CME INTERNISTAS

Migrañas Crónicas

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Dr. Francisco Josè Cornejo Maza, MD, PHD

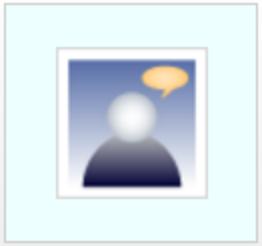
Dr Luis Ernesto Gonzalez Sanchez, MD, PHD

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Introduction

PREV NEXT >>>



Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Headaches and migraines are a common cause of disability and poor quality of life. In particular, chronic migraine (CM) represents the most common form of chronic headache seen in US clinics. Yet, CM remains an underdiagnosed and, consequently, an undertreated disorder. The scenarios that follow illustrate the specific nuances of selecting evidence-based pharmacotherapy and building comprehensive multimodal treatment plans in patients presenting with migraine headache.

PREV NEXT >>>

frequent attacks. He reported an average monthly frequency of 4 attacks, each of which lasted at least 7 hours. These headaches are extremely disabling and cause him to miss work. He uses ibuprofen 400-600 mg to treat moderate to severe attacks. The patient has no comorbid illnesses and takes no other medications. His general physical and his neurological exams were normal.

Please review the statements below and assess whether they are consistent with, or not consistent with, your current clinical approach by clicking on each statement and dragging it into the appropriate column.

Consistent	Drag Items Right or Left	Not Consistent
Ask the patient about the number of pain-free days per month	Counsel the patient to take ibuprofen 400-600 mg as needed for mild as well as moderate-to-severe attacks	Make the diagnosis of episodic migraine because the patient reported an average monthly frequency of 4 attacks
Ask the patient about the number of days per month when he treats his headache		
Use Migraine Disability Assessment (MIDAS) questionnaire to evaluate for headache-related disability		
Rule out secondary headache because the patient has a long (6-year) history of migraine headache		
Use headache calendar to help identify triggers, patterns of medication overuse, and the frequency of headache attacks		

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Pre Test

1) Which of the following medications is approved by the Food and Drug Administration (FDA) to prevent headaches in adults with CM?

- A) OnabotulinumtoxinA
- B) Topiramate
- C) Both A and B
- D) Timolol
- E) Divalproex sodium

2) Propranolol is an appropriate preventive treatment choice for patients with episodic migraine (EM) and comorbid depression.

- A) True
- B) False

3) Cognitive behavioral therapy (CBT) adds benefit in preventing migraine headache when combined with pharmacotherapy for CM.

- A) True
- B) False

4) Nonpharmacologic treatment modalities, such as CBT, can help patients adhere to their pharmacologic treatment for migraine.

- A) True
- B) False

4) Nonpharmacologic treatment modalities, such as CBT, can help patients adhere to their pharmacologic treatment for migraine.

- (●) A) True
- ( ) B) False

5) A 27-year-old woman is diagnosed with both CM and medication overuse headache. She is using over-the-counter [OTC] analgesic medications on 20 days a month. Which of the following is a rational treatment approach for this patient?

- ( ) A) Wean the patient off her acute medication before prescribing preventive therapy
- ( ) B) Prescribe preventive therapy and discontinue acute medication
- (●) C) Prescribe preventive therapy and switch the patient to a different acute medication to be used ≤2 times per week
- ( ) D) None of the above

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Pre Test Score

PREV NEXT >>>

Your score: 80%

Average score: 66%

Median score: 60%

At the end of this activity, you will have the opportunity to review your responses, faculty commentary, and peer scores for each question.

PREV NEXT >>>

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Introducing Mary

PREV NEXT >>>

Case Summary: Mary, a 24-year-old medical student who was diagnosed with CM and MOH

In the first Case Challenge in this CME curriculum, Optimizing Differential Diagnosis and Treatment Strategies for Headaches and Migraines, we talked about Mary, a 24-year-old medical student with a 12-year history of migraine.

Migraine Headache History

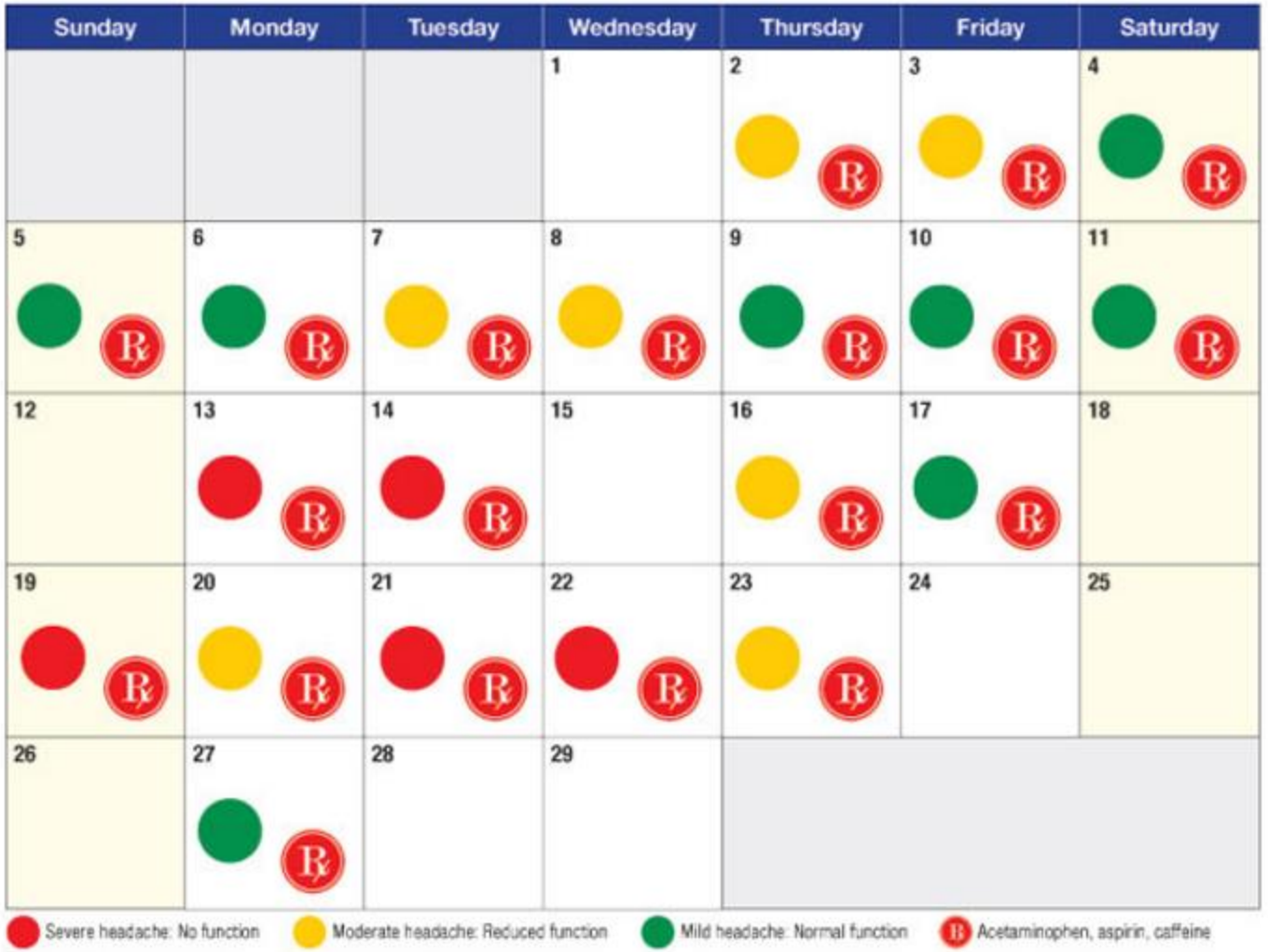
Mary reported having about one severe attack every 6 weeks. Over the past two years her migraine attacks without aura became much more frequent than those associated with aura. Mary's migraine pain is mostly bilateral and localized to the frontal and temporal head region. When intense and severe, her headaches tend to lateralize to either side, are accompanied by nausea, and are exacerbated by physical activity. Mary reported daily sensitivity to light and noise.

