NEW ADVANCES IN MIGRAINE MANAGEMENT

THE ROLE OF CGRP-TARGETED THERAPY

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LEARNING OBJECTIVES

1. Distinguish the key features of migraine to improve diagnosis and refine treatment
2. Recognize the benefits and limitations of traditional approaches to migraine management
3. Describe the safety and efficacy of novel approaches to migraine management targeting the calcitonin gene-related peptide (CGRP) pathway
4. Employ a patient-centered approach to migraine management that fosters open communication and self-management strategies

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>Cluster</td>
<td>Intracranial (SAH, vasculitis, dissection, central vein thrombosis, tumor, abscess, meningitis</td>
</tr>
<tr>
<td>Other primary headaches</td>
<td>Metabolic (CO₂ retention, CO poisoning)</td>
</tr>
<tr>
<td>Medication overuse headache (MOH)</td>
<td>Post-traumatic headache syndrome</td>
</tr>
</tbody>
</table>

HEADACHE TIME COURSE

- Minutes
- Days
- Weeks/Months
- Months/Years

Vascular
Infectious
Inflammatory/Neoplastic
Secondary Headaches
Primary Headaches

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MIGRAINE FACT CHECK

Migraine is...
- Top 10 leading causes of disability in the world
- The leading cause of ED visits in the US

Prevalence of any form of headache
- 93% in men
- 99% in women

% of people who experience migraine at some point
- 8% of men
- 25% of women

% of all migrainers who receive preventive treatment
- 40%


PHASES OF A MIGRAINE ATTACK

Adapted from Cady RK. Headache. 2008;48(9):1415-1416.

TRANSFORMATION OF MIGRAINE

Catalysts of Transformation
- Overuse of acute treatment (>2/week)
- Analgesic use with each attack
- Head or neck trauma
- Genetics

ICHD-3 DIAGNOSTIC CRITERIA | EPISODIC VS CHRONIC MIGRAINE

A Patient with a diagnosis of migraine

Headache on ≥ 15 days/month for > 3 months

On ≥ 8 days/month for >3 months, fulfilling any of the following:
1. Day with migraine
2. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative


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“PIN” THE MIGRAINE DIAGNOSIS | HISTORY

During the last 3 months, did you have the following with your headaches? (YES/NO)

**P** Photophobia
- Light bothered you (a lot more than when you don’t have headaches)

**I** Impairment
- Your headaches limited your ability to work, study, or do what you need to do

**N** Nausea
- You felt nauseated or sick to your stomach

2/3 YES = Migraine


WHY IS MIGRAINE FREQUENTLY MISTAKEN FOR SINUS HEADACHE?

- Pain is often located over the sinuses
- Migraine is frequently triggered by weather changes
- Tearing and nasal congestion common during attacks
- Sinus medication may help migraine


DIAGNOSIS OF SINUSITIS IS BASED ON THE PRESENCE OF ≥ 2 MAJOR OR 1 MAJOR AND > 2 MINOR SYMPTOMS

<table>
<thead>
<tr>
<th><strong>MAJOR SYMPTOMS</strong></th>
<th><strong>MINOR SYMPTOMS</strong></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 taste 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></td>
<td>Fatigue</td>
</tr>
</tbody>
</table>


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LISTEN TO THE HEAD!

IMAGING PATIENTS WITH MIGRAINE

Patients with migraine and normal neurologic exam (meta-analysis)

Significant intracranial pathology 0.18%

99.82%

Primary  Secondary

Choosing Wisely

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

HEADACHE LAB TESTS

CBC

ESR

T4, TSH, thyroid Peroxidase Ab

52-year-old Female
- 40 + headaches daily
- Unresponsive to indomethacin
- Short lasting neuralgiform headaches with conjunctival erythema and tearing

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45-year-old Male
- Nightly headaches x 2 week
- Pain so severe he extracted his own teeth!

