on individual patient characteristics.

## STATEMENT OF NEED

Chronic headache is a common and costly neurological disorder. Estimates suggest that about 11 percent of adult populations in Western countries are affected by migraine.<sup>1</sup> Prevalence is highest during the peak productive years—between the ages of 25 and 55,<sup>2</sup> accounting for the significant economic impact of the condition.

Despite the significant impact of migraine on the individual and society, diagnosis and management remain challenging. Studies indicate that between 56 percent and 91 percent of chronic headache sufferers seek treatment from healthcare providers, yet only one-third report having received a diagnosis of a specific headache condition.<sup>3</sup> As recently stated in a publication by Olesen, et al., “there is a huge unmet need for better pharmacotherapy.”<sup>4</sup>

For the majority of patients presenting for neurological evaluation of headaches, effective headache prophylaxis is the key to improved outcomes. Preventative treatments, however, are generally underutilized.<sup>1</sup> One study found that approximately 90 percent of migraineurs have moderate to severe pain, but most “treat their headaches with acute treatments to the exclusion of preventive drugs.”<sup>5</sup> Indications for preventive therapy include frequent or very severe headaches, excessive acute medication use, severe disability, and patient preference.<sup>6</sup> However, evidence suggests that most patients do not pursue effective prophylactic treatment. As of 2015, the Migraine Research Foundation says only 4% of migraine sufferers who seek medical care consult headache and pain special-

ists. Depression, anxiety, and sleep disturbances are common for those with chronic migraine.<sup>7</sup>

Many effective prophylactic medications are associated with significant adverse events (AEs) and often take a few months to notice clinical improvement. In addition, some patients prefer to avoid daily medication and patient compliance can be an issue.<sup>5</sup>

Most preventive medications for migraine, such as many beta-adrenergic blockers, antidepressants, and anticonvulsants, have not been rigorously studied for the treatment of chronic migraine (CM).

Discovered by serendipity, onabotulinum toxin A (BoNT-A) represents the only drug specifically approved for CM prophylaxis after randomized and rigorous studies.<sup>9</sup> Clinicians usually perform BoNTA injections every three months, and pain relief typically begins in less than two weeks. Recent clinical trials demonstrate that BoNTA is effective in the treatment of chronic migraine,<sup>10,11</sup> leading to approval by the US Food and Drug Administration of BoNTA for CM prophylaxis. There are many other reports of BoNTA use in other headache disorders, such as tension-headache, episodic migraine, cluster headache and nummular headache.<sup>12-25</sup>

Medical devices represent a new, growing, and important avenue that headache specialists must familiarize themselves with. When asked about the biggest developments in headache care at the end of 2014, David Dodick, MD, President of American Headache Society, Editor in Chief of Cephalalgia, and Professor of Neurology at the Mayo Clinic, listed the FDA approval of two noninvasive minimal risk devices for the acute (sTMS) and preventive (Cefaly®) treatment of migraine.<sup>26</sup> “Long term efficacy and their place in migraine therapy awaits further study and experience but they may represent a non-drug and non-invasive treatment option for some patients,” he said.

In February 2015, the American Headache Society updated its acute migraine guidelines, providing a new analysis on the strength of the evidence.<sup>27</sup> “Some of the newer drugs in combination work. We have evidence, for example, for the new DHE inhaled product, for the sumatriptan patch, and for new formulations of non-steroidals,” said study author Stephen Silberstein, MD, FACP of Jefferson University Hospitals, in Philadelphia.

**Unmet Need to Treat Chronic Migraine and Cardiovascular Disease.** Numerous studies have described a relationship between chronic migraine and stroke, and there is emerging evidence that migraine is also associated with cardiovascular disease, according to a 2015 study.<sup>28</sup> The combination of

migraine and both cerebrovascular and cardiovascular disease has implications for therapy, the authors said, and noted some drugs are contraindicated to treat migraine attacks (ergots, triptans) or for migraine prevention in patients after transient ischemic attack (TIA)/ischemic stroke. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with cerebral bleeding. Some drugs for the treatment of acute migraine attacks are contraindicated in patients with symptomatic coronary heart disease. "Given the large number of patients with comorbid migraine and cardiovascular as well as cerebrovascular disease, there is an unmet need to treat these patients," the authors write.

