Meeting the Challenges of Migraine Treatment: From Early Diagnosis to Symptom Relief

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Faculty Disclosure

- **Dr Buse**: consultant: Eli Lilly and Company; research support: Allergan, Avanir Pharmaceuticals, Inc.
Learning Objectives

• Distinguish migraine headache from other types of headache
• Develop management strategies that emphasize patient engagement, adherence to medication and lifestyle changes, and comprehensive symptom relief
• Assess the value of new medications and new delivery systems to optimize treatment for patients with acute migraine headache
Migraine Is Common

2011 National Health Interview Survey: Severe Headache or Migraine in Last 3 Months

% of population

Age (years)

18-44
45-54
55-64
65-74

26.1
25.7
18
11.8

Women

12.7
10.8
9.7
6.9

Men

National Center for Health Statistics. Hyattsville, MD; Public Health Service; 2012.
Severe Migraine Is Ranked in the Highest Disability Class by the World Health Organization

Severe Migraine
Active Psychosis
Dementia
Quadriplegia

Unipolar Major Depression
Blindness
Paraplegia

Mild Intellectual Disability
Down Syndrome

Below-the-Knee Amputation
Deafness

INCREASING DISABILITY

Disability Class 4
Disability Class 5
Disability Class 6
Disability Class 7

Migraine Is Debilitating

Negative Impact on:

- Sex life: 43%
- Love: 31%
- Finding friends: 10%
- Social position: 37%
- Leisure time: 59%
- Finances: 30%
- Family situation: 67%
- Pursuing studies: 48%
- Work attendance: 76%
- Pursuing career: 27%

Migraine Pathways: Sensitization

Activated central neuron (thalamus)
Sensitized peripheral neuron (trigeminal ganglion)
Cutaneous allodynia
Throbbing pain

Meningeal blood vessel
Pain perception

Sensitized central neuron (trigeminal cervical complex)
Muscle tenderness
What Happens During a Migraine Attack?

Clinical Phases of Migraine

Prodrome
- Fatigue
- Food craving
- Muscle pain
- Cognitive change
- Mood change
- Sensory disruption

Aura (if present)
- Visual
  - Scintillating scotoma
- Sensory
- Motor

Headache
- Localization
- Throbbing
- Nausea
- Vomiting
- Photophobia
- Phonophobia

Postdrome
- Fatigue
- Gastrointestinal upset
- Cognitive change
- Muscle pain
- Mood change

Evolution of Migraine Symptoms

≤1 hour

~4-72 hours

American Headache Society.
Differential Diagnosis of Primary Headaches

- Sinus headaches or infection often misdiagnosed when correct diagnosis is migraine
- In 90% of cases, clinician- or self-diagnosed sinus headache is migraine

Landmark Study: How Likely Is it That a Headache Is Migraine?

- Prospective, open-label study of patients with episodic headache (N = 1203), >90% seen in primary care
- Self-report or physician diagnosis of migraine almost always correct
- Self-report or physician diagnosis of nonmigraine almost always later found out to be migraine
- Migraine should be the default diagnosis for recurrent and disruptive headache that is brought to the attention of a healthcare clinician

### Migraine vs Tension Headache: A Common Misdiagnosis

<table>
<thead>
<tr>
<th>Migraine</th>
<th>Tension-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 of the following 4:</td>
<td>≥2 of the following:</td>
</tr>
<tr>
<td>• Unilateral (59% of migraines)</td>
<td>• Bilateral</td>
</tr>
<tr>
<td>• Pulsating (85% of migraines)</td>
<td>• Not pulsating</td>
</tr>
<tr>
<td>• Moderate-severe intensity</td>
<td>• Mild-moderate intensity</td>
</tr>
<tr>
<td>• Aggravated by routine physical activity</td>
<td>• Not aggravated by routine physical activity</td>
</tr>
<tr>
<td>≥1 of the following</td>
<td>No nausea/vomiting</td>
</tr>
<tr>
<td>• Nausea/vomiting (73% of migraines)</td>
<td>One or neither: photophobia/phonophobia</td>
</tr>
<tr>
<td>• Photophobia/phonophobia (~80% of migraines)</td>
<td></td>
</tr>
<tr>
<td>Not attributable to another disorder</td>
<td>Not attributable to another disorder</td>
</tr>
</tbody>
</table>

