Updates for Migraine Management in Primary Care

A CME-certified Grand Rounds Activity

Educational Objectives

At the conclusion of this activity, participants should be able to:

• Examine the epidemiology, differential diagnosis, and impact of migraine within the primary-care patient population
• Describe the pathophysiology of migraine, including the role of calcitonin gene-related peptide (CGRP)
• Delineate current standards of pharmacologic and nonpharmacologic management for the preventive and acute management of migraine
• Assess clinical safety and efficacy data for emerging therapeutic agents for the prevention and treatment of migraine

Several Types of Headaches (HAs)

Primary Examples
• Migraine
• Tension type
• Cluster

Secondary Examples
• Infectious (Meningitis, Sinusitis)
• Space occupying lesion (abscess, mass)
• Blinding (SAH)
• Vascular (venous sinus thrombosis, cervical artery dissection)
• Rheumatologic (GCA)
• Ophthalmological (angle-closure glaucoma, optic neuritis)
• Neurological (trigeminal neuralgia, post-herpetic neuralgia)
• Idiopathic intracranial hypertension
• Others (acute hypertension, CO poisoning)

Primary and Secondary Examples
Our focus today will be migraines

Lizzy, a 31-year-old Mother

• Asks you for help with her sinus headaches. She has been getting them for several years but they are occurring almost daily now.
• Predominantly frontal and maxillary in location; not throbbing.
• Takes acetaminophen almost daily, along with pseudoephedrine preparations and occasional loratadine when she has watery eyes and nasal congestion.
• What else do you need to know to help Lizzy?
• What treatments could be offered?

Migraine Impact and Epidemiology

• One in five US adults has migraine
  – 28 million persons have migraine each year in the US
• Prevalence
  – Women 25% (lifetime)
  – Men 8% (lifetime)
  – ~70% of migraineurs have positive family history in first-degree relative
• 5–9 million PCP office visits per year in US due to migraines
  – 5 million headache annual visits to US EDs
  – Ranks #5 for annual emergency department visits
  – Associated with ~$17 billion/year in direct and indirect healthcare costs

Differentiating Migraine from Other Types of Headache

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Activity Slides 1
Basics of the History and Physical Exam

**Headache Screening**
- Evaluate
  - Patient walking, body language
  - Assess symmetry of CN, motor, sensory, coordination, DTRs
  - Palpate head, arteries, trigger points
  - Examine neck for stiffness and ROM
  - Perform fundoscopic exam
  - Examine oral cavity/TMJ

- Inquire about
  - Timing/frequency
  - Exacerbating factors/triggers

  - What meds have been tried
  - Use/overuse of meds
  - Location
  - Intensity
  - Nature of pain
  - Associated symptoms
    - Visual, motor, sensory, GI

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**Episodic Migraine (EM) Recognition by ICHD Criteria**

**Migraine without Aura (1.1)**
- At least FIVE Attacks with:
  - At least 2 of the following
    - Unilateral
    - Pulsating
    - Moderate to severe pain
    - Aggravated by or avoidance of routine physical activity
  - At least 1 of the following
    - Nausea and/or vomiting
    - Photo and phonophobia
  - No organic disease

**Migraine with Aura (1.2.1-6)**
- At least TWO Attacks with:
  - At least 1 fully reversible symptom without motor
    - Visual + and/or -
    - Sensory + and/or -
    - Dysphasic speech
  - At least 2 of the following
    - At least one aura symptom develops gradually over ≥5 min or different symptoms occur in succession over ≥5 min
    - Each symptom lasts ≥5 and ≤60 min
  - 1.1 begins with aura or in ≤60 min
  - No organic disease

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**Chronic Migraine (CM)**
- Headache ≥15 days/month AND duration ≥4 hours/day x >3 mo
  - Not just "more" episodic migraine!
  - Evolves as complication of EM (2.5%/year)
  - More disabling with higher costs
  - Risk factors include:
    - Comorbidities (anxiety, depression, obesity)
    - Iatrogenic factors (medication type and frequency of use)
  - Can be reversed; goal is revert back to episodic migraine

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**Understanding the Chronology of Migraine**

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**Migraine Evolution**

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**ID Migraine™ – A Validated Screener**

**Closing the HA Diagnosis Gap**

Choose Yes or No
- When you have a HA, do you feel nauseated or sick to your stomach?
- When you have a HA, does light bother you (a lot more than when you don’t have a HA)?
- During the last 3 months, have your HAs limited your ability to work, study, or do what you needed to do?

