Managing Migraine:
Primary Care for Primary Headaches

Jeffrey Unger, MD

Disclosures:
Speakers Bureau: Novo Nordisk, Abbott Diabetes, Janssen
Consultant: Novo Nordisk, Abbott Diabetes, Bayer
Research Grants: Novo Nordisk, GSK, Abbott Diabetes, Merck, Sanofi, Lilly, Pfizer
Stock Ownership: Novo Nordisk, Tandem Diabetes
Managing Migraine: Primary Care for Primary Headaches

Jeff Unger, MD, FAAFP, FACE
Director, Unger Primary Care Concierge Medical Group
Rancho Cucamonga, CA.
Assistant Professor of Family Medicine, UC Riverside School of Medicine

Disclosures

Jeff Unger, MD, FAAFP, FACE serves as a speaker for Amgen Pharmaceuticals and a consultant for Teva Pharmaceuticals.

Learning Objectives

1. Utilize evidence-based strategies to diagnose patients presenting with headache;
2. Identify associated conditions (e.g. depression), and red flags for potentially life threatening causes of headache;
3. Use evidence-based recommendations to prescribe treatment for patients presenting with acute or emergent headache pain;
4. Develop collaborative management plans, emphasizing patient education on avoiding triggers that cause headache, and adherence to prescribed treatment strategies;
5. Discuss newer pharmacologic targets for managing patients with Chronic Migraine.
Prevalence of Headache in the General Population

Prevalence of any form of headache was 93% in men and 99% in women. Among men, 8% had, at some point, experienced migraine compared with 25% of women. Migraine is the 2nd most disabling disease state in the world (low back pain is most disabling).


Primary vs Secondary Headaches

<table>
<thead>
<tr>
<th>PRIMARY</th>
<th>SECONDARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO structural or metabolic abnormality</td>
<td>Structural or metabolic abnormality</td>
</tr>
<tr>
<td>□ Tension type</td>
<td>□ Extracranial (sinusitis, otitis media, glaucoma, TMJ)</td>
</tr>
<tr>
<td>□ Migraine</td>
<td>□ Intracranial (SAH, vasculitis, dissection, central vein thrombosis, tumor, abscess, meningitis)</td>
</tr>
<tr>
<td>□ Cluster</td>
<td>□ Metabolic (CO2 retention, CO poisoning)</td>
</tr>
<tr>
<td>□ Other primary headaches</td>
<td></td>
</tr>
</tbody>
</table>

Headache Time Course

- Vascular
- Infectious
- Inflammatory/Neoplastic
- Secondary Headaches
- Primary Headaches

- Minutes
- Days
- Weeks/Months
- Months/Year
Diagnostic Red Flags and Comfort Signs

**Red Flags:**
- First or worst
- Abrupt onset
- Fundamental change in pattern
- New headache onset in patients ≤ 5 or ≥ 50 years of age
- Cancer, HIV, pregnancy
- Neurological dysfunction + headache
- HA onset with seizure or syncope
- HA onset with exertion, sex or Valsalva
- Abnormal vital signs
- In children, HA get progressively worse over time

**Comfort signs:**
- Stable pattern ≥ 6 months
- Long history of same headaches
- In children recurring, INTERMITTENT
- Normal neurologic exam
- Occur with menstruation
- +FH of same
- Known consistent triggers

Definition of Migraine

A stable pattern of recurrent disabling headaches without evidence of underlying cause.

Migraineurs have a genetic sensitivity towards severe, disabling headaches.

Migraineurs are born with a very sensitive nervous system.

The goal of migraine management is to allow the migraineur to learn to reduce their neurological sensitivity.

Migraine events disrupt normal neurologic brain function which increases the likelihood of having additional events.

Migraineurs are Born with a Genetically Predisposed Sensitive Neurological System

**Triggers:**
- Stress
- Hormonal changes
- Skipping meals
- Specific food (cheap red wine, caffeine)
- Sleep disruptions
- Medications and med overuse
- Weather
- Minor head trauma

**Protective factors:**
- Standardized sleep patterns
- Regular meals
- Exercise
- Stress management
- Pro-active treatment for menstrual migraine and prodrums
- Post menopause treatment
- Avoidance of triggers
- Reduction caffeine usage
Phases of a Migraine Attack (3-5 days Duration)

Prodrome: Symptoms
- Irritability - 48%
- Nausea - 43%
- Muscle pain/tenderness - 38%
- Change in energy level - 30%
- Change in mood - 24%
- Change in appetite - 21%
- Yawning - 21%

Migraine: Spreading Cortical Depression and Aura
Patient Describing Aura

Neck Pain During Migraine

Prevalence
- 75% of subjects

Descriptions
- 69% - tightness
- 17% - stiffness
- 5% - throbbing
- 5% - other

82% had previously been given a diagnosis of tension-type headache.