Migraine vs Tension Headache: A Common Misdiagnosis

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**ACTION ITEM:** Differentiate between migraine and other primary headaches to ensure early and appropriate treatment

Case Study: Joanne, Age 47

- Married; 2 grown sons
- She works part-time as an English teacher at a local community college
- She is in generally good health but complains of recurrent “tension headaches” (2-3 times/mo) for the last 6 months
- The headaches have not been relieved by nonprescription analgesics
- Her vital signs are normal and she takes no prescription medications
- Her sister also has debilitating headaches, but has not seen a clinician
What is the first step in diagnosing Joanne’s condition?

1. Brain magnetic resonance imaging (MRI) scan
2. Headache diary
3. Headache history
4. Response to a trial of medication

Use your keypad to vote now!
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Diagnosis: Importance of Headache History

- How does the headache begin?
  - Precipitating event, illness, injury
- Frequency and patterns
  - Any significant changes
- Location
- Quality and intensity
- Time to peak intensity
- Duration
- Warning symptoms and aura
- Associated symptoms and level of disability
- Triggers and aggravating or relieving factors
- Headache diary is helpful
Importance of a Headache Diary

- Helps to identify
  - Triggers
  - Location
  - Warning signals
  - Length
  - Stress, exercise, other related events
- Records intensity of pain
- Monitors treatment progress

A headache diary consists of tracking the following information:

<table>
<thead>
<tr>
<th>Date</th>
<th>Time (start/finish)</th>
<th>Intensity (rate 1-10: most severe being 10)</th>
<th>Preceding Symptoms</th>
<th>Triggers</th>
<th>Medication (and dosage)</th>
<th>Relief (complete/moderate/none)</th>
</tr>
</thead>
</table>
Importance of a Headache Diary

- Helps to identify
  - Triggers
  - Location
  - Warning signals
  - Length
  - Stress, exercise, other related events

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- Monitors treatment progress

A headache diary consists of tracking the following information:

**ACTION ITEM:**
Emphasize to patients the importance of keeping a headache diary to identify triggers and nature of headache and to assess treatment progress.
Case Study (cont’d): Joanne

• Joanne’s headaches last from a few hours to up to a day
• She reports no aura
• Joanne says the severity is sometimes moderate, but is sometimes severe enough that she has to lie down
• Loud noises and bright lights make the headache worse, and sometimes her neck becomes sore
• She sometimes feels congested and has a runny nose
• She no longer feels comfortable babysitting for her grandchildren for fear that she will be disabled by a headache
Given this information, what is the most likely diagnosis for Joanne?

1. Migraine with aura
2. Migraine without aura
3. Sinus headache
4. Tension-type headache

Use your keypad to vote now!
Given this information, what is the most likely diagnosis for Joanne?

1. Migraine with aura
2. Migraine without aura
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Use your keypad to vote now!
Migraine With Aura: Criteria Used in Research Settings

- A. ≥1 attack fulfilling criteria B and C
- B. ≥1 of these fully reversible aura symptoms:
  - Visual, sensory, speech and/or language, motor, brain stem, retinal
- C. ≥2 of the following 4 characteristics:
  - ≥1 aura symptom spreads gradually over ≥5 minutes and/or ≥2 symptoms occur in succession
  - Each individual aura symptom lasts 5-60 minutes
  - ≥1 aura symptom is unilateral
  - Aura accompanied, or followed within 60 minutes, by headache
  - Not better accounted for by another diagnosis; transient ischemic attack excluded
- Aura present in only about one-third of patients with migraine

Value of Migraine Self-Assessment Questionnaires

- **MIDAS™¹**
  - 7 questions measure impact of migraine frequency
  - 4 grades of disability: I = little or none, II = mild, III = moderate, IV = severe
- **HIT-6™²**
  - 6 questions measure impact of headache severity
  - Questions answered “never” (6 points) to “always” (13 points)
  - Total score of ≥50 suggests significant impact
- **MIDAS and HIT-6 correlate well (r = .52); used together, may improve assessment of disability³**
- Both questionnaires available at http://www.migraineresourcenetwork.com

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HIT = Headache Impact Test; MIDAS = Migraine Disability Assessment.