2/3 Yes for migraine:
- Sensitivity: 0.81
- Specificity: 0.75

Positive predictive value of 93% in primary care setting
Indications for Diagnostic Testing

**Green Flags**
- Stable pattern >6 months
- Long-standing HA history
- Family history of similar HA
- Normal exams

**Red Flags**
- Systemic symptoms: fever, weight loss
- Secondary risk factors: HIV, cancer
- Neurologic symptoms or signs
- Onset: new, sudden, abrupt, or split-second
- Older: especially >50 years
- Pattern change

Diagnostic testing indicated if ANY red flags are present.

Diagnostic testing NOT indicated if only green flags present.


If Indicated, Which Diagnostic Test?

- CT or MRI? With or without contrast?
  - Yield minimal without neurologic signs: <1% identify cause for HA
  - MRI: greater detail, more false positives
  - MRI for posterior fossa disease
  - MRI + MRA for suspected aneurysm/other vascular lesions
  - CT without contrast to R/O subarachnoid hemorrhage

- Weigh radiation exposure with CT, renal contrast concerns with CT and MRI vs potential yield of study

- CHOOSING WISELY: Don’t perform neuroimaging studies in patients with stable headaches that meet criteria for migraine


Back to Lizzy

- Further history: she used to have more common migraine headaches as a teen; these changed over time to less intense, daily “sinus” type headaches
  - In 2 studies, 86-88% of patients self diagnosed as sinus headaches actually met ICHD criteria as migraine or probable migraine1,2
  - Based on diary review, 94% of headaches that prompt a visit to the PCP are migraine type headaches3
  - You diagnose Lizzy with migraines; the appropriate treatments you provide help reduce her headaches by >50% over next couple of months

Key Takeaways

- If a patient self diagnoses their headache, don’t assume they’re right!!
- Migraine is the most common cause of headache that brings a patient to the doctor
- Recurring moderate to severe headache is migraine until proven otherwise
- Migraine patients can experience many different types of HAs from the same underlying mechanism
- Prompt treatment may restore normal neurologic function and prevent the evolution of EM to CM

Ricky, a 31-year-old CPA

- Has history of very occasional migraines since his early 20s. Naproxen and/or a triptan usually provided relief
- Started new job 6 months ago, requiring him to work long hours
- Headaches have increased and now occur several days a week, especially on most weekend days for the last few months
- He is now taking an abortive medication most days a week

The Many Manifestations of Migraine
And Current Approaches to Management
Updates for Migraine Management in Primary Care

**Headache Treatment**
- **Education**
- **Acute (abortive)**
  - Taken after attack has begun to relieve pain and disability and stop progression
- **Preventive**
  - Taken to reduce attack frequency, severity, and duration of attacks
- **Non-pharmacologic (behavioral, neuromodulation, complementary/alternative)**

**Principles of Management for the Patient**
- Establish realistic expectations
  - >50% reduction with prevention
  - >70% relief with acute treatment
  - There is no cure!
- Encourage patients to participate in their care
  - Keep a headache diary, identify triggers
  - Accept that some Rx side effects are inevitable
  - Optimize behavioral management
  - Acute: administer treatment early; do not use more than 2-3x/week or 9 days/month
  - Prevention: follow guidelines for drug/complementary/alternative treatments
  - Regular patient follow-up with dose/drug/combination changes as needed

**Behavioral Strategies**
1. **Sleep** – 6 to 8 hours, consistent within 1 hour to bed/time (even weekends)
2. **Exercise** – Any better than none; aerobic >> nonaerobic
3. **Stress management** – Biofeedback/relaxation, cognitive-behavioral, time management
4. **Substance use** – Taper caffeine to maximum 1-6 oz/cup
5. **Eat** – Fresh, non-processed, small, frequent healthy meals/snacks