**Pipeline.** Until now, only an acute class of drugs (triptans) have been specifically designed and approved for migraine. However, monoclonal CGRP (calcitonin gene-related peptide) antibodies represent a new class of biologics designed for migraine prevention. "While many potential migraine drug targets have emerged over the past 30 years, none have been more thoroughly investigated and appear more promising than CGRP and its receptor," according to Dr. Dodick. "The preliminary efficacy and safety findings from these studies are very encouraging." Confirmation will await the completion of two other Phase II studies with two other antibodies and future Phase III studies.

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Computer or smart phone with internet access.

Web Browser (IE 7.0+ or Webkit/Mozilla Compatible) with JavaScript enabled.

A telefax machine.

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Randolph W. Evans, MD, has served on the Speaker's Bureau for Allergan, Depomed, Pernix, and Teva. He has served as a Consultant/Advisory board member for Lilly.

Deborah I. Friedman, MD, MPH, has served as a Speaker and Consultant for Allergan and has received Grant support from Autonomic Technologies, Inc, Merck, ElectroCore, and Eli Lilly. She has served as a Consultant /Advisory Board member for Avanir and Supernus and Advisory Board/Speaker for Teva Pharmaceuticals.

Paul G. Mathew, MD, has served as a Consultant/Advisory board member for Analgesic Solutions and Teva Pharmaceuticals.

Stephen D. Silberstein, MD, has served as a Consultant/ Advisory board member for Alder Biopharmaceuticals, Allergan, Inc., Amgen, Avanir Pharmaceuticals, Inc., Curelator, Inc., Depomed, Dr. Reddy's Laboratories, eNeura, Inc. ElectroCore Medical, LLC, Lilly USA, Supernus Pharmaceuticals, Inc., Teva Pharmaceuticals, and Trigemina, Inc.

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# The Changing Landscape of Chronic Migraine: Insights on Patient Assessment and Integration of Newer Treatment Strategies

An estimated three million Americans have chronic migraine (CM); approximately 80 percent of affected individuals are women. Data suggest that four out of five migraineurs are undiagnosed.<sup>1</sup> Additionally, many individuals are incorrectly diagnosed with tension headache, sinus headache, or stress headache.<sup>2,3</sup> Furthermore, research suggests that up to one-third of patients diagnosed with migraine do not use acute migraine-specific therapies.<sup>1</sup>

Arriving at an accurate diagnosis of migraine is essential to ultimately uncovering a diagnosis of chronic migraine. Identification of chronic migraine is a clinical challenge, yet the need for accurate diagnosis is paramount. Once the diagnosis of chronic migraine is reached, the clinician must assess two factors:

- 1.) Is there a secondary cause of headaches?
- 2.) Does this patient over-use acute medicines?

Management of chronic migraine differs from other headache types. The patient with a confirmed diagnosis of

## CHRONIC MIGRAINE DIAGNOSIS

*International Classification of Headache Disorders, 3rd Edition, Beta Version, (ICHD3)*, classifies Chronic Migraine as:

- $\geq 15$  headache days per month
- For at least three months
- Eight days of which must be migraine

“When questioning patients about headache frequency, it is essential to clarify that the question refers to any headache. Some migraineurs may consider ‘low-grade’ headaches insignificant to their neurological evaluation for migraine.”

chronic migraine is eligible for certain prophylactic treatments, and the documented diagnosis may be a pre-requisite for insurance coverage of certain treatments. Of note, research suggests that while over one-third of migraineurs are eligible for preventive treatments, only three to 13 percent currently use them.<sup>4</sup>

Diagnosis of chronic migraine is guided by the *International Classification of Headache Disorders, 3rd Edition, Beta Version, (ICHD3)*, which has been widely used in practice since its publication in 2013.<sup>5</sup> Episodic migraine is distinguished from chronic migraine based on total headache days per month. The patient is considered to have CM when he or she experiences 15 headache days per month, for at least three months, eight days of which must be migraine. In short, a patient is diagnosed with chronic migraine even when all of his/her headaches do not truly meet criteria for migraine. It should be noted that data show that patients with chronic migraine tend to have more than 15 headache days per month, on average, but

may have fewer than 15 headaches in a given month.<sup>6</sup> By definition, a patient could have eight days of migraine a month with 16 headache days overall, and be diagnosed with chronic migraine. In contrast, a patient with 14 days of severe migraine a month and no other headache type does not, by definition, have chronic migraine.