Mary's Headache Diary

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4

Mary reported having about one severe attack every 6 weeks. Over the past two years her migraine attacks without aura became much more frequent than those associated with aura. Mary's migraine pain is mostly bilateral and localized to the frontal and temporal head region. When intense and severe, her headaches tend to lateralize to either side, are accompanied by nausea, and are exacerbated by physical activity. Mary reported daily sensitivity to light and noise.

Mary's Headache Diary



A close look at the headache diary revealed that Mary has a near-daily headache, and is using analgesic medications

A close look at the headache diary revealed that Mary has a near-daily headache, and is using analgesic medications (acetaminophen, aspirin, caffeine) on more than 15 days per month.

Based on this information, and after ruling out secondary causes, Mary received diagnoses of CM and MOH.

Migraine-Related Disability Assessment
Based on Mary's headache diary, she has a disabling headache 5 days a month, where she cannot function at all, and a moderate severity headache on 7 days a month, where her function is reduced. Thus, Mary's migraine has a marked negative effect on her ability to function.

Past Medical History
Mary had asthma as a child but no longer experiences symptoms.

Previous Medications for Headache/Migraine
Mary has tried a triptan sample a few years ago, but did not find it to be effective. She has received a prescription for amitriptyline 25 mg in the past as a preventive option through her primary care physician. However, she discontinued this treatment after about six weeks because of a 12-lb weight gain and excessive daytime lethargy.

Mary has also been tried on topiramate at a dose of 25 mg twice a day, which she discontinued after one month due to cognitive impairment. She had difficulty concentrating, difficulty finding words, and difficulty with expressive language function.

Physical Examination
Mary's general physical and neurological examination was normal. She had no abnormal focal or lateralizing neurological findings.

Current Medications
A birth control pill (a combination of drospirenone and ethinyl stradiol); ibuprofen and a combination of acetaminophen/aspirin/caffeine to treat her migraine attacks, as necessary.

PREV
NEXT >>>

David W. Dodick, MD
Professor
Director, Headache Division
Director, Sport Neurology and Concussion Program
Department of Neurology, Mayo Clinic
Phoenix, AZ

Case (cont'd)

As a CM patient, Mary needs treatment with preventive medication that is administered regularly to reduce the number of her migraine attacks and improve her functioning.[1,2] All CM patients also need treatment with acute medication to be taken once attacks of moderate or severe intensity occur. In this particular patient, not only do you need to start thinking about preventive options for migraine, but you also need to address her medication overuse.[3]

The overall goal of preventive therapy for migraine is to reduce disability and improve patient function. To that end, preventative therapy aims to achieve the following:[4,5,6]

1. **Reduce attack frequency, severity, and duration**. Although many clinicians might think that reducing attack frequency is the key goal of treatment, it is not the only goal. Reducing attack severity and duration can be profoundly important for patients as well. For example, you may start a preventive medication in a patient and not be able to substantially reduce the frequency of headache. However, if you've reduced the severity of headache, that can be profoundly helpful for the patients, especially if they have suffered for a very long period of time with near-daily, daily, or continuous headache. Sometimes I like to tell my patients: "We're going to make your yellow and red calendar headache days turn green." In other words, I tell them that we are aiming to have their headache days be mild and not impair their ability to function.

2. **Reduce acute medication use and potential for MOH**. In addition to predisposing the patient to developing MOH, acute medication overuse is also a risk factor for progression from EM to CM.[7]

3. **Improve response to treatment of acute attacks**. Often, after being put on effective preventive medication,

frequency is the key goal of treatment, it is not the only goal. Reducing attack severity and duration can be profoundly important for patients as well. For example, you may start a preventive medication in a patient and not be able to substantially reduce the frequency of headache. However, if you've reduced the severity of headache, that can be profoundly helpful for the patients, especially if they have suffered for a very long period of time with near-daily, daily, or continuous headache. Sometimes I like to tell my patients: "We're going to make your yellow and red calendar headache days turn green." In other words, I tell them that we are aiming to have their headache days be mild and not impair their ability to function.

2. **Reduce acute medication use and potential for MOH**. In addition to predisposing the patient to developing MOH, acute medication overuse is also a risk factor for progression from EM to CM.[7]

3. **Improve response to treatment of acute attacks**. Often, after being put on effective preventive medication, patients find themselves using acute therapy (eg, triptans or OTCs) less. Also, the duration of their attacks shortens after taking acute therapy. For example, instead of lasting for two days, they're able to get rid of an attack within an hour. Thus, improving the response to acute medication and lowering the need for acute medication are important goals of a preventive treatment.

4. **Improve function and reduce disability.** I have all of my patients complete a migraine-related disability assessment. It can be a Migraine Disability Assessment (MIDAS) scale, or the Headache Impact Test (HIT-6). These assessment tools give me an idea of how active or inactive the patient's disease is. Also these tools provide a surrogate measure of outcome. For example, if the patient's initial MIDAS score was 60, and after being placed on a preventive therapy their MIDAS score reduced to 15, I know that they're going to be substantially improved.