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


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**TRIPTAN PRACTICAL STRATEGIES**

- **Treat early** after migraine onset
- **Use highest dose** formulation
- **Expect to be pain free** and associated **symptom free within 2hrs**

**Migraine diary**
- Frequency, intensity, duration

**Nausea**
- Ondansetron 4-8 mg
- SQ injection or nasal spray

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**WHEN TO CONSIDER PREVENTIVE THERAPY**

- Migraine significantly interferes with daily routine, despite acute treatment
- Attack frequency ≥ 4 attacks/month
- Acute medication ineffective, contraindicated, over-used, or not tolerated
- Patient preference
- Presence of uncommon migraine conditions

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**BASIC RULES FOR PREVENTIVE MEDICATIONS**

**DOSING**
- Begin with the **lowest possible dose** and increase slowly
- Stop dose escalation when adverse events occur, or when efficacy or target dose achieved

**CONSIDER COMORBIDITIES & CO-EXISTING CONDITIONS**
- Depression, epilepsy, insomnia, hypertension, obesity, etc.
- Monotherapy might be optimal for treating two disorders (e.g., a small dose of tricyclic antidepressant for both migraine and depression)

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**TRIPTAN PRACTICAL STRATEGIES**

**IF**...Headache worsens after 2 hours
- Repeat dose x 1

**IF**...Headache worsens typically after initial dosing
- Reduce dose of triptan by 50% and add NSAID

**IF**...No response to triptan
- Use “rescue” therapy
**BASIC RULES FOR 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

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**TREATMENT OF CHRONIC MIGRAINE**

- Maximize behavioral interventions
- Stop MOH agents
- Address any co-morbidities (MDD, GAD, sleep disturbances, obesity)
- Maximize acute treatment outcomes
- Consider nerve blocks
- Referral for refractory patients
- Employ preventative medications:
  - AEDs, Mg²⁺, β-blockers, TCAs
  - Botulinum toxin A
  - CGRP inhibitors

**MOH** - medication overuse headache

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**PREVENTIVE MEDICATIONS FOR MIGRAINE**

**EPISODIC**
- β-blockers
- Anticonvulsants
- Antidepressants

**CHRONIC**
- OnabotulinumtoxinA

**EPISODIC & CHRONIC**
- CGRP receptor mAb
- CGRP ligand mAb

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**WHEN TO USE CGRP INHIBITORS**

**Diagnosis** of ICHD-3 migraine with or without aura (8–14 monthly headache days)* AND inability to tolerate (due to side effects) or inadequate response to a 6-week trial of ≥ 2 of the following:
- Topiramate
- Divalproex sodium/valproate sodium
- β-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
- Tricyclic antidepressant: amitriptyline, nortriptyline
- SNRI: venlafaxine, duloxetine
- Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

* If 4-7 monthly headache days, then also require at least moderate disability (MIDAS >11; HIT-6 >50)


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**TRADITIONAL VS NEW PREVENTIVE TREATMENTS**

<table>
<thead>
<tr>
<th></th>
<th>TRADITIONAL</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Designed for other therapeutic areas</td>
<td>Designed for primary migraine prevention (EM, CM, MOH*)</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>40-50% reduction in HA frequency, may lose effectiveness in MOH*</td>
<td>≥ 50% reduction in HA frequency: lower all acute medication use</td>
</tr>
</tbody>
</table>

*MOH: Medication overuse headache


**RATIONALE FOR CGRP MODULATION**

- Released from trigeminovascular afferents
- Potent vasodilator
- Causes perivascular plasma protein extravasation and nociceptive pain
- CGRP levels elevated in migraineurs
  - Migraine-specific triptans block CGRP release
- CGRP induces migraine-like headache in susceptible individuals
- CGRP enhances transmission of pain signals in the CNS


**CGRP INHIBITORS**

<table>
<thead>
<tr>
<th>PHARMACOLOGIC TARGET</th>
<th>INDICATION</th>
</tr>
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<tbody>
<tr>
<td>Erenumab (Aimovig)</td>
<td>CGRP receptor</td>
</tr>
<tr>
<td>Fremanezumab (Ajovy)</td>
<td>CGRP ligand, episodic &amp; chronic migraine</td>
</tr>
<tr>
<td>Galcanezumab (Emgality)</td>
<td>CGRP ligand</td>
</tr>
<tr>
<td>Eptinezumab (Not approved)</td>
<td></td>
</tr>
</tbody>
</table>