A diagnostic challenge often is distinguishing migraine from other headache types. Attempts to classify the type of headache based on the response to a specific treatment (i.e., if the patient responds to a triptan, then the headache is migraine) are not appropriate. Such strategies assume the patient has access to triptans, which may not be the case. In addition, some patients may have unequal responses between triptans, or may not respond to triptans at all. For example, if a patient does not respond well to sumatriptan, he/she may be labeled as not having migraine, when he/she would respond well to orally dissolving rizatriptan, which was never prescribed.<sup>7</sup>

When questioning patients about headache frequency, it is essential to clarify that the question refers to any

headache. Some migraineurs may consider “low-grade” headaches insignificant to their neurological evaluation for migraine. If patients do not inform the clinician of these headaches, then an accurate diagnosis may not be possible. In addition to asking individuals how frequently they experience a headache, a confirmatory follow-up question would be to ask about headache-free days. Simply inquire how many days per month the patient is completely pain-free. This may yield a more accurate sense of the patient’s experience.

Additionally, patients may fail to report certain characteristics of their headaches during clinical examination, so that migraines become miscategorized. Eliciting patient experience of photo- or phonophobia, for example, may require follow-up and indirect questioning. In one study, patients who self-reported that they did not experience photophobia would, on subsequent questioning, reveal that they preferred to be in a dark room while experiencing a headache. In fact, in that study, up to 85 percent of subjects who denied photo- or phonophobia eventually



**Dr. Evans:** We all often have this experience where a patient will come in and say, I’ve only had eight headache days per month, only talking about their migraines and not even mentioning their low grade or milder headaches to you. And then along those same lines they’ll say, “Oh, I have a little bit of a headache today but the lights aren’t bothering me.” And many people say, “Oh, this is just the patient’s typical tension type headache.” But then you turn the lights down and they’re much more comfortable. In chronic migraine, it is easy for the clinician to get an underestimate of frequency if you don’t ask for the number of all headache days or headache-free days.

**Dr. Friedman:** We do the MIDAS scale on all of our patients. And many of them don’t include mild headache days, because to the patient it just doesn’t count. Whereas for us, it would change the diagnosis. And I think that physicians and neurologists that don’t see a lot of headache patients probably make the mistake of not asking about all headache days.

**Dr. Evans:** We did a prospective study in 2008 where we asked 85 consecutive migraineurs whether light/noise bothered them during a headache, which 24% denied.<sup>8</sup> If they said, no, then we asked, “During a headache, would you prefer to be in bright sunlight or in a dark room and would you prefer to be in a room with loud music or a quiet room?” 93% endorsed these questions when they initially said “No” to light/noise sensitivity.

**Dr. Friedman:** I think you can also make the same point about nausea. Asking patients about nausea is just as problematic. Many people interpret nausea as vomiting. And if you don’t ask them, “Can you eat during a headache?” then likely you’re not going to get the full picture.

**TABLE 1. SUMMARY OF PATIENT ASSESSMENT STRATEGIES**

- Question patients about all headache days, not just migraine days.
- Note that patients may self-classify certain “low-grade” headaches as inconsequential to the neurological evaluation.
- Also ask about number of headache-free days.
- Use follow-up questions about symptoms such as photo- or phonophobia. For example, “Would you rather be in a dark room during migraines?”
- Consider administering the MIDAS questionnaire. Provide coaching to assure accurate assessment.

volunteered that they preferred to avoid noise or light during headaches when asked additional questions (see Evans comments).<sup>8</sup> In clinical practice, gauging a patient’s response after turning down the lights in an examination room may also be useful to determine the presence of photophobia. Interestingly, many patients prefer the dark, even in the absence of a headache at the time of the clinic visit.

Similarly, patients who deny experiencing nausea may ultimately admit to feeling “queasy” or otherwise suggesting that they experience nausea. Consider that patients may not understand the word nausea but may admit they feel as if they want to vomit.

The MIDAS (Migraine Disability Assessment) questionnaire continues to be a useful tool for assessing the frequency, quality, and impact of headache on a given patient,<sup>9</sup> although patients often need individual coaching and instruction to fill it out correctly. The MIDAS may be administered to all patients as a screening tool in the waiting room or exam room.

The patient’s experience of migraine, its frequency and its relative impact on daily function and quality of life may all be factors in selecting preventive and rescue medications. Given that oral preventive therapies are all associated with potential side effects, the relative benefit of treatment—weighed against the patient’s disease experience—versus side effects requires consideration.