5. **Prevent progression to CM** in patients with EM.

References

PREV NEXT >>>

Credits: *1 AMA PRA Category 1 Credit™*

Management Question 1

PREV NEXT >>>

The treatment of CM that is associated with acute medication overuse involves which of the following?

- A) Immediate cessation of the overused medication
- B) Switch to another acute medication
- C) Start a preventative medication and attempt to limit the use of acute medications to ≤2 days per week
- D) Parenteral dihydroergotamine or corticosteroids to minimize withdrawal headache

PREV NEXT >>>

Next page

Credits: 1 AMA PRA Category 1 Credit™

Question Review

PREV NEXT >>>

✓ **The treatment of CM that is associated with acute medication overuse involves which of the following?**

A) Immediate cessation of the overused medication

B) Switch to another acute medication

C) Start a preventative medication and attempt to limit the use of acute medications to ≤2 days per week

D) Parenteral dihydroergotamine or corticosteroids to minimize withdrawal headache

Your Answer: C) Start a preventative medication and attempt to limit the use of acute medications to ≤2 days per week
Correct!

Management Question Commentary

David W. Dodick, MD
Professor
Director, Headache Division
Director, Sport Neurology and Concussion Program
Department of Neurology, Mayo Clinic
Phoenix, AZ

Answer A:
Immediate cessation of the overused medication would not be an optimal choice. In the case of opioids or butalbital-containing analgesics, a severe withdrawal syndrome could result.[1] In the case of analgesics and migraine-specific drugs, abrupt withdrawal without substituting another acute medication, leads to a marked increase in frequency and severity of migraine symptoms and unnecessary suffering for the patient.[1,2] The likelihood of relapse and recidivism is higher with such an approach.

Answer B:
Switching to another acute medication would not be an optimal choice because the patient may start overusing the new medication as well. While switching is a reasonable acute strategy, in the absence of a bridge and/or preventive strategy, continued overuse and frequent headache would likely persist.[3]

Answer C:
As mentioned before, reducing acute medication use and potential for MOH is one of the goals for preventive therapy for migraine. In the CM patient who has already developed MOH, attempting to restrict acute medication to ≤2 days per week is a reasonable strategy.[4] Preventative therapy should also be initiated in this patient to minimize withdrawal symptoms in addition to other benefits.

Director, Sport Neurology and Concussion Program
Department of Neurology, Mayo Clinic
Phoenix, AZ

Answer A:
Immediate cessation of the overused medication would not be an optimal choice. In the case of opioids or butalbital-containing analgesics, a severe withdrawal syndrome could result.[1] In the case of analgesics and migraine-specific drugs, abrupt withdrawal without substituting another acute medication, leads to a marked increase in frequency and severity of migraine symptoms and unnecessary suffering for the patient.[1,2] The likelihood of relapse and recidivism is higher with such an approach.

Answer B:
Switching to another acute medication would not be an optimal choice because the patient may start overusing the new medication as well. While switching is a reasonable acute strategy, in the absence of a bridge and/or preventive strategy, continued overuse and frequent headache would likely persist.[3]

Answer C:
As mentioned before, reducing acute medication use and potential for MOH is one of the goals for preventive therapy for migraine. In the CM patient who has already developed MOH, attempting to restrict acute medication to ≤2 days per week is a reasonable strategy.[4] Preventative therapy should also be initiated in this patient to minimize withdrawal symptoms in addition to other benefits.

Answer D:
Putting Mary on parenteral dihydroergotamine or corticosteroids to minimize withdrawal headache would not be an optimal choice because it requires either patient hospitalization or strategies for which there is no evidence.[1,2]

References

PREV
NEXT >>>

HOW WOULD YOU APPROACH TREATING A PATIENT WITH MOH?

DAVID W. DODICK, MD

Due to lack of randomized controlled studies and inherent heterogeneity of MOH, no universal consensus exists on the optimal way to treat these patients.[1,2,3,4] Most experts agree, however, that withdrawal of the overused medication(s) is necessary and advisable particularly because of the potential for systemic toxicity related to frequent drug intake. Patients with MOH also need pharmacologic and educational/behavioral support to manage withdrawal symptoms (ie, rebound headache) and prevent relapse.[4]

A recent systematic review of the world's literature concluded that considering current available evidence and the systemic toxicity of overusing acute headache medication, discontinuation of the overused medication with the addition of preventive medication is the most appropriate approach.[1] Appropriately sized, randomized, controlled trials evaluating the safety and long-term efficacy of preventive medication plus early discontinuation of overuse versus preventive medication alone versus early discontinuation of overuse alone are needed.

A rational approach for Mary would be to minimize the use of acute medication (ie, ibuprofen and a combination of acetaminophen/aspirin/caffeine) to no more than 2 days per week.[5] It is also reasonable to discontinue use of ibuprofen and the acetaminophen/aspirin/caffeine combination, and switch her to a different acute medication. For example, you might step the therapy up to use a triptan for her moderate-to-severe headaches. Mary reported that she used a triptan before and hasn't found it to be effective, so it is advisable to use a different triptan than the one she had before. It would also be appropriate to initiate a preventive medication to reduce withdrawal symptoms, reduce headache frequency, and minimize the risk of relapse or treatment failure.[1]

References

use a triptan for her moderate-to-severe headaches. Mary reported that she used a triptan before and hasn't found it to be effective, so it is advisable to use a different triptan than the one she had before. It would also be appropriate to initiate a preventive medication to reduce withdrawal symptoms, reduce headache frequency, and minimize the risk of relapse or treatment failure.[1]

References

STEPHEN D. SILBERSTEIN, MD

It would be challenging to reduce Mary's acute medication use to less than 2 days per week in the absence of preventative therapy. I would strongly recommend initiating preventative therapy for CM in this patient while attempting to reduce her current acute medication to less than 2 days per week.[1,2] Alternatively, I would initiate preventative therapy and switch her to a different acute regimen, as recommended above by Dr. Dodick.

References

We invite you to post your thoughts and comments in the learner forums associated with the above discussion. In order to access these forums, you must have completed the brief health professional validation process. To complete this now, please click on the link below.

Validate

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

CME COMPANION

(+) What is CMECompanion?

Welcome Dr. Luis Ernesto Gonzalez Sanchez

Logout

PLANNER

TRACKER

PERFORMANCE

NETWORK

PROFILE

Management Question 2

PREV NEXT >>>

Which preventive treatment would you prescribe for Mary?