“Even My Hair Hurts”

(alldynia)

Cutaneous alldynia
- “Hair hurts”
- Painful when:
  - Shaving
  - Combing hair
  - Touching scalp
  - Resting head on pillow
  - Pulling hair back (wearing a ponytail)
  - Wearing eyeglasses or contact lenses
  - Wearing hat or headband
Migraine Pathogenesis

Genetic predisposition

Triggers evoke aberrant firing of neurons resulting in cortical spreading depression (CSD).

CSD activates the release of neurokinins and CGRP causing vascular dilation and increased platelet adhesiveness.

Neuronal flow into the nucleus caudalis can eventually cause nausea, vomiting, dizziness, and severe head pain.

“PIN” The Migraine Diagnosis | History

During the last 3 months, did you have the following with your headaches?

(YES/NO)

<table>
<thead>
<tr>
<th>P</th>
<th>Photophobia</th>
<th>Light bothered you (a lot more than when you don’t have headaches)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Impairment</td>
<td>Your headaches limited your ability to work, study, or do what you need to do</td>
</tr>
<tr>
<td>N</td>
<td>Nausea</td>
<td>You felt nauseated or sick to your stomach</td>
</tr>
</tbody>
</table>

2/3 YES = Migraine

Episodic Migraine vs Chronic Migraine

Frequent Episodic Migraine: < 15 Headache Days/Month

Chronic Migraine: > 15 headache days per month with 8 days being migraine-like headaches

Brain sensitivity is heightened. No time for neurological recovery between attacks

Brain can recover between attacks
Free Iron Deposition in the PAG
In a Patient With CDH

Barriers and Pitfalls in Primary Headache Diagnosis

Heads evaluated within Primary Care are rarely due to secondary causes.
Remember, migraine is a neurologic event, not a pathologic process based upon vasodilation and constriction.
Be cautious of patient-directed diagnoses: “Sinus, stress, or allergic headaches”
Most patients will have tried OTC meds prior to seeking professional consultation.
“Sinus headaches” and neck pain…think migraine

Physical Exam

Vital signs!
Look for any focal neurological findings
Listen to the head!
Feel the scalp and neck muscles
Listen to the Head!

Headache Lab Tests
- CBC
- ESR
- T4, TSH, Thyroid Peroxidase Antibody

Heather History
- Recurrent disabling headaches
- Light Sensitivity
- Nausea
- Vomiting
- + Family History
- Lasts 4-72 hours
Imaging Patients With Migraine

Patients with migraine and normal neurologic exam
Meta-analysis

99.82%
0.18%
Significant intracranial pathology

Choosing Wisely
DO NOT perform neuroimaging studies in patients with stable headaches that meet criteria for migraine
(American Academy of Neurology)

One Nerve Pathway:
Multiple Symptoms of Migraine

Does Peter Have Sinus Headaches?
Diagnosis of Sinusitis is Based on the Presence of at Least 2 Major or 1 Major + > 2 Minor Symptoms

<table>
<thead>
<tr>
<th>Major Symptoms</th>
<th>Minor Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purulent nasal discharge</td>
<td>Headache</td>
</tr>
<tr>
<td>Nasal congestion or obstruction</td>
<td>Ear pain, pressure or fullness</td>
</tr>
<tr>
<td>Facial congestion or fullness</td>
<td>Halitosis</td>
</tr>
<tr>
<td>Facial pain or pressure</td>
<td>Dental pain</td>
</tr>
<tr>
<td>Loss of sense or smell</td>
<td>Cough</td>
</tr>
<tr>
<td>Fever (acute sinusitis only)</td>
<td>Fever (for subacute or chronic sinusitis)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>


Nasal Endoscopy

No Headache
With a moderate to severe "sinus" headache
1 hour after treatment with sumatriptan 6mg SC

Strategies for Migraine Treatment

Lifestyle interventions
Acute treatment
- To stop pain and prevent progression
Preemptive treatment
- To preempt a predictable headache with a time-limited trigger
Preventive treatment
- To decrease frequency
Rescue therapy
- When all else fails

Photos courtesy of Jeff Unger, MD

Behavioral Approaches to Migraine Treatment

- No meal skips
- Relaxation exercises
- Exercise
- Sleep hygiene
- Stop smoking
- 2 cups java per day
- Stop analgesics > 2× weekly

Acute Migraine Treatment Goals

- Headache free in 2 hours
- Acute medication not needed >2 times/week
- Relief of associated symptoms
- Headache does not come back for 24 hours
- Back to full function in 2 hours
- Little to no side effects from medication