Chronic migraine is a recognized and scientifically supported diagnosis. Yet, some patients may have received an inaccurate diagnosis like sinus headache<sup>3</sup> in the past

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“Multiple factors may contribute to non-adherence. Poor tolerability may be a common contributing factor. The old adage of ‘Start low and go slow,’ may be especially appropriate to the management of migraine. Migraineurs as a group appear anecdotally to have increased sensitivity to medication side effects. Patients who experience troublesome unwanted side effects of a drug may discontinue it, despite any potential benefit.”

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and may be reluctant to accept that they actually have migraine.

### MIGRAINE PROPHYLAXIS

The only treatment FDA approved for prevention of chronic migraine is onabotulinotoxinA (Botox, Allergan) injection. However, several oral therapies are approved for prevention of episodic migraine, and others are used off-label for the prevention of episodic or chronic migraine.

Any oral therapy used as a preventative is expected to provide optimal effect only after six to eight weeks of continuous dosing. Failure to allow a sufficient trial at the target dose can lead prescribers and patients to label a treatment as a failure, when it might have proven effective had it been given a sufficient trial.

Adherence is a significant issue in preventive migraine care. Research shows that rates of therapeutic adherence are low across chronic disease states, including life-threatening conditions.<sup>10</sup> Consider that among patients with myocardial infarction, nearly one-third had discontinued at least one medication by six months,<sup>10</sup> and it is no surprise headache patients are non-adherent. Research on adherence in CM is scant, but one analysis shows therapeutic adherence in adult headache patients may be as low as 25 percent.<sup>11</sup>

Multiple factors may contribute to non-adherence. Poor tolerability may be a common contributing factor. The old adage of “start low and go slow,” may be especially appropriate to the management of migraine. Migraineurs as a group appear anecdotally to have increased sensitivity to medication side effects. Patients who experience troublesome unwanted side effects of a drug may discontinue

**TABLE 2. PREVENTIVE MEDICATIONS FOR CHRONIC MIGRAINE WITH TARGET DOSES OR DOSE RANGES**

**Randomized controlled trials**

- OnabotulinumtoxinA 155 units (FDA approved)
- Topiramate 100-200 mg daily
- Divalproex sodium 500 mg bid
- Gabapentin 800 mg tid
- Tizanidine 8 mg tid
- Amitriptyline 100 mg daily
- Fluoxetine 40 mg daily
- Candesartan 16 mg daily
- Propranolol 160 mg long acting daily

**Open Label**

- Pregabalin 150 mg bid
- Zonisamide 100-400 mg daily
- Atenolol 50 mg daily
- Olanzapine 2.5-35 mg daily
- Methylergonovine maleate 0.2-0.4 mg tid
- Memantine 10-20 mg daily in divided doses
- Combined?

*From Evans RW. Prevention of chronic migraine. Practical Neurology; 2013; Nov/Dec, 29.*

it, despite any potential benefit. Conversely, certain side effects, such as mild sedative effects, may be beneficial for certain patients with chronic headache and sleep disturbances.

Medication side effects may be minimized or avoided with lower doses of medication. Titration is a useful strategy to achieve balance between drug efficacy and tolerability. When writing a prescription with a target maximum dose and titration instructions, advise patients that they need not achieve the maximum if they experience sufficient benefit at a lower dose.

The evidence for efficacy for chronic migraine<sup>12</sup> is different than for episodic migraine (Table 2). In brief, onabotulinumtoxinA and topiramate have each shown efficacy in large placebo-controlled randomized trials. Divalproex sodium, gabapentin, tizanidine, amitriptyline, fluoxetine, propranolol, atenolol, candesartan, zonisamide, methylergonovine maleate, and possibly memantine may be alternatives.

OnabotulinumtoxinA injections are approved for prevention of CM. In clinical trials, it was shown to reduce the frequency and severity of headache days.<sup>13</sup> In an analysis of patients with medication overuse headache, while OnabotulinumtoxinA injections were not associated with a reduction in headache frequency compared to placebo, active treatment was associated with a significant reduction in acute pain drug use.<sup>14</sup> OnabotulinumtoxinA has also been shown to improve depression scores among patients with CM.<sup>15</sup> While injections provided in the office may be associated with improved adherence compared to daily medication use, the non-responder rate, potential costs, and lack of head-to-head comparisons against oral therapies are all factors to assess clinically.<sup>16</sup>

Poly-pharmacy may be worth considering for long-term patient management.<sup>17</sup> When a patient experiences benefit but has incomplete response on one drug, adding a second drug from a different class may provide better control than switching to a new drug entirely.