• After it is explained to her that her symptoms and history are more consistent with migraine without aura, Joanne is surprised because she thought migraines were always associated with an aura

• She says that she “is happy to know what is going on” and wants to know what to do about it
What is the next step in Joanne’s evaluation?

1. Asking more questions about headache impact
2. Brain MRI
3. Prescription for a triptan
4. Referral to a neurologist

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Use your keypad to vote now!
Clinician-Patient Communication Is Improved With Open-Ended Questions

- How do migraines make you feel?
- What other pain do you have besides headache?
- How does migraine affect your daily life?
- Can you describe the impact migraines have on your work, family, and social life?
- How do your migraines affect you between attacks?
- Do headaches affect others in your family?

Involve patient in decision making

Common Migraine Triggers

- Stress or “let-down” from stress
- Irregular meals, dehydration
- Irregular caffeine, chocolate, nuts, bananas, etc
- Irregular sleep (particularly excessive sleep)
- Weather, changes in weather
- Light, sunlight exposure
- Sensitivity to odors (osmophobia)
- Air travel, change in barometric pressure
- Menstrual period
- Alcohol
Medications That May Exacerbate Migraines

- Oral contraceptives
- Hormone replacement
- Selective serotonin reuptake inhibitors
- Steroids (tapering)
- Decongestants
- Short-acting sedatives
- Some bone density medications
- Proton-pump inhibitors

Migraine Diagnostic Considerations

• No single criterion necessary or sufficient for diagnosis
• Up to one-third of patients have neurologic aura
• International Headache Society criteria do not require gastrointestinal symptoms
• Vomiting occurs in less than one-third of patients
• 41% of patients report bilateral pain
• 50% of time, pain is nonpulsating

Red Flags: SSNOOP

S  Systemic involvement (fever, myalgias, weight loss)

Systemic disease (cancer, AIDS)

N  Neurologic symptoms or signs

O  Onset sudden (thunderclap headache)

O  Onset after age 50 years

P  Pattern of change: progressive headache/fewer headache-free periods; change in type of headache

• Be alert to signs/symptoms of secondary headache

Collaborative Care of Migraine

• Migraine is chronic and requires patients and clinicians to work together toward common therapeutic goals
• Invitation to understand and address all migraine-related health issues and comorbidities
• Integration of assessment tools and relevant patient education
• Opportunities for patients and clinicians to improve communication and understanding of migraine
• Recognition of “stages” in evolution from episodic to chronic migraine provides opportunity to develop strategies that personalize care on the basis of disease progression
• Using this model, preventive therapy is central to migraine management

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**ACTION ITEM:**
Participate in a collaborative care model of migraine to improve communication, involve patients in decision making, and focus on prevention

### Behavioral Interventions and Collaborative Care

<table>
<thead>
<tr>
<th>Nurse Practitioners, Physician Assistants, Physicians</th>
<th>Psychology/Behavioral Specialists</th>
<th>Physical Therapy/Occupational Therapy</th>
<th>Techniques for All Patients</th>
<th>Techniques Based on Patient Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Medical communication</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Adherence</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Relaxation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Stress</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Dialectic behavioral therapy</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

Treatment/Prevention With Lifestyle Modification: Consistency Is Key

- Don’t skip meals
- Six 8-oz glasses of water per day
- Caffeine <200 mg/d
- Prophylactic medications
- Sleep
- Exercise
Treatment/Prevention With Lifestyle Modification: Consistency Is Key

Don’t skip meals

Caffeine <200 mg/d

ACTION ITEM: Provide patient education and encourage use of nonpharmacologic interventions for treatment/prevention
Nonspecific Treatments