- A) OnabotulinumtoxinA injections
- B) Nortriptyline
- C) Topiramate
- D) Propranolol

PREV NEXT >>>

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Question Review

PREV NEXT >>>

✓ **Which preventive treatment would you prescribe for Mary?**

A) OnabotulinumtoxinA injections

B) Nortriptyline

C) Topiramate

D) Propranolol

Your Answer: A) OnabotulinumtoxinA injections
Correct!

PREV NEXT >>>

CME COMPANION

(+) What is CMECompanion?

Welcome Dr. Luis Ernesto Gonzalez Sanchez

Logout

PLANNER

TRACKER

PERFORMANCE

NETWORK

PROFILE

Management Question Commentary

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Answers A-D:

Since CM was recognized as a subtype of migraine only a few years ago, only a limited number of clinical trials evaluated pharmacologic therapies specifically in these patients, and no guidelines for prevention or treatment of CM have been published thus far.[1] **Two medications with strongest supporting evidence in CM are topiramate and onabotulinumtoxinA, and onabotulinumtoxinA is the only drug currently approved by the FDA to prevent headaches in adult patients with CM.**[1,2]

Beyond that, the management of patients with CM draws on the experience of treating other migraine subtypes, especially EM. However, it is unclear whether agents that are recommended for the prevention of EM are also effective in treating CM.[1]

The American Academy of Neurology (AAN) published evidence-based recommendations on preventive treatments for EM in 2012.[3,4] These recommendations are based on the Level of clinical evidence available in the literature. The Level A (established efficacy) and Level B (probably effective) preventive medications are listed in the table below.

The American Academy of Neurology (AAN) published evidence-based recommendations on preventive treatments for EM in 2012.[3,4] These recommendations are based on the Level of clinical evidence available in the literature. The Level A (established efficacy) and Level B (probably effective) preventive medications are listed in the table below.

Table 1: Evidence-Based AAN Recommended Medications for Prevention of EM[1,2]

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or Class II studies)
Anticonvulsants	**Antidepressants**
Divalproex sodium[a] Sodium valproate Topiramate[a]	Amitryptyline Venlafaxine
β-Blockers	
Propranolol[a] Metoprolol Timolol[a]	Atenolol Nadolol
Triptans (MRM[b])	
Frovatriptan	Naratriptan Zolmitriptan
Other	
Petasites	

[a] FDA approved.
[b] Perimenstrual dose.
AAN, American Academy of Neurology; EM, episodic migraine; MRM, menstrually related migraine.

[1] Silberstein SD, Holland S, Freitag F, et al; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78:1337-1345.
[2] Holland S, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78:1346–1353.

Divalproex sodium, topiramate, propranolol, and timolol are indicated for the preventive treatment of EM.[3,4] Other medications listed under level A — sodium valproate, metoprolol, and petasites—are not FDA-approved, but have a very robust evidence-base for their use. Frovatriptan's efficacy for menstrually related migraine is supported by several randomized, placebo-controlled trials.

The 2012 Canadian Headache Society (CHS) guidelines aim to assist the practitioner in choosing an appropriate prophylactic medication for a patient with EM based on current evidence in the medical literature and expert consensus.[5] The recommendation strength is based on the panel's own experience on how efficacious, safe, and tolerable they found the medications to be in their practice.

Table 2: CHS-Recommended Medications for Prevention of EM[1]

Drug	Recommendation Strength	Quality of Evidence
Topiramate	Strong	High
Propranolol	Strong	High
Metoprolol	Strong	High
Amitryptiline	Strong	High
Nadolol	Strong	Moderate
Gabapentin	Strong	Moderate
Candesartan	Strong	Moderate
Butterbur	Strong	Moderate
Riboflavin	Strong	Low
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low

CHS, Canadian Headache Society; EM, episodic migraine.
[1] Pringsheim T, Davenport W, Mackie G, et al; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012; 39(2) Suppl 2: S1 – S59.

EM, episodic migraine.

Answer A:
The efficacy and safety of onabotulinumtoxinA in patients with CM have been demonstrated in two 24-week, double-

EM, episodic migraine.

Answer A:
The efficacy and safety of onabotulinumtoxinA in patients with CM have been demonstrated in two 24-week, double-blind, randomized, placebo-controlled clinical studies called Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical trials.[6,7] Of note, more than 65% of the entire pooled PREEMPT population was overusing acute headache medication (with exception of opioids) at baseline. However, the efficacy and safety of onabotulinumtoxinA in CM patients with medication overuse was similar to the overall patient population.[8] Thus, onabotulinumtoxinA injections would be a rational choice for Mary.

Answer B:
There is no evidence for the use of nortriptyline for migraine prevention and the patient had already experienced adverse effects from amitriptyline.[3,4,5]

Answer C:
Topiramate efficacy in prevention of CM is supported by several double-blind, randomized, placebo-controlled clinical trials.[9,10,11,12] A post hoc analysis of subjects enrolled in 2 topiramate trials revealed that more than 37% of CM patients in the United States and 78% of CM patients in the European Union were overusing acute medication for headache.[13] Topiramate was both effective and safe in that patient group. Topiramate could be a good choice for Mary except that she has history of using this medication and discontinuing it due to cognitive side effects.

Two double-blind pilot studies compared onabotulinumtoxinA and topiramate as preventive therapy in CM patients and found similar efficacy.[14,15] One of the studies found that onabotulinumtoxinA was generally better tolerated than topiramate with mostly local (eg, muscle weakness near injection sites) rather than systemic (eg, cognitive deficits) adverse effects and resulted in fewer treatment-related discontinuations.[15] Thus, onabotulinumtoxinA would be a better preventive option for Mary.

Answer D:
Propranolol is endorsed by both AAN and CHS guidelines for prevention of episodic migraine[3,4,5]; however, its efficacy in preventing CM has not been established.

References

David W. Dodick, MD
Professor
Director, Headache Division
Director, Sport Neurology and Concussion Program
Department of Neurology, Mayo Clinic
Phoenix, AZ

Final Treatment Plan for Mary:

Mary was counseled to discontinue her OTC medications (ibuprofen and acetaminophen/aspirin/ caffeine combination) because they are likely to exacerbate her migraine headache due to excessive use. As an alternative acute therapy for her migraine attacks, she was prescribed:

- Mild-moderate headache: naproxen sodium 550 mg and metaclopramide 10 mg as needed for nausea
- Moderate-severe headache: eletriptan 40 mg; may repeat in 2 hours if needed or within 24 hours

It was explained to Mary that she may experience withdrawal symptoms from abrupt discontinuation of her OTCs, but that her new acute therapy regimen should help with that. To gradually treat her MOH and to prevent a future relapse, Mary was instructed to limit her new acute treatment regimen to a maximum of 3 days per week for the first week, and to a maximum of 2 days per week thereafter.