Triptans

- Sumatriptan
  - Oral: 25, 50, 100 mg
  - Subcutaneous: 4 or 6 mg
- Zolmitriptan
  - Oral: 2.5, 5 mg
  - ODT: 2.5, 5 mg
  - Nasal: 5 mg
- Naratriptan
  - Oral: 1, 2.5 mg
- Rizatriptan
  - Oral: 5, 10 mg
  - ODT: 5, 10 mg
- Almotriptan
  - Oral: 6.25, 12.5 mg
- Frovatriptan
  - Oral: 2.5 mg
- Eletriptan
  - Oral: 20, 40 mg
- Sumatriptan/Naproxen
  - Oral: 150 mg/500 mg

*OCT = orally disintegrating tablet*
Triptan Practical Strategies

- Treat early after migraine onset
- Migraine diary: Frequency, intensity, duration
- Use highest dose formulation
- Nausea: Ondansetron 4-8 mg SQ injection or nasal spray
- Expect to be pain free and associated symptom free within 2hrs

Early Intervention: Triptan Efficacy vs. Pain Intensity

![2 Hour Pain Free Response]

- Mild
- Moderate
- Severe

Pain Intensity When HA Treated

Adopted from Cady RK et al. SPECTRUM Study. Headache 2000 38:173

When To Consider Preventive Therapy

- Migraine significantly interferes with patient’s daily routine, despite acute treatment
- Attack frequency >1/wk
- Acute medication ineffective, contraindicated, over-used, or not tolerated
- Patient preference
- Presence of uncommon migraine conditions
Preventive Medications for Migraine

Traditional vs New Preventive Treatments

<table>
<thead>
<tr>
<th>Target</th>
<th>Traditional</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designed for other therapeutic areas</td>
<td>Designed for primary migraine prevention (EM, CM, MOH*)</td>
<td></td>
</tr>
<tr>
<td>Side Effects &amp; Tolerability</td>
<td>Numerous side effects</td>
<td>Minimal; similar to placebo</td>
</tr>
<tr>
<td>Time to Onset</td>
<td>2–4 months for effectiveness</td>
<td>&lt; 1 week – 1 month</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>~30% reduction in HA frequency; may lose effectiveness in MOH*</td>
<td>≥75% reduction in HA frequency; lower all acute medication use</td>
</tr>
</tbody>
</table>

*MOH: Medication overuse

American Academy Neurology
American Headache Society
Preventive Recommendations

Level A
- Divalproex Sodium
- Sodium valproate
- Topiramate
- Metoprolol
- Propranolol
- Timolol
- Frovatriptan(*)

Level B
- Amitriptyline
- Venlafaxine
- Atenolol
- Nadolol
- Naratriptan (*)
- Zolmitriptan(*)

* menstrual migraine
Basic Rules For Traditional Preventive Medications

**TREATMENT LENGTH**
- 2–3 months to determine efficacy
- 6-months may be necessary for maximal response

**TARGET GOALS**
- ↓ in frequency, severity, and/or duration of acute attacks

**FAMILY PLANNING**
- Potential adverse fetal effects of antimigraine medications

---

**Herbal Preventives**

- **Butterbur (Petadolex)** 75 mg twice a day
- **B2 (Riboflavin)** 400 mg a day*
- **Magnesium** 250-400 mg a day*
- **Feverfew** 3 dried leaves daily*

*Effective for pediatric migraine

---

**CGRP (Calcitonin-gene related peptide) and Migraine**

- CGRP is released from various locations in the body during times of physiologic or emotional stress
- CGRP sensitizes trigeminal afferents recruiting other nerves which can potentiate migraine
- As more nerves become sensitized, the thalamus becomes activated and patient develops central sensitization
- CGRP levels sampled from the external jugular vein are increased during migraine compared with controls who do not have migraine
- CGRP infusions can trigger migraine in migraineurs, but NOT healthy controls.
- CGRP inhibitors block migraine progression and reduce frequency, intensity and duration of migraine
- CGRP inhibition allows brain to recover more fully from a migraine event
- A brain which has not fully recovered from a migraine event is more reactive. Another migraine will follow

Frequent migraines, result in more frequent events
CGRP and Migraine

CGRP Inhibitor Prevents Migraine

CGRP Monoclonal Antibodies Prevent Receptor Activation
CGRP Inhibitors

<table>
<thead>
<tr>
<th>PHARMACOLOGIC TARGET</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galcanezumab</td>
<td>CGRP w/humanized antibody</td>
</tr>
<tr>
<td>(Emgality)</td>
<td>Cluster Headaches</td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>CGRP w/humanized antibody (CGRP ligand binding)</td>
</tr>
<tr>
<td>Erenumab</td>
<td>CGRP receptor with humanized antibody</td>
</tr>
<tr>
<td>Eptinezumab (Not approved)</td>
<td>CGRP w/humanized antibody</td>
</tr>
</tbody>
</table>