- Antiemetics
- Combination NSAIDs
- Opiates (only for limited use in very severe migraine)
- Corticosteroid (intravenous) (rescue therapy)
- Butalbital/aspirin/caffeine: approved for tension headache; sometimes used for migraine, but not approved for this purpose
Acute Treatment of Migraine: Triptans

- Selective $5\text{-HT}_{1\text{B/1D}}$ receptor agonists
- Pretreatment pain severity strongest predictor of pain relief
- Patients who do not respond to one triptan may respond to another

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Route</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Oral, a subcutaneous, nasal</td>
<td>Oral: 25, 50, 100; nasal: 5, 20; injection: 4, 6</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Oral, ODT</td>
<td>5, 10</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Oral, ODT, nasal</td>
<td>Oral, ODT: 2.5, 5; nasal: 5</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Oral</td>
<td>6.25, 12.5</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Oral</td>
<td>20, 40</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Oral</td>
<td>1, 2.5</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Oral</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*aCombination with naproxen also approved in adult and pediatric patients.
5-HT = 5-hydroxytryptan; ODT = orally disintegrating tablet.

Pharmacokinetics of Triptans

<table>
<thead>
<tr>
<th>Rapid Onset</th>
<th>Longer Half-life</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Naratriptan</td>
<td>Tablet/ODT</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Frovatriptan</td>
<td>Nasal spray</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td></td>
<td>Nasal powder</td>
</tr>
<tr>
<td>Almotriptan</td>
<td></td>
<td>Injection</td>
</tr>
<tr>
<td>Eletriptan</td>
<td></td>
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Formulations:
- Tablet/ODT
- Nasal spray
- Nasal powder
- Injection
Acute Treatment of Migraine: Ergots, Diclofenac

• Ergots
  – Also 5-HT$_{1B/1D}$ receptor agonists
  – More side effects than triptans but longer lasting
  – Less frequently used
  – Formulations
    • DHE mesylate (tablet, injection, nasal spray; orally inhaled formulation in development)
    • Ergotamine tartrate
    • Ergotamine tartrate + caffeine
• Diclofenac potassium for oral solution (packets)
  – NSAID specifically approved for migraine
New Delivery Device: Transcranial Magnetic Stimulation

• Generally available only through headache centers

Positioning of device for treatment

Acute Treatment Principles

- Treat at least 2 attacks with the same medication
- If medication is ineffective:
  - Ensure that no other medications are interfering with response
  - Treat early in the attack
  - Maximize dose
  - Change formulation/route of administration
  - Change drug
  - Add drug
  - ? combination therapy (eg, sumatriptan/naproxen)
  - ? prophylactic treatments
Acute Treatment Principles

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  - Maximize dose
  - Change formulation/route of administration
  - Change drug
  - Add drug

**ACTION ITEM:**
Treat at least 2 migraines with same medication; consider alternatives if medication remains ineffective
Case Study (cont’d): Joanne

• Joanne is using sumatriptan tablets
• Initially, these provided good relief, but about 3 weeks ago her headaches started getting more frequent and more severe and she asks for more medication
• She has started to add aspirin/acetaminophen to her headache regimen
• Reviewing her headache diary with her, you see that her headaches were more frequent than she reported: 6 or 7/mo
• You suspect that Joanne is having medication-overuse headache
Is Joanne a candidate for preventive therapy?

1. No
2. Not sure
3. Not until she has had a trial of other acute medications
4. Yes

Use your keypad to vote now!
Is Joanne a candidate for preventive therapy?

1. No
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4. Yes

Use your keypad to vote now!
Epidemiologic studies suggest that approximately 38% of migraineurs would benefit from preventive therapies, but only 11% currently receive them.