As preventative therapy for her migraine, Mary was prescribed onabotulinumtoxinA injections (total dose 200 units). Mary was counseled about the benefits of preventive therapy in reducing the severity and frequency of her migraine attacks, lessening potential withdrawal symptoms from discontinuation of her OTCs and minimizing risk of MOH relapse or treatment failure.

Mary was also advised on helpful nonpharmacologic interventions, including receiving proper amounts of sleep, practicing regular exercise, and adhering to a healthy diet.

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Case Summary: Beth, a 47-Year-Old Postal Worker With a Diagnosis of CM

As you may recall from the Case Challenge 2: Evaluating Migraine-Related Disability, a previous posting in this CME series, Beth is a 47-year-old postal worker with a 12-year history of migraine attacks without aura. Beth is married and has a son, age 15. Beth does not smoke or drink alcohol, but she drinks coffee multiple times a day.

Migraine Headache History
Last time Beth presented with a nearly-daily headache, where she reported having migraine attacks 4 or 5 days per week. Her mild-to-moderate attacks last 5 hours each and are typically worse in the morning. They are characterized by unilateral pain and photophobia. Based on the frequency, characteristics, and duration of Beth's headaches and after ruling out secondary causes, Beth received a diagnosis of CM.

Migraine Disability Assessment
Beth's total MIDAS score of 55 revealed severe disability from her migraines. She reported having a headache on 62 days over the past 3 months, and she rated these as moderately painful (4 on a scale of 0 = no pain at all, and 10 = pain as bad as it can be).

Past Medical History
Beth had a kidney stone removed last year.

Physical Examination
Beth's general physical and neurological examinations were normal.

- Blood pressure: 125/80 mm Hg
- Pulse: 74 beats per minute

As you may recall from the Case Challenge 2: Evaluating Migraine-Related Disability, a previous posting in this CME series, Beth is a 47-year-old postal worker with a 12-year history of migraine attacks without aura. Beth is married and has a son, age 15. Beth does not smoke or drink alcohol, but she drinks coffee multiple times a day.

Migraine Headache History

Last time Beth presented with a nearly-daily headache, where she reported having migraine attacks 4 or 5 days per week. Her mild-to-moderate attacks last 5 hours each and are typically worse in the morning. They are characterized by unilateral pain and photophobia. Based on the frequency, characteristics, and duration of Beth's headaches and after ruling out secondary causes, Beth received a diagnosis of CM.

Migraine Disability Assessment

Beth's total MIDAS score of 55 revealed severe disability from her migraines. She reported having a headache on 62 days over the past 3 months, and she rated these as moderately painful (4 on a scale of 0 = no pain at all, and 10 = pain as bad as it can be).

Past Medical History

Beth had a kidney stone removed last year.

Physical Examination

Beth's general physical and neurological examinations were normal.

- Blood pressure: 125/80 mm Hg
- Pulse: 74 beats per minute
- BMI: 22
- No papilledema
- VA 20/20 OU
- Color plates normal
- No other neurological findings

Current Medications

Sumatriptan and ibuprofen to treat her migraine attacks 1 to 2 days per week.

PREV NEXT >>>

COMORBID CONDITIONS IN CM AND HOW THEY INFLUENCE TREATMENT CHOICES

STEPHEN D. SILBERSTEIN, MD

Based on the diagnosis of CM, before prescribing treatment, what else would you want to know about Beth's health?

CM patients often suffer from both neurologic and medical comorbidities that may influence disease prognosis, treatment choice, and affect clinical outcomes. In the American Migraine Prevalence and Prevention (AMPP) study, patients with CM were approximately twice as likely to have depression, anxiety, and chronic pain as patients with EM.[1] Other disorders that are often seen in CM patients include respiratory disorders (ie, asthma, bronchitis, and chronic obstructive pulmonary disease), cardiac risk factors (eg, hypertension and high cholesterol), diabetes, and obesity.[1] Therefore, a comprehensive treatment plan includes evaluating and managing comorbid disorders, practicing good sleep hygiene, and avoiding triggers for migraine attacks.[2,3]

Regimen selection for CM should be individualized based on the patient's coexistent disorders, and treatments that may exacerbate these conditions should be avoided.[4] For example, beta blockers may potentially exacerbate depressive symptoms.[4,5] Conversely, certain treatments for headache disorders may offer additional benefit to patients with certain comorbidities. For example, patients with tachycardia or hypertension may find beta-blockers helpful in both relieving their migraine symptoms and treating the comorbid cardiovascular disorder.[3] Further, patients with a comorbid chronic pain disorder, such as neuropathy, may benefit from treatment with certain headache preventatives, such as gabapentin, botulinum toxin, or tricyclic antidepressants.[6,7,8] This treatment approach may be especially advantageous since chronic pain disorders are often underdiagnosed and undertreated.[3]

When monotherapy does not sufficiently improve both the migraine and the comorbid disorder,

When monotherapy does not sufficiently improve both the migraine and the comorbid disorder, then polytherapy should be considered.[3,4] In other words, specific treatment of both conditions with separate medications.

References

DAVID W. DODICK, MD

In addition, obesity is a common condition among migraine sufferers, and it is important to remember that use of preventive medications such as tricyclic antidepressants and divalproex sodium could cause weight gain and exacerbate conditions associated with obesity, such as hypertension and diabetes mellitus.[1]

References

We invite you to post your thoughts and comments in the learner forums associated with the above discussion. In order to access these forums, you must have completed the brief health professional validation process. To complete this now, please click on the link below.

Validate

PREV

NEXT >>>

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Beth's Case (cont'd)

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Beth mentioned that she drinks coffee multiple times a day because she often has trouble sleeping at night and needs caffeine to "get her through the day." More detailed inquiry into Beth's insomnia and mood reveals that her son is a rebellious teenager and she is worried about his performance in school and social life. Given that insomnia is one of the symptoms of major depressive disorder,[1] a disease often comorbid with CM,[2] Beth was asked to complete a PHQ-9 Questionnaire to screen her for depression. Beth's PHQ-9 score of 15 indicated moderate-to-severe depression.[3]

References

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Management Question 3

Based on Beth's dual diagnosis of CM and depression, which preventive medication would you choose to treat Beth's migraine?