**Guidelines for Initiating Migraine Prevention Therapy**
- **Goals:** reduce disability and medication overuse
- Many migraineurs qualify for prevention, few are offered it
- **Institute preventive strategies if:**
  - 2 attacks/mo with disability totaling >3 d/mo
  - Recurring HA significantly interfering with patient’s daily routine despite acute Rx
  - Presence of uncommon migraine conditions: hemiplegic migraine, prolonged aura, migrainous infarction
  - Patient preference, cost considerations, med intolerance
  - Acute medications overused >2 d/wk, ineffective, intolerable side effects, or contraindicated

**Acute (Abortive) Migraine Medications**
- **Non-specific**
  - NSAIDs
  - Combination analgesics
  - Corticosteroids
  - Neuroleptics/antiemetics
- **Specific**
  - Triptans
  - Ergotamine/DHE

**Migraine Preventive Therapies**

**Level of Evidence/Effect** | Drug Class/Agent
--- | ---
**Level A** | Established Efficacy
Antiepileptic drugs: Divalproex sodium, valproic acid, topiramate, lamotrigine
Beta blockers: Metoprolol, propranolol, nadolol
Triptans: Frovatriptan (for menstrual-related migraine)
Antiplatelet receptor blockers: Candesartan (studies now suggest level A efficacy)**
**Level B** | Probably Effective
Antidepressants/SNRI/SSRI/TCA: Venlafaxine, amitriptyline, mirtazapine
Beta blockers: Atenolol, metoprolol
Triptans: Zolmitriptan, sumatriptan (for menstrual-related migraine)
**Level C** | Possibly Effective
ACE inhibitors: Lisinopril
Nitrite drugs: Nitroglycerine, pindolol
Alpha agonists: Clonidine, methyldopa
Antiemetics: Dimenhydrinate, scopolamine
Antihistamines: Cyproheptadine

Start low and go slow. Allow 2-3 months for full effect

CHOOSING WISELY
Don’t recommend prolonged or frequent use of OTC pain meds for headache

NSAID = non-steroidal antiinflammatory drug; DHE = dihydroergotamine.

**New Formulations (FDA-approved)**
- Breath-powered intranasal sumatriptan dry powder
- New sumatriptan autoinjectors

**New Formulations (In development)**
- Microneedle array skin patches (zolmitriptan, sumatriptan)
- Orally inhaled (zolmitriptan, DHE)
- New intranasal delivery: dry powder, enhanced permeation
- Sumatriptan liquid spray
- Gepants: 5-HT1F receptor agonist (lasmiditan)

*In >2 Class I Trials; †In 1 Class I or 2 Class II studies; ‡In 1 Class II Study

Silberstein SD et al. Neurology. 2012;78;1337-1345. **Not in original paper Not approved for migraine prevention

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Treatment for Chronic Migraine

Institute Behavioral Strategies and Prevention Medications

- Specific FDA-approved medication: OnabotulinumtoxinA
  - Approved for prophylaxis of chronic migraine (≥15 headache days/month)
  - 8-9 fewer HA compared to 6-7 with placebo
  - 31 injection sites into head/neck Q 3 mo
  - Boxed warning re: possibility for spread causing weakness in distant area(s)

- OnabotulinumtoxinA blocks the presynaptic release of neurotransmitters, as an endopeptidase that interrupts the vesicle docking process

Key Takeaways

- Successful treatment of migraines includes a comprehensive approach of patient education, behavioral strategies, pharmacologic therapies and non-pharmacologic interventions
- Consider preventive medications for prolonged, severe or complicated HAs, or if abortive therapies are required more than 2x/week

Insights into Migraine Pathophysiology

- Maria, a 38-year-old Female
  - Migraines began when she was 14
  - Currently compliant with topiramate 50 mg BID; uses a triptan as needed
  - In the last 3 months, her headaches have increased from 1x/wk to 3-4 days/wk despite optimal lifestyle management and trigger avoidance; they are not always relieved despite prompt triptan use

Migraine Pathogenesis

Calcitonin Gene Related Protein (CGRP) First Identified as a Potential Mediator of Trigeminal Inflammation