<table>
<thead>
<tr>
<th>Headache-Related Impairment</th>
<th>Headache Frequency, Days per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>–</td>
</tr>
<tr>
<td>Some</td>
<td>–</td>
</tr>
<tr>
<td>Severe/bedrest</td>
<td>Consider</td>
</tr>
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Behavioral Interventions

- Avoid triggers
- Relaxation training
- Biofeedback
- Electromyography biofeedback
- Cognitive behavioral therapy
- Combination treatment
  - Combination behavioral modalities
  - Combination behavioral + pharmacologic interventions

Prevention of Episodic Migraine: Food and Drug Administration–Approved Agents

Start with low dose and increase weekly to effect

<table>
<thead>
<tr>
<th></th>
<th>Formulation</th>
<th>Starting → Maintenance Dose (mg/d)</th>
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</thead>
<tbody>
<tr>
<td>Sodium valproate,</td>
<td>Tablets, immediate-/delayed-release capsules</td>
<td>500 → 1000</td>
</tr>
<tr>
<td>divalproex sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Tablets, oral solution</td>
<td>80 → 160-240</td>
</tr>
<tr>
<td>Timolol</td>
<td>Tablets</td>
<td>10 → 30</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Tablets, sprinkle capsules</td>
<td>25 → 100</td>
</tr>
</tbody>
</table>

FDA-Approved Agents for Chronic Migraine

• Onabotulinumtoxin type A
Treatments Also Used for Prophylaxis

- NSAIDs
- Other β-blockers
- Tricyclic antidepressants (eg, amitriptyline)
- Gabapentin
- Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers
- Petasites (butterbur root)
- Magnesium
- Vitamin B2 (riboflavin)
- Coenzyme Q10

Principles of Preventive Pharmacotherapy

- Start at a low dose
- Give each treatment an adequate trial
- Preventive pharmacotherapy should be continued for at least several months
- Avoid interfering, overused, and contraindicated drugs
- Re-evaluate therapy
- Women of childbearing potential should understand risks
- Involve patients in their care to maximize adherence
- Consider comorbidities and choose medications to treat several coexisting disorders where possible
- Choose a drug based on efficacy, patient preferences, headache profile, adverse effects

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**ACTION ITEM:**
When starting preventive pharmacotherapy, start at low dose, consider comorbidities, and respect patient preferences

On the Horizon: Potential New Medications/Formulations for Migraine

- Orally inhaled DHE
- CGRP-blocking monoclonal antibodies
- Small-molecule CGRP receptor antagonists
- Neurally acting antimigraine agents that target 5-HT$_{1F}$ receptors
  - Lasmiditan (COL-144)
- Glutamate receptor antagonist
Case Study Conclusion

- Joanne has been taking topiramate sprinkle capsules for preventive therapy; she likes the convenience of sprinkling them on her food
- At 6 months, she reports that her headaches occur no more than once or twice a month; when they do occur, she uses sumatriptan
- She hasn’t missed a day of work in several months
- Her relationship with her husband has improved
- She wonders if she should continue with a headache diary and how long she should continue with preventive therapy
Differentiate between migraine and other primary headaches to ensure early and appropriate treatment

Emphasize to patients the importance of keeping a headache diary to identify triggers and nature of headache and to assess treatment progress

Participate in a collaborative care model of migraine to improve communication, involve patients in decision making, and focus on prevention

Provide patient education and encourage use of nonpharmacologic interventions for treatment/prevention

Treat at least 2 migraines with same medication; consider alternatives if medication remains ineffective

When starting preventive pharmacotherapy, start at low dose, consider comorbidities, and respect patient preferences

PCE Promotes Practice Change
Q & A
How effective are nonpharmacologic options such as feverfew, magnesium, co-enzyme Q10, and vitamin B2?
What is the effect of oral contraceptive pills on migraine with aura?
Does menopause have an impact on migraine frequency or severity?
What is cognitive behavioral therapy and how is it helpful in migraine?
What is the impact of migraine on the brain? Is there an association between migraine and stroke?
With headache onset after the age of 50, what are important components of the diagnosis?
In a patient with a cardiac history and severe migraines, are triptans safe?
What is the mechanism of action of onabotulinumtoxinA? Does its administration require training?
Do auras always start before migraine pain, or can they occur simultaneously?
What is a vestibular migraine?
If a patient is taking topiramate for preventive therapy and suddenly has an increase in the number of headaches, what is the next step?
How should we treat children with migraines?