CGRP Inhibitors | Efficacy

% of patients with ≥ 50% reduction in the average number of headache days/month

<table>
<thead>
<tr>
<th></th>
<th>EPISODIC MIGRAINE</th>
<th>CHRONIC MIGRAINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galcanezumab</td>
<td>54-62%&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>27%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>40%</td>
<td>38-41%</td>
</tr>
<tr>
<td>Erenumab</td>
<td>38%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>38-42%</td>
</tr>
<tr>
<td>Eptinezumab</td>
<td>49-56%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>57-61%</td>
</tr>
</tbody>
</table>

Specific Migraine Treatment With Anti-CGRP mAb: Effects of Erenumab in Chronic Migraine

<table>
<thead>
<tr>
<th>Erenumab (Aimovig®)</th>
<th>Week 4</th>
<th>Baseline</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Change in Monthly Migraine Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=281)</td>
<td>−2.7</td>
<td></td>
<td>−3.6</td>
<td>−4.2</td>
</tr>
<tr>
<td>Erenumab 70 mg (n=188)</td>
<td>−5.1</td>
<td></td>
<td>−6.5</td>
<td>−7.5</td>
</tr>
<tr>
<td>Erenumab 140 mg (n=187)</td>
<td>−6.0</td>
<td></td>
<td>−7.0</td>
<td>−7.5</td>
</tr>
</tbody>
</table>
Specific Migraine Treatment With Anti-CGRP mAb: Effects of Galcanezumab in Chronic Migraine

Galcanezumab (Emgality®) REGAIN

Month 1
Baseline
Month 2
Month 3

Placebo (n=281)
Galcanezumab 120 mg
Galcanezumab 240 mg

LS Mean Change From Baseline (SE)
-2.7
-4.6
-4.8

* P <0.01
† P <0.001

Specific Migraine Treatment With Anti-CGRP mAb: Effects of Fremanezumab in Chronic Migraine

Fremanezumab (Ajovy®) HALO

Week After First Injection

Placebo (n=371)
Fremanezumab quarterly (N=375)
Fremanezumab monthly (N=375)

LS Mean Change From Baseline in Average Number of Headache Days per Month

Baseline
-2.5
-4.6
-4.3

Fremanezumab was equally effective in preventing EM and CM whether administered subcutaneously monthly or quarterly. (primary endpoint)

Difference between fremanezumab quarterly and placebo during 12-week period: -1.8 ± 0.3 days/month (P<0.001)
Difference between fremanezumab monthly and placebo during 12-week period: -2.1 ± 0.3 days/month (P<0.001)

CGRP Inhibitors | Safety

<table>
<thead>
<tr>
<th>Erenumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
<th>Eptinezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic SEs</td>
<td>No systemic effects (vs other biologics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI (constipation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory (nasopharyngitis, URI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, UTI, arthralgia, dizziness, anxiety, fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aimovig/aimovig_pi_hcp_english.ashx
(2) https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761089s000lbl.pdf
(3) https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761063s000lbl.pdf
CGRP Inhibitors | Administration

<table>
<thead>
<tr>
<th>Mode of Delivery</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galcanezumab (Emgality)</td>
<td>Self-inject with autoinjector or prefilled syringe Monthly</td>
</tr>
<tr>
<td>Fremanezumab (Ajovy)</td>
<td>Self-inject with prefilled syringe Monthly or every 3 months</td>
</tr>
<tr>
<td>Erenumab (Aimovig)</td>
<td>Self-inject with autoinjector Monthly</td>
</tr>
<tr>
<td>Eptinezumab (Not approved)</td>
<td>IV infusion Every 3 months</td>
</tr>
</tbody>
</table>

Menstrual Migraine Prevention Option

Frovatriptan 2.5 mg BID x 6 days beginning 2 days prior to onset of period
Frovatriptan 10 mg at onset of period
Frovatriptan 2.5 mg qd x 6 days beginning 2 days prior to onset of period

Migraine Rescue Strategies

- Olanzapine 10 mg PO
- Quetiapine 100 mg PO
- Magnesium Sulfate 1 gram IV Push
- Occipital nerve block*
- Sphenopalatine ganglion block*

* Use a “sphenocath”

* = Office procedure by a family physician
IV Magnesium-Abort Migraine Within 15 Seconds! NO KIDDING…

- 1 gram IV push over 1-2 minutes
- Side effect: severe hot flash lasting < 1 minute
- Eliminates migraine and migraine associated symptoms within 2-3 minutes
- Works best for HA < 24 hour duration. For HA > 24 hour duration use depakon 500 mg IV push over 3-5 minutes

Summary

Headaches evaluated within primary care are rarely due to secondary causes

Migraine diagnosed when there is presence of nausea, photophobia and/or disability during headaches

- "Sinus headaches" and neck pain…think migraine

Avoid drugs that contain opioids and Butalbital as they cause MOH (American Academy of Neurology)

Consider use of CGRP inhibitors for patients who have failed other preventative agents