**MIGRAINE BY THE NUMBERS**

**3 Million:** Estimated number of Americans who have chronic migraine (CM).

**80%:** Approximate proportion of affected individuals who are women.

**4 out of 5:** Suggested proportion of undiagnosed migraineurs.

Divalproex sodium is now contraindicated in women of child-bearing potential for the treatment of migraine, although it is not contraindicated in pregnant women treated for epilepsy. Therefore, it is not as commonly used as other AEDs for migraine prevention. Topiramate is more widely used, and is generally associated with a favorable safety profile. It should be noted that topiramate also has been associated with risk for birth defects and is not recommended for migraine prevention in pregnant women.

AEDs used in migraine prevention have been associated with side effects such as sleepiness, GI intolerance, pares-

thesias, and CNS effects.<sup>18</sup> In one study, half of patients who had discontinued prophylactic topiramate at one year had done so as a result of intolerable side effects.<sup>19</sup> When an extended-release formulation of an AED is available, clinical experience suggests that it may be associated with better tolerability.

When patients fail to respond to medication, questioning is essential. Patients may, for example, acknowledge lack of adherence. In the case of generics, a patient well-controlled on one formulation may experience a change in efficacy if switched to a different formulation of the same

**TABLE 3. RESCUE THERAPIES FOR MIGRAINE**

**Specific medications**

- Effective (Level A)
- Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]
- Dihydroergotamine (nasal spray, inhaler)
- Probably Effective (Level B)
- Ergotamine and other forms of dihydroergotamine

**Non-specific medications**

- Effective (Level A)
- Acetaminophen
- Nonsteroidal anti-inflammatory drugs: aspirin, diclofenac, ibuprofen, and naproxen
- Opioids (butorphanol nasal spray)
- Sumatriptan/naproxen
- Combination acetaminophen/aspirin/caffeine
- Probably Effective (Level B)
- Ketoprofen
- IV and IM ketorolac, flurbiprofen, intravenous magnesium (in migraine with aura)
- Combination of isometheptene compounds, codeine/acetaminophen and tramadol/acetaminophen
- Antiemetics: prochlorperazine, droperidol, chlorpromazine, and metoclopramide

—*Headache*. 2015 Jan;55(1):3-20

active drug. Checking patient blood levels may elucidate either a lack of drug absorption or failure to take medication.

The SNRI's as a class are generally benign and seem to be fairly effective for numerous pain disorders including headache.

Occipital nerve blocks (ONB), popular for acute migraine treatment, have been suggested to have a preventive effect in CM, as well. In one study, 30 percent of subjects who received occipital nerve blocks (2.5 ml 0.5% bupivacaine plus 0.5 ml (20 mg) methylprednisolone) had at least a 50 percent reduction in moderate or severe headache days. However, this decrease was similar to the reduction in headache days among controls (2.75 ml normal saline plus 0.25 ml 1% lidocaine without epinephrine).<sup>20</sup>

Long-term outcomes with ONB may be optimized with relatively large volume injections or the combined injection of the occipital nerve along with trigger point injections (TPI), although this has not been formally studied. A survey of headache specialists revealed that TPIs are widely performed. While 69 percent of specialists performed NBs, 75 percent performed TPIs. The most common indications for the use of NBs were occipital neuralgia and chronic migraine (CM), and the most common indications for the use of TPIs were chronic tension-type headache and CM.<sup>21</sup>

### ABORTIVE THERAPIES

Triptans and dihydroergotamine are considered to be effective headache-specific rescue treatments, while effective non-specific treatments include acetaminophen, nonsteroidal anti-inflammatory drugs (aspirin, diclofenac,

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“Just as it is important to educate patients on the diagnosis of migraine, as opposed to other headache types, it can also be helpful to educate them on the fact that migraine is an actual disease process with a genetic basis. Typically, patients will identify family members also affected.”

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ibuprofen, and naproxen), opioids (butorphanol nasal spray), sumatriptan/naproxen, and the combination of acetaminophen/aspirin/caffeine.<sup>22</sup> (Table 3)

Despite the concerns associated with opioid prescribing, their use is at times unavoidable in the management of migraine. In fact, for certain groups, such as pregnant women or those with cardiovascular disease and/or gastrointestinal bleeds, opioids may be a safe option where other agents are contraindicated.