**EPISODIC MIGRAINE AVERAGE DECREASE IN MONTHLY MIGRAINE DAYS**

<table>
<thead>
<tr>
<th></th>
<th>Erenumab¹</th>
<th>Fremanezumab²</th>
<th>Eptinezumab³</th>
<th>Galcanezumab⁴</th>
<th>Galcanezumab⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Monthly Migraine Days (Weeks 1–12)</td>
<td>Placebo: 70</td>
<td>Placebo: 64</td>
<td>Placebo: 70</td>
<td>Placebo: 64</td>
<td>Placebo: 70</td>
</tr>
<tr>
<td></td>
<td>-2.9</td>
<td>-2.2</td>
<td>-3.9</td>
<td>-4.3</td>
<td>-3.2</td>
</tr>
<tr>
<td></td>
<td>-3.7</td>
<td>-3.0</td>
<td>-3.9</td>
<td>-4.6</td>
<td>-4.7</td>
</tr>
<tr>
<td></td>
<td>-4.3</td>
<td>-4.6</td>
<td>-4.3</td>
<td>-4.3</td>
<td>-4.6</td>
</tr>
</tbody>
</table>


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**CHRONIC MIGRAINE**

Average Decrease in Monthly Migraine Days

<table>
<thead>
<tr>
<th>Erenumab 1</th>
<th>Fremanezumab 2</th>
<th>Eptinezumab 3</th>
<th>Galcanezumab 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg</td>
<td>140 mg Placebo</td>
<td>Q1 month Q3 months Placebo</td>
<td>120 mg Placebo 240 mg Placebo</td>
</tr>
<tr>
<td>-6.6</td>
<td>-6.6</td>
<td>-4.6</td>
<td>-8.3</td>
</tr>
<tr>
<td>100 mg</td>
<td>200 mg Placebo</td>
<td>Q3 months Placebo</td>
<td>120 mg Placebo</td>
</tr>
<tr>
<td>-4.6</td>
<td>-4.8</td>
<td>-4.6</td>
<td>-4.8</td>
</tr>
<tr>
<td>3000 mg</td>
<td>Placebo</td>
<td>Q1 month Placebo</td>
<td>120 mg Placebo</td>
</tr>
<tr>
<td>-4.3</td>
<td>-4.6</td>
<td>-4.6</td>
<td>-4.6</td>
</tr>
<tr>
<td>140 mg</td>
<td>Placebo</td>
<td>Q1 month Placebo</td>
<td>240 mg Placebo</td>
</tr>
<tr>
<td>-6.6</td>
<td>-6.6</td>
<td>-6.6</td>
<td>-6.6</td>
</tr>
</tbody>
</table>


**CGRP INHIBITORS | SAFETY**

- **Erenumab 1**
- **Fremanezumab 2**
- **Galcanezumab 3**
- **Eptinezumab 4**

**Systemic SEs**

- **No systemic effects (vs other biologics)**
- **Injection site reactions**
- **GI (constipation)**
- **Respiratory (nasopharyngitis, URI)**
- **Nausea, UTI, arthralgia, dizziness, anxiety, fatigue**

**(1) https://www.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><strong>Galcanezumab</strong></td>
<td>Self-inject with autoinjector or prefilled syringe</td>
</tr>
<tr>
<td><strong>Fremanezumab</strong></td>
<td>Self-inject with prefilled syringe</td>
</tr>
<tr>
<td><strong>Erenumab</strong></td>
<td>Self-inject with autoinjector</td>
</tr>
<tr>
<td><strong>Eptinezumab</strong></td>
<td>IV infusion</td>
</tr>
</tbody>
</table>

**MIGRAINE RESCUE STRATEGIES**

- **Olanzapine 10 mg PO**
- **Quetiapine 100 mg PO**
- **Magnesium sulfate 1g IV Push**
- **Occipital nerve block***
- **Sphenopalatine ganglion block***
  - Use a “sphenocath”

*Office procedure by a primary care clinician


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**SUMMARY**

- Prevention should be based on patient preference and risk for increased medication overuse

- **Standard definition of success**
  - 50% headache response, or 50% migraine response

- Consider use of **CGRP inhibitors** for patients who have failed other preventive agents
  - Lack of need for slow dose escalation
  - Rapid onset of therapeutic benefits
  - Favorable tolerability profiles