- A) Metoprolol
- B) Topiramate
- C) Amitryptiline
- D) Flunarizine

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Question Review

PREV NEXT >>>

Based on Beth's dual diagnosis of CM and depression, which preventive medication would you choose to treat Beth's migraine?

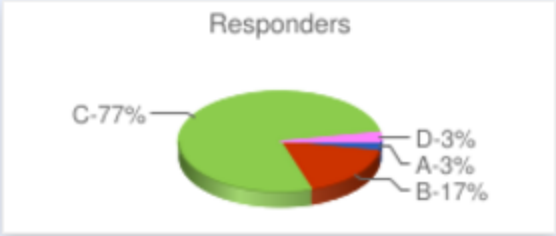
A) Metoprolol

B) Topiramate

C) Amitryptiline

D) Flunarizine

Your Answer: C) Amitryptiline
Correct!



Management Question Commentary

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Answer A:
Metoprolol or any other beta blocker would not be a good choice for Beth because it may potentially exacerbate depression.[1,2]

Answer B:
Topiramate would not be a good choice for Beth because although numerous clinical trials support its efficacy in patients with CM, she has a history of kidney stone and topiramate can increase the risk of hypocitraturia, a recognized promoter of renal stone disease.[3]

Answer C:
Amitryptiline is the only well-studied antidepressant that has consistent evidence in preventing EM attacks.[4,5] Although only small and underpowered studies suggest possible efficacy for amitryptiline in patients with CM, it would be a reasonable choice for Beth, particularly given the presence of insomnia, depression, and a BMI of 22.

Answer D:
Flunarizine would not be a good option for Beth because it may potentially exacerbate her depression.[2]

References

Beth's Case (cont'd)

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Case (cont'd)

Beth was prescribed amitryptiline at the initial dose of 10 mg taken at night, and increase to 25 mg after 5 days. Amitryptiline does not abort acute migraine attacks, and Beth will still need to take ibuprofen and sumatriptan for that.[1] Beth is instructed to take abortive medications only when her headaches are moderate to severe to avoid MOH.[2]

References

[1] Silberstein SD, Holland S, Freitag F, et al; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1337-1345.

[2] Snow V, Weiss K, Wall EM, et al; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med*. 2002;137:840-849.

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

To build a comprehensive treatment plan in patients with headache and migraine, nonpharmacological therapies including behavioral therapy, regular exercise, and sleep schedule should be integrated with pharmacological interventions.[1,2]

Biobehavioral techniques used in chronic headache include relaxation training, meditative therapy (abdominal breathing exercises), progressive muscle relaxation, visualization/guided imagery, thermal biofeedback, electromyography biofeedback, and CBT.[1,2] These biobehavioral therapies can help the patient to identify and avoid potential triggers for migraine and mitigate its effects. Additional reasons for employing nonpharmacological treatments include poor tolerance and low response to preventive medication, history of medication overuse, pregnancy, and deficient stress/pain coping strategies.[3]

Regular exercise should be encouraged because it has also been shown to be effective for the prevention of migraine. In one randomized, placebo-controlled trial of 91 adults with migraine, exercising for 40 minutes 3 times a week was as effective as relaxation therapy or topiramate.[4]

Likewise, acupuncture was recently shown to decrease the number of headache days compared with topiramate in a non-blind, randomized clinical trial of 66 CM patients.[5]

Neurologists and headache and pain specialists should form multidisciplinary teams with migraine nurse specialists, primary care providers, psychologists and alternative therapy specialists to implement a multimodal treatment plan

Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

To build a comprehensive treatment plan in patients with headache and migraine, nonpharmacological therapies including behavioral therapy, regular exercise, and sleep schedule should be integrated with pharmacological interventions.[1,2]

Biobehavioral techniques used in chronic headache include relaxation training, meditative therapy (abdominal breathing exercises), progressive muscle relaxation, visualization/guided imagery, thermal biofeedback, electromyography biofeedback, and CBT.[1,2] These biobehavioral therapies can help the patient to identify and avoid potential triggers for migraine and mitigate its effects. Additional reasons for employing nonpharmacological treatments include poor tolerance and low response to preventive medication, history of medication overuse, pregnancy, and deficient stress/pain coping strategies.[3]

Regular exercise should be encouraged because it has also been shown to be effective for the prevention of migraine. In one randomized, placebo-controlled trial of 91 adults with migraine, exercising for 40 minutes 3 times a week was as effective as relaxation therapy or topiramate.[4]

Likewise, acupuncture was recently shown to decrease the number of headache days compared with topiramate in a non-blind, randomized clinical trial of 66 CM patients.[5]

Neurologists and headache and pain specialists should form multidisciplinary teams with migraine nurse specialists, primary care providers, psychologists and alternative therapy specialists to implement a multimodal treatment plan for optimizing patient outcomes in CM.[1,2,3]

References

[1] Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc.* 2015;90:408-414.

[2] Dougherty C, Silberstein SD. Providing care for patients with chronic migraine: diagnosis, treatment, and management. *Pain Pract.* 2015;15:688-692.

[3] Weeks RE. Application of behavioral therapies in adult and adolescent patients with chronic migraine. *Neurol Sci.* 2013;34(suppl 1):S11-S17.

[4] Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate

Biobehavioral techniques used in chronic headache include relaxation training, meditative therapy (abdominal breathing exercises), progressive muscle relaxation, visualization/guided imagery, thermal biofeedback, electromyography biofeedback, and CBT.[1,2] These biobehavioral therapies can help the patient to identify and avoid potential triggers for migraine and mitigate its effects. Additional reasons for employing nonpharmacological treatments include poor tolerance and low response to preventive medication, history of medication overuse, pregnancy, and deficient stress/pain coping strategies.[3]

Regular exercise should be encouraged because it has also been shown to be effective for the prevention of migraine. In one randomized, placebo-controlled trial of 91 adults with migraine, exercising for 40 minutes 3 times a week was as effective as relaxation therapy or topiramate.[4]

Likewise, acupuncture was recently shown to decrease the number of headache days compared with topiramate in a non-blind, randomized clinical trial of 66 CM patients.[5]

Neurologists and headache and pain specialists should form multidisciplinary teams with migraine nurse specialists, primary care providers, psychologists and alternative therapy specialists to implement a multimodal treatment plan for optimizing patient outcomes in CM.[1,2,3]

References

[1] Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc.* 2015;90:408-414.