An important aspect of prescribing opioids to minimize abuse is to set limits and avoid medication overuse. Patients can be counseled that the prescriber is writing for 12 to 15 acetaminophen with codeine or hydrocodone per month, for example. Establish clearly that this is the maximum and will not change. There is some evidence that the risk of rebound with an opiate is decreased relative to a barbi-



**Dr. Mathew:** In my practice, when I titrate a medication, although we often use weekly titrations, I tell the patient, “If you’re feeling somewhat comfortable with a particular dose, hang out there for a couple of weeks, see how you do. If you’re feeling just fine, there’s no need to reach the goal dose that’s written on the prescription.”

I think it’s empowering to allow patients to be in charge of their own therapeutic decision making and I tell them, “nobody knows your body as well as you. If you find a low dose that works well for you, I’m happy that you’re on a lower dose of medication that controls your symptoms.”

**Dr. Friedman:** I do the same thing.



**Dr. Silberstein:** I think that the intermittent use of infrequent opioids, butalbital, is not a problem... When it becomes more frequent, it is a problem. The only patient I can never get better are those who are on chronic opioids.

**Dr. Mathew:** So do you try to get these patients that use chronic opioids on methadone or suboxone? I've had patients make that switch and they do amazingly well. If there's zero hope of getting them off their opioids, transitioning them to suboxone or methadone is a good option.

turate, such as butalbital, with or without caffeine which may occur with use more than four days per month.<sup>23</sup>

Ketoprofen, intravenous and intramuscular ketorolac, flurbiprofen, intravenous magnesium (in migraine with aura), and the combination of isometheptene compounds, codeine/acetaminophen and tramadol/acetaminophen, the antiemetics prochlorperazine, droperidol, chlorproma-

zine, and metoclopramide are all considered probably effective.<sup>24</sup> Injectable ketorolac works rapidly and effectively for many migraineurs.

The role of NSAIDs in medication overuse headache is controversial, as some prescribers feel there is no or limited risk. The risk of GI effects associated with NSAIDs may be more clinically important than the risk for MOH.

There now are two approved devices available in the US for management of CM. The Cefaly device (Cefaly Technology) is currently available by prescription. Data suggest a 50 percent responder rate for the device over three months, with reductions in attack frequency and headache days. Subjects using Cefaly reduced acute medication intake by 37 percent.<sup>25</sup>

The Spring TMS (eNeura), although approved by the FDA, still has a limited distribution to individuals who are part of a registry. In a clinical study of migraine with aura, early application of sTMS resulted in increased freedom from pain at two hours compared with sham stimulation. Pain freedom was sustained 24 to 48 hours after treatment.<sup>26</sup>

### Therapeutic Pipeline

Awaiting approval for migraine is the noninvasive Vagal Nerve Stimulator (nVNS). This is a non-drug treatment approach for both episodic and chronic migraine. Data suggest that the treatment modality may be of benefit for acute migraine and cluster headache attacks.<sup>27</sup>

Sphenopalatine ganglion stimulation, which has been studied in cluster headache,<sup>28</sup> may be investigated for chronic migraine.

The neuropeptide calcitonin gene-related peptide (CGRP) has been indicated as playing a critical role in the central and peripheral pathways leading to a migraine attack.<sup>29</sup> Four companies have monoclonal antibodies in late-stage development: three against CDGRP and one against the CGRP receptor. Preliminary efficacy data are

### MIGRAINE COMORBIDITIES<sup>31</sup>

*In the migraine group, Grassini and Nordin found that 15.2, 19.9 and 25.8% had at least one of the functional somatic syndrome, psychiatric disorder and inflammatory disease diagnoses, respectively.*

The percentage of patients with migraine who reported each co-morbid diagnosis:

Fibromyalgia.....	8.6%
Irritable Bowel Syndrome.....	7.3%
Chronic Fatigue Syndrome.....	3.3%
Exhaustion syndrome.....	9.9%
Depression.....	9.9%
Panic disorder.....	4.6%
Asthma.....	6.6%
Allergic rhinitis.....	15.2%
Chronic sinusitis.....	3.3%



**Dr. Friedman:** We screen for depression, anxiety and post-traumatic stress disorder. We ask them questions about their medical history and medical comorbidities. All those things we try to take into account when we prescribe a medication.

**Dr. Mathew:** I ask in quite a bit of detail about sleep history, and some of my most rewarding clinical experiences have been helping patients discover that they actually have sleep apnea, which can manifest as headache when untreated.