- 1st discovered as a potent vasodilator
- Initially considered important in migraine because of its potential peripheral actions
  - Vasodilation
  - Neuroinflammation
- Belongs to calcitonin family (calcitonin, amylin, adrenomedullin, intermedin) In humans, α-CGRP and β-CGRP isoforms

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### New, Emerging and Alternative Approaches to Treating Migraine Headaches

**CGRP in Migraine**
- Potent vasodilator of cerebral arteries
- Released into jugular venous system during migraine
- Serum CGRP levels elevated in CM
- CGRP infusion evokes migraine
- Small-molecule CGRP-receptor antagonists (gepants) effectively abort migraine attacks
- Large molecule anti-CGRP and anti-CGRP-receptor monoclonal antibodies (mAbs) prevent EM and CM
  - Because of large size, potential to cross blood brain barrier limited
  - mAb activity likely peripheral


### Small Molecule Approach
**CGRP-Receptor Antagonists: The Gepants**
- Development of older gepants stopped because of liver toxicity
- Newer, safer gepants in development:
  - For acute treatment of episodic migraine
    - BI 44370 TA (oral): effective vs placebo in phase II
    - Rimegepant: effective vs placebo in phase III
  - For preventive treatment of episodic migraine
    - Atogepant vs placebo underway in phase II for migraine prevention
    - Rimegepant: phase 2 in progress
- Gepants have NEVER failed on EFFICACY


### Large Molecule Approach
**Four Monoclonal Antibodies to CGRP or its Receptor Approved or in Development**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Emphasis</th>
<th>Origin</th>
<th>Indication</th>
<th>Regulatory status</th>
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<td>Fully human</td>
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</tr>
</tbody>
</table>

All antibodies target CGRP receptor or ligand.

### Rimegepant – Phase III Trial for Abortive Use
Safety and tolerability comparable to placebo, including LFTs

Lipton et al. presented at AHS June 2018.

### Erenumab (FDA Approved): Phase III Studies
**Migraine Day Reduction vs Placebo**


**Erenumab phase III EM prevention**

**Erenumab registration trial CM prevention**

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Updates for Migraine Management in Primary Care

**Galcanezumab (FDA Approved): Phase III Studies**

- **Stauffer V et al.** Headache. 2017;57(suppl 3):190 (abstract PS18).
- **Detke HC et al.** AHS meeting, June 8-11 2017 (late-breaking abstract PS-89LB).

**Migraine Day Reduction vs Placebo at 3 Months**

- **Galcanezumab phase III EM prevention (EVOLVE-1)**
  - Placebo (n = 281)
  - Galcanezumab 120 mg
  - Galcanezumab 240 mg
  - ***P <0.001 (at each month)

- **Galcanezumab phase III CM prevention (REGAIN)**
  - Placebo (n = 281)
  - Galcanezumab 120 mg
  - Galcanezumab 240 mg
  - **P <0.01***

**Fremanezumab (FDA Approved): Phase III Studies (HALO)**

- **Aycardi E et al.** Headache. 2017;57(suppl 3):129-130 (abstract IOR05).

**Change from Baseline in Headache Days of at Least Moderate Severity (Migraine Days) at 3 Months**

- Placebo
- Fremanezumab 225 mg
- Fremanezumab 675 mg
- LS mean (+/- SE) change from baseline
- **P <0.0001***

**Key Takeaways**

- New agents in development target molecules involved in migraine pathogenesis
- One such target is CGRP, a potent vasodilator of peripheral and cerebral arteries
  - Small molecules: gepants, taken orally for acute treatment
  - Large molecules: monoclonal antibodies (mAbs) injected monthly or quarterly for preventive treatment
- All mAbs display positive results, have quick onset, are well tolerated with low discontinuation rates
- Another class in development includes the “ditans,” serotonin1F receptor agonists
- None of the newer agents is associated with vasoconstriction
- As with all new agents, close vigilance is warranted