[2] Dougherty C, Silberstein SD. Providing care for patients with chronic migraine: diagnosis, treatment, and management. *Pain Pract.* 2015;15:688-692.

[3] Weeks RE. Application of behavioral therapies in adult and adolescent patients with chronic migraine. *Neurol Sci.* 2013;34(suppl 1):S11-S17.

[4] Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia.* 2011;31:1428-1438.

[5] Yang CP, Chang MH, Liu PE, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. *Cephalalgia.* 2011;31:1510-1521.

PREV NEXT >>>

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

CME COMPANION

(+) What is CMECompanion?

Welcome Dr. Luis Ernesto Gonzalez Sanchez

Logout

PLANNER

TRACKER

PERFORMANCE

NETWORK

PROFILE

Management Question 4

PREV NEXT >>>

Which of the following is NOT an added benefit of CBT in treating CM?

- A) Improvement of headache
- B) Adherence to pharmacotherapy
- C) Improvement of modifiable risk factors of CM
- D) None of the above

PREV NEXT >>>

Credits: *1 AMA PRA Category 1 Credit™*

Question Review

PREV NEXT >>>

Which of the following is NOT an added benefit of CBT in treating CM?

A) Improvement of headache

B) Adherence to pharmacotherapy

C) Improvement of modifiable risk factors of CM

D) None of the above

Your Answer: C) Improvement of modifiable risk factors of CM
Incorrect! The correct answer is D) None of the above

PREV NEXT >>>

COMPANION

(+) What is CMECompanion?

Welcome Dr. Luis Ernesto Gonzalez Sanchez

Logout

PLANNER

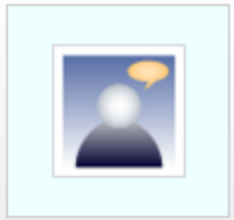
TRACKER

PERFORMANCE

NETWORK

PROFILE

Management Question Commentary



Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Answers A through D:
The rationale of cognitive-behavioral therapies (CBT) in CM is that it helps patients become aware of factors that precipitate or aggravate their headaches so that they can learn to progressively modulate the frequency and duration of the attacks. The goals of CBT in CM are:[1]

- To reduce frequency and severity of migraine attacks/days of headache
- To decrease disability and improve patients' health-related quality of life
- To reduce medication overuse
- To diminish intake of poorly tolerated or unwanted preventive medication
- To develop coping strategies for chronic headache
- To enhance individual control of pain
- To reduce CM-related stress
- To treat modifiable risk factors of CM

Several studies assessed the role of complementary and alternative therapies in CM. CBT, in particular, was found to add benefit when combined with medical treatment. A randomized clinical trial evaluated the efficacy of CBT plus amitriptyline in CM children and adolescents aged 10 to 17 years.[2] In this study, 135 youth patients (79% female) diagnosed with CM were recruited and randomized to the CBT plus amitriptyline group (n = 64) or the headache

Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

Answers A through D:
The rationale of cognitive-behavioral therapies (CBT) in CM is that it helps patients become aware of factors that precipitate or aggravate their headaches so that they can learn to progressively modulate the frequency and duration of the attacks. The goals of CBT in CM are:[1]

- To reduce frequency and severity of migraine attacks/days of headache
- To decrease disability and improve patients' health-related quality of life
- To reduce medication overuse
- To diminish intake of poorly tolerated or unwanted preventive medication
- To develop coping strategies for chronic headache
- To enhance individual control of pain
- To reduce CM-related stress
- To treat modifiable risk factors of CM

Several studies assessed the role of complementary and alternative therapies in CM. CBT, in particular, was found to add benefit when combined with medical treatment. A randomized clinical trial evaluated the efficacy of CBT plus amitriptyline in CM children and adolescents aged 10 to 17 years.[2] In this study, 135 youth patients (79% female) diagnosed with CM were recruited and randomized to the CBT plus amitriptyline group (n = 64) or the headache education plus amitriptyline group (n = 71). A greater reduction in headache days and migraine-related disability was observed in the CBT plus amitriptyline group, as compared to the headache education plus amitriptyline group.[2]

Also, CBT may improve medication adherence in CM patients, including those with psychiatric comorbidities. Patients with low self-efficacy are more likely to have a poor adherence to a wide range of treatments across chronic disorders.[3,4] However, self-efficacy could be augmented through CBT, and headache patients who feel more confident in their ability to control their migraines were shown to persist in adhering to their prescribed regimens.[3,4] CBT enables patients to recognize their cognitive errors and teaches them adoptive behaviors, where they learn to persist throughout symptom fluctuations and are prepared to cope with side effects.[3]

Finally, depression and anxiety are some of the modifiable risk factors for CM that can be helped with CBT.[5,6,7]

References

Several studies assessed the role of complementary and alternative therapies in CM. CBT, in particular, was found to add benefit when combined with medical treatment. A randomized clinical trial evaluated the efficacy of CBT plus amitriptyline in CM children and adolescents aged 10 to 17 years.[2] In this study, 135 youth patients (79% female) diagnosed with CM were recruited and randomized to the CBT plus amitriptyline group (n = 64) or the headache education plus amitriptyline group (n = 71). A greater reduction in headache days and migraine-related disability was observed in the CBT plus amitriptyline group, as compared to the headache education plus amitriptyline group.[2]

Also, CBT may improve medication adherence in CM patients, including those with psychiatric comorbidities. Patients with low self-efficacy are more likely to have a poor adherence to a wide range of treatments across chronic disorders.[3,4] However, self-efficacy could be augmented through CBT, and headache patients who feel more confident in their ability to control their migraines were shown to persist in adhering to their prescribed regimens.[3,4] CBT enables patients to recognize their cognitive errors and teaches them adoptive behaviors, where they learn to persist throughout symptom fluctuations and are prepared to cope with side effects.[3]

Finally, depression and anxiety are some of the modifiable risk factors for CM that can be helped with CBT.[5,6,7]

References

[1] Carod-Artal FJ. Tackling chronic migraine: current perspectives. *J Pain Res.* 2014;7:185-194.

[2] Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. *JAMA.* 2013;310:2622-2630.

[3] Seng EK, Rains JA, Nicholson RA, et al. Improving medication adherence in migraine treatment. *Curr Pain Headache Rep.* 2015;19:24.

[4] Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. *Headache.* 2014;54:278-289.

[5] Bigal ME, Lipton RB. What predicts the change from episodic to chronic migraine? *Curr Opin Neurol.* 2009;22:269-276.

[6] Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache.* 2008;48:16-25.