**Dr. Silberstein:** We ask about snoring and ask the patient's wife. And we find out that many people have sleep apnea. They keep the sleep disorder doctors very busy.

**Dr. Mathew:** On the other side of the coin, sometimes I invite the spouse of the headache patient to come to a visit and convince them to have a sleep evaluation. In some cases, they're the ones with sleep apnea and with treatment the headache patients do much better because they can get a good night's sleep.

positive and they all appear quite safe.<sup>30</sup> The side effect profile appears similar to placebo.

A nasally-delivered formulation of oxytocin is in development for the US market (Trigemina, Inc.) for migraine, having been used outside the US for some time.

### PATIENT COUNSELING AND COMORBIDITIES

Chronic migraine is a disease of comorbidities. Among the many comorbidities associated with are psychiatric comorbidities, depression, anxiety, mood disturbances, sleep disorders. Other possible comorbidities include fibromyalgia and irritable bowel syndrome.<sup>31</sup> It is incumbent on the neurologist to address these potential comorbidities and their impact with patients. Patients may require additional therapy to treat these comorbidities.

Patients can also benefit from the recommendation of non-medicinal approaches to stress-reduction and lifestyle

improvement. Diet, exercise, stress-management improvement strategies are top-line. Cognitive behavioral therapy (CBT), bio-feedback, and therapy sessions may not be covered by insurance, but lower-cost options might exist. Web-based CBT programs are available at low cost and with patient convenience, though these have not been widely studied.

For patients with multiple comorbidities, such as obesity, high blood pressure, diabetes, and migraines referral for gastric bypass surgery may be appropriate. These individuals have improvement of their headaches, as well as sleep apnea, diabetes, and high blood pressure.

Just as it is important to educate patients on the diagnosis of migraine, as opposed to other headache types, it can also be helpful to educate them on the fact that migraine is an actual disease process with a genetic basis. Typically, patients will identify family members also affected.

When a patient is convinced they have an actual disease process and not just a figment of their imagination or something that's in their psyche they may be more amenable to following their treatment plan instead of resisting the clinician and believing something else causes their headaches.

A discussion of "alternative treatments" for migraine is also warranted. In short, the evidence for most of these is inconclusive at best. While clinical experience with magnesium, riboflavin, or CoQ10 is not particularly promising, these are generally safe and available cost-effectively over-the-counter treatments. Therefore, patients who wish to

#### SELECTED AGENTS IN THE PIPELINE

- Noninvasive Vagal Nerve Stimulator (nVNS)
- Sphenopalatine ganglion stimulation
- Calcitonin gene-related peptide (CGRP) monoclonal antibodies in late-stage development: three against CDGRP and one against the CGRP receptor
- Nasally-delivered formulation of oxytocin



**Dr. Friedman:** I tell patients my goal is to try to get them to have episodic headache. Because I think once you get somebody back to episodic, or at least not daily, it becomes easier to treat. Sometimes you can do it, sometimes you can't.

**Dr. Silberstein:** I tell them there's an 80% chance of getting a significant improvement. And whether that means less headache days or less frequent severe headache days. And I tell them that if the first thing we do doesn't work, there are numerous other alternatives.

We're looking for new interventions all the time. So I give them hope even if the first plan of treatment doesn't work.

do so may be counseled to use these agents in addition to prescription therapy.

Butterbur extract is an alternative agent that requires caution. In light of emerging hepatic safety concerns, this agent generally is not recommended.

### REALISTIC EXPECTATIONS

To effectively manage patients with chronic migraine, the clinician must reflect a positive attitude and set realistic goals. The goals may vary based on the patient and their specific presentations. For example the goal for one patient may be to have very few headaches that are easily managed with a symptomatic treatment. For another, the goal may be to reduce the intensity of daily headaches even if the frequency does not diminish. Patients may be disappointed if they expect to achieve permanent headache freedom.