**Sophie, a 55-year-old Female**

- Diagnosed with episodic migraines over 20 years ago. Now has history of CAD and decided to embrace a “clean” lifestyle. She no longer wants to use naproxen and a triptan. She has begun an aerobic exercise regimen and her sleeping schedule has improved; however, she continues to experience headaches 5 times a month.
- She is asking you if there are any non-pharmacologic therapies that she could use to reduce her migraines?
Updates for Migraine Management in Primary Care

Neuromodulation/Complementary and Alternative Treatments

**Single-Pulse Transcranial Magnetic Stimulation (tTMS)**
Approved for Acute and Preventive Treatment

- **Rental – $150/month for first 3 months; $200/month for the first year thereafter**

- **Single-Pulse Transcranial Magnetic Stimulation (sTMS)**
  - Approved for Acute and Preventive Treatment
  - **BL=baseline**

  - **Acute – N=164 (82 sham); 2 pulses 30 sec apart within 1 hour of aura onset.**
  - **Primary outcome** = 2 hours pain free: 39% sTMS vs 22% sham P=0.0179

  - **Mean Reduction of Headache Days from Baseline**
  - **Performance Goal**
    - **Full Analysis Set**
      - **Per Protocol (PP; mean reduction in acute med use)**

  - **BL Days = 9.06**
  - **BL Days = 9.07**

  - **NS**
  - **P=0.054**

  - **50% responder rates**
  - **P=0.023**

  - **Active Sham**
  - **Cost: $400 to buy, can return for money back within 60 days, $25 q2-3 mos. for replacement electrodes**

- **Transcutaneous Supraorbital Neurostimulator (tSNS)**
  - Device covers the supratrochlear and supraorbital nerves
  - FDA approved: for acute and preventive migraine treatment
  - 67-patient RCT; turn it on and wear it 20 minutes/day

  - **Change in HA days (NS)**
  - **P=0.23**
  - **50% responder rates**
  - **P=0.032**

  - **Active Sham**

  - **Cost: $400 to buy, can return for money back within 60 days, $25 q2-3 mos. for replacement electrodes**

- **Non-invasive Vagal Nerve Stimulator (nVNS)**
  - Handheld, patient-controlled device that:
    - Preferentially activates vagal afferents, not vagal efferent pathways that cause bradycardia and bronchoconstriction
    - Inhibits rat CSD, central trigeminovascular, and thalamocortical pathways
  - Approved in US for acute treatment of migraine as well as episodic cluster headache
  - No serious AEs, minimal-risk device

- **Investigational Device**
  - Nerivo Migra
  - Proven high efficacy, rapid pain relief
  - 100% safe, no side effects, no limitations on use
  - No significant AEs

  - **Modulates Descending Tracts in the brain**
  - **Small, affordable**
  - **Simple, intimate, comfortable**

- **Complementary and Alternative Considerations**
  - Riboflavin
  - Magnesium
  - Acupuncture
  - Spinal/osteopathic manipulation
  - Physical therapy
  - Exercise
  - Yoga

  - Tai Chi
  - Melatonin
  - Hypnotherapy
  - Cold therapy
  - Massage
  - Homeopathy
  - Coenzyme Q10
Key Migraine Takeaways

- Recurring HA with disability is migraine until proven otherwise
- Patients should institute acute therapies as soon as possible after headache onset
- Use of acute meds >9 days/month can lead to medication overuse or transformation to chronic migraine
- Preventive treatment should be offered early to reduce adverse outcomes
- Newer modalities such as CGRP antagonists, neuromodulators and complementary options may supplement the therapeutic benefits offered by traditional therapies

Residency Connect

- In development
- Site to extend educational experience for Residents/Fellows
  - Online webcourses
  - Clinical tools and apps
  - Patient resources
- Place to make connections with colleagues
- Sign-up to be notified of the launch at:  http://residencyconnect.rockpointe.com/

CME Credit

- Post-activity Survey and CME Evaluation
  - If you’re seeking CME credit, please take a moment to answer the Post-activity Survey questions on your form
  - Your answers are important and will help us identify remaining educational gaps and shape future CME activities
  - After the post-activity survey, please complete the rest of the Evaluation form and ensure you fill in your name and demographic information after the questions
  - Return all forms to on-site CME staff

Thank you for joining us today!