[7] American Psychiatric Association. (2010). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Washington, DC: APA.

PREV NEXT >>>

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Treatment Outcomes for Beth

Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

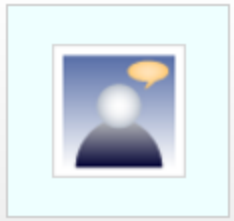
Treatment Outcomes for Beth

Beth was counseled about the benefits of CBT, and how she is more likely to achieve her treatment goals if she strictly adheres to her therapeutic regimen. She was also counseled to limit her caffeine intake because it can exacerbate her migraine. She called 6 days later saying that her migraines are under better control and that she is sleeping better at night. Beth also reported that she is now seeing a psychologist specializing in CBT on a weekly basis. A month later her headache diary revealed that she has used less rescue medication, and the duration of her headaches is shorter.

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

Closing Commentary



Stephen D. Silberstein, MD, Chair
Director, Jefferson Headache Center
Department of Neurology
Jefferson Hospital for Neuroscience
Philadelphia, PA

We hope that these interactive cases have demonstrated how you can select evidence-based acute and preventive therapy for migraine based on a patient's symptom profile, presence of medication overuse, prior response to medications, medical comorbidities, and patient preference. We also hope that these cases have shown you the benefits of combining pharmacotherapy with nonpharmacological approaches to reduce migraine-related debility and improve outcomes of patients with CM.

Title: Selecting Evidence-Based Pharmacologic Therapy and Designing Multimodal Treatment Plans for Migraine and Headache

Credits: 1 *AMA PRA Category 1 Credit™*

References

American Psychiatric Association. (2010). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Washington, DC: APA.

Aurora SK, Dodick DW, Turkel CC, et al; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30:793-803.

Bigal ME, Lipton RB. What predicts the change from episodic to chronic migraine? *Curr Opin Neurol.* 2009;22:269-276.

Buse DC, Manack A, Serrano D, et al. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry*. 2010;81:428-432.

Cady RK, Schreiber CP, Porter JA, et al. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache.* 2011;51:21-32.

Carod-Artal FJ. Tackling chronic migraine: current perspectives. *J Pain Res.* 2014;7:185-194.

Chiang CC, Schwedt TJ, Wang SJ, et al. Treatment of medication-overuse headache: a systematic review. *Cephalalgia.* 2015. [Epub ahead of print]

Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, et al. Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. *Br J Clin Pharmacol*. 2014;77:958-964.

with topiramate: a systematic review. *Br J Clin Pharmacol*. 2014;77:958-964.

Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia.* 2007;27:814–823.

Diener HC, Dodick DW, Aurora SK, et al; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia.* 2010;30:804-814.

Diener HC, Dodick DW, Goadsby PJ, et al. Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse. *Cephalalgia.* 2009;29:1021-1027.

Diener HC. Detoxification for medication overuse headache is not necessary. *Cephalalgia*. 2012;32:423-427.

Dodick DW, Turkel CC, DeGryse R, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache.* 2010;50:921-936.

Dougherty C, Silberstein SD. Providing care for patients with chronic migraine: diagnosis, treatment, and management. *Pain Pract.* 2015;15:688-692.

Evers S, Jensen R; European Federation of Neurological Societies. Treatment of medication overuse headache—guideline of the EFNS headache panel. *Eur J Neurol.* 2011;18:1115-1121.

Finocchi C, Villani V, Casucci G. Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. *Neurol Sci*. 2010;31:S95-S98.

Food and Drug Administration. FDA approves Botox to treat chronic migraine. Press release. October 15, 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm/ Accessed August 20, 2015.

Gupta R, Lahan V. Insomnia associated with depressive disorder: primary, secondary, or mixed? *Indian J Psychol Med.* 2011;33:123-128.

Holland S, Silberstein SD, Freitag F, et al; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78:1346-1353.

and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78:1346-1353.

Kristoffersen ES, Lundqvist C. Medication-overuse headache: a review. *J Pain Res.* 2014;7:367-378.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16:606-613.

Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxinA (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache.* 2009;49:1466-1478.

Mehta S, Guy S, Lam T, et al. Antidepressants are effective in decreasing neuropathic pain after SCI: a meta-analysis. *Top Spinal Cord Inj Rehabil.* 2015;21:166-173.

Oh HM, Chung ME. Botulinum toxin for neuropathic pain: a review of the literature. *Toxins* (Basel). 2015;7:3127-3154.

Olesen, J. Detoxification for medication overuse headache is the primary task. *Cephalalgia.* 2012;32:420-422.

Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. *JAMA.* 2013;310:2622-2630.

Pringsheim T, Davenport W, Mackie G, et al; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* 2012;39(suppl 2):S1-S59.

Rossi P, Jensen R, Nappi G, et al; COMOESTAS Consortium. A narrative review on the management of medication overuse headache: the steep road from experience to evidence. *J Headache Pain.* 2009;10:407-417.

Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache.* 2008;48:16-25.

Seng EK, Rains JA, Nicholson RA, et al. Improving medication adherence in migraine treatment. *Curr Pain Headache Rep.* 2015;19:24.

Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache.* 2009;49:1153-1162.

Silberstein SD, Dodick D, Freitag F, et al. Pharmacological approaches to managing migraine and associated comorbidities—clinical considerations for monotherapy vs. polytherapy. *Headache.* 2007;47:585-599.

Silberstein SD, Dodick D, Freitag F, et al. Pharmacological approaches to managing migraine and associated comorbidities—clinical considerations for monotherapy vs. polytherapy. *Headache.* 2007;47:585-599.

Silberstein SD, Holland S, Freitag F, et al; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1337-1345.

Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache.* 2007;47:170-180.

Silvestrini M, Bartolini M, Coccia M, et al. Topiramate in the treatment of chronic migraine. *Cephalalgia.* 2003;23:820-824.

Snow V, Weiss K, Wall EM, et al; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med.* 2002;137:840-849.

Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc.* 2015;90:408-414.

Vécsei L, Majláth Z, Balog A, et al. Drug targets of migraine and neuropathy: treatment of hyperexcitability. *CNS Neurol Disord Drug Targets*. 2015;14:664-676.

Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia.* 2011;31:1428-1438.

Weeks RE. Application of behavioral therapies in adult and adolescent patients with chronic migraine. *Neurol Sci.* 2013;34(suppl 1):S11-S17.

Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. *Headache.* 2014;54:278-289.

Yang CP, Chang MH, Liu PE, et al. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. *Cephalalgia.* 2011;31:1510-1521.

PREV NEXT >>>