Clinicians have many effective treatments at their disposal, and there are more in the pipeline. By making an accurate diagnosis, assessing the impact of headaches on the patient, identifying comorbidities, and working with patients to establish treatment goals, the physician can devise regimens that provide relief for patients with chronic migraine. ■

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### CME QUESTIONS THE CHANGING LANDSCAPE OF CHRONIC MIGRAINE: INSIGHTS ON PATIENT ASSESSMENT AND INTEGRATION OF NEWER TREATMENT STRATEGIES

1 *AMA PRA Category 1 Credit*™

Expires December 2016

1. True or False: According to the International Classification of Headache Disorders, 3rd Edition, Beta Version, (ICHD3), a patient with 14 headache a month, all of which are severe migraine can be diagnosed with chronic migraine.
  - a. True
  - b. False
2. Although research on adherence in chronic migraine is scant, one analysis shows therapeutic adherence in adult headache patients may be as low as...
  - a. 10 percent
  - b. 15 percent
  - c. 20 percent
  - d. 25 percent
3. Which of the following are FDA-approved for prevention of chronic migraine? Choose all that apply.
  - a. Amitriptyline
  - b. Divalproex sodium
  - c. OnabotulinutoxinA injection
  - d. Topiramate
4. In clinical trials, subjects receiving occipital nerve blocks (ONB) for migraine prevention saw a \_\_\_\_\_ reduction in moderate or severe headache days.
  - a. At least 30%
  - b. At least 40%
  - c. At least 50%
  - d. At least 60%
5. Opioids may a safe option for migraine rescue therapy where other agents are contraindicated, such as in:
  - a. Young children
  - b. Pregnant women or those with cardiovascular disease
  - c. Those with a history of psychosis
  - d. None of the above
6. True or False: Drug developers are exploring neuropeptide calcitonin gene-related peptide (CGRP) because it is indicated as playing a critical role in the central and peripheral pathways leading to a migraine attack.
  - a. True
  - b. False

**The Changing Landscape of Chronic Migraine: Insights on Patient Assessment and Integration of Newer Treatment Strategies**

December 10, 2015- December 9, 2016

Deborah Friedman, MD, Paul G. Mathew, MD, FAHS, Randolph W. Evans, MD, Stephen D. Silberstein, MD



Participant Information – Required for Certificate	
Full Name:	<input type="checkbox"/> MD/DO <input type="checkbox"/> NP <input type="checkbox"/> RN » License Number: _____ » Licensing State: _____ <input type="checkbox"/> PharmD <input type="checkbox"/> RPh » License Number: _____ » Licensing State: _____ » DOB: _____ <input type="checkbox"/> Other: _____
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Would you like your certificate sent to you via email? <input type="checkbox"/> Yes <input type="checkbox"/> No	
What is your specialty?	
<i>I certify that I completed this CME activity.</i> The actual amount of time spent on this activity was: _____ hr _____ min	
Signature: _____	

**1. Please rate the impact of the following objectives:**

*As a result of attending this activity, I am better able to:*

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Distinguish between various forms of chronic headache, including migraine, new daily persistent headache, tension headache, hemicrania continua, and cluster headache.	<input type="checkbox"/>				
Identify the challenges of chronic headache management, including the impact of the disease on affected individuals and the economic burden on affected individuals and society.	<input type="checkbox"/>				
Describe principles of acute and preventive therapy for chronic headache and their limitations.	<input type="checkbox"/>				
Recognize the indications for prophylactic migraine therapy and effectively initiate prophylactic treatment.	<input type="checkbox"/>				
Utilize optimal preventive and palliative approaches for chronic headache based on individual patient characteristics.	<input type="checkbox"/>				

**2. Please rate the projected impact of this activity on your competence\* and/or performance: \*competence is defined as the ability to apply knowledge, skills, and judgment in practice (knowing how to do something).**

	Yes	No	No Change
This activity increased my competence.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
This activity will improve my performance.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**3. Please identify how you will change your practice as a result of attending this activity (select all that apply).**

- Create/revise protocols, policies, and/or procedures
- Change the management and/or treatment of my patients
- This activity validated my current practice; no changes will be made
- Other, please specify: \_\_\_\_\_

**4. Please indicate any barriers you perceive in implementing these changes.**

- Cost
- Lack of experience
- Lack of opportunity (patients)
- Lack of resources
- Lack of time to assess/counsel patients
- Reimbursement/insurance issues
- Patient compliance issues
- Lack of consensus or professional guidelines
- Do not agree with recommendations
- No barriers
- Other, please specify: \_\_\_\_\_

**5. Will you attempt to address these barriers in order to implement changes in your competence and/or performance?**  N/A

- No – Why not? \_\_\_\_\_
- Yes – How? \_\_\_\_\_

**6. Do you feel the activity was free of commercial bias\* or influence?**  Yes  No, please explain: \_\_\_\_\_

\_\_\_\_\_ \*Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.