Financial Disclosures

Speakers Bureau: Amgen, Teva, Eli Lilly
When is imaging indicated in the evaluation of headache and what is the imaging study of choice?
Imaging in Headache

*Most patients do not need imaging*

- Thunderclap / worst headache of my life
- New headaches in someone over 50
- Change in headache character / pattern
- Headache with exertion (sex, exercise)
- Onset with fever or illness
- Complicated features (weakness, numbness, change in speech, tinnitus, incoordination)

American Academy of Neurology guidelines 2014
CT vs MRI

- CT better for bone or blood, quick, easy
- MRI better for subtle parenchymal changes, I almost always order with and without contrast
- CTA better than MRA for posterior circulation
- MRV may be helpful in some cases
- 4V angiogram is only modality that can identify vascular anomalies smaller than 3mm
What is the best initial treatment and when should prophylactic treatment be considered for treatment of migraines?
Pathophysiology of Migraine = Trigemino-Vascular Theory

- Walls of large cerebral arteries, meningeal arteries, & venous sinuses are innervated by trigeminal nerve sensory fibers (nociceptive)
- Trigeminal projections are activated and release vasoactive neuropeptides including CGRP, substance P, neurokinin A
- Neurons activated in the TNC and upper cervical spinal cord
- Synapse in thalamus which modulates cortical afferents
- Project to somatosensory, visual, and diffuse areas of the cortex
- Sensitization of the brainstem trigemino-cervical complex

Goadsby et al. Pysiol Rev 2017; 97: 553-622
Peripheral and central sensitization Feedback loop

How I approach headache management

• Set expectations up front
• Patience: 6 weeks to see a change
• Trial and error
• Balance benefits with side effects
• Tailor each treatment plan to the individual
Preventative Treatment

- More than 6 headache days per month or 4 with disability such as requiring bed rest
- AMPP study demonstrated significant impact of migraine on not only the patient but the family
- Goals are to reduce the number of events as well as the severity
- Benefit of reduced need for abortive meds
- Anti-depressants, anti-hypertensives, anti-epileptics
- Onabotulinum toxin
- CGRP antagonism
- Neuromodulation

Source:
A Comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study and American Migraine Prevalence and Prevention (AMPP) Study: Demographics and Headache-Related Disability.
Liston RB,1,2, Manack Adams A,2, Buse DC,3,6, Fanning KM,6, Reed ML,6.
# Migraine Prophylaxis

What the evidence shows...

## Table 1. Classification of Pharmacologic Agents for Migraine Prophylaxis

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<th>Level A&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>e</sup> Possibly/probably ineffective.


Source: References 2, 3.
Who progresses from episodic to chronic migraine?

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<th>Non-Modifiable</th>
<th>Modifiable Factors</th>
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<td>• Genetics</td>
<td>• Medication overuse</td>
</tr>
<tr>
<td>• Age</td>
<td>• Stress</td>
</tr>
<tr>
<td>• Race</td>
<td>• Sleep disturbance</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
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What does the evidence report as the best options for management of chronic headaches?
## Migraine Prophylaxis

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Onabotulinum Toxin: Chemodenervation

- 30 years of safety data
- 31 injections every 12 weeks
- Inhibits release of pain mediators thereby decreasing peripheral / central sensitization
- Efficacy improves over time
- FDA approved for chronic migraine, 15 or more headache days
- AE: allergy, neck pain, drooping eyelid

New Target: CGRP

- Increased in CSF in migraine
- CGRP levels are normalized by triptans
- CGRP infusion triggers migraines
- It is the most abundant neuropeptide expressed in the trigeminal pathways. It is found in 35-50% of trigeminal neurons
- Implicated in vasodilation, nociception and mast cell degranulation

Cernuda et al, Neurology 2013; 81:1191-1196
<table>
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<th>Fremanezumab</th>
<th>Galcanezumab</th>
<th>Eptinezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous or intravenous</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Monthly</td>
<td>Monthly or quarterly</td>
<td>Monthly</td>
<td>Quarterly</td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td>28 days</td>
<td>31 days</td>
<td>27 days</td>
<td>~32 days</td>
</tr>
<tr>
<td><strong>Human Sequences</strong></td>
<td>Human (100% human)</td>
<td>Fully Humanized (&gt;95% human)</td>
<td>Humanized (&gt;90% human)</td>
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<td><strong>Target</strong></td>
<td>CGRP receptor</td>
<td>CGRP ligand</td>
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<td><strong>IgG subtype</strong></td>
<td>IgG2</td>
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<td>IgG4</td>
<td>IgG1</td>
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Comparison of Anti-CGRP Monoclonal Antibodies

Fremanezumab\(^ {1,2}\)  
Quarterly HALO EM | Monthly HALO EM  
---|---  
-2.2 | -2.2  
-1.3 | -1.5  

Erenumab\(^ {3,4}\)  
70 mg ARISE | 70 mg STRIVE | 140 mg STRIVE  
---|---|---  
-1.0 | -1.4 | -1.9  
† | † | †  

Galcanezumab\(^ {5,6}\)  
120 mg EVOLVE-1 | 120 mg EVOLVE-2 | 240 mg EVOLVE-1 | 240 mg EVOLVE-2  
---|---|---|---  
-1.9 | -2.0 | -1.8 | -1.9  
† | † | † | †  

Eptinezumab\(^ {7,a}\)  
30 mg PROMISE-1 | 100 mg PROMISE-1 | 300 mg PROMISE-1  
---|---|---  
-1 | -0.8 | -1.2  
* | ** | †  

Mean Placebo (Δ days):  
-2.2  
1–3  

Data measured (months):  
3 | 4–6 | 4–6 | 1–6 | 1–6 | 1–6 | 1–3 | 1–3 | 1–3

\(^{a}\) Estimate from manual calculation using mean change from baseline values. * P<0.05 vs placebo; ** P<0.01 vs placebo; † P>0.001 vs placebo. EM, episodic migraine; LSM, least-squares mean; SE, standard error.

Neuromodulation

- Transcranial Magnetic Stimulation
- External Trigeminal Nerve Stimulation
- Noninvasive Vagal Nerve Stimulation
- Sphenopalatine Ganglion Stimulation
- Occipital Nerve Stimulation
- Caloric Vestibular Stimulation, DBS
Transcranial Magnetic Stimulation

How does it work?

- Inhibits CSD, modulates thalamo-cortical signaling

Acute treatment of migraine
- RCT, N=164 (82 in each group)
- Migraine with aura
- Pain freedom at 2h
  - 39% vs 22%

Preventive treatment of migraine
- Open label, N=132
- Mostly EM, BL = 9 days
- Performance goal (PG) = statistically-derived estimate of placebo effect

- Reduction in headache days
- Reduction in disability
- Reduction in acute medication use

>50% Reduction

* P < 0.0001

Lipton et al., Lancet Neurol 2010:9:373-80

Starling et al., Cephalgia 2018
External Trigeminal Nerve Stimulation

- Transcutaneous targets supraorbital and supratrochlear nerves > trigeminal nerve
- Goal of normalization of trigeminal pain modulation
- Central effects: FDG-PET normalization of fronto-temporal hypometabolism

### Acute treatment of migraine
- RCT, N=106
- EM and CM
- Intervention: 1h eTNS session
- Primary endpoint

\[
\begin{align*}
\text{Mean change in pain score at 1h} & \\
\text{-59%} & \quad \text{vs} \quad \text{-30%}
\end{align*}
\]

### Preventive treatment of migraine
- RCT, N=67, episodic migraine
- Intervention: 20min daily x 3 months
- Primary outcome measure
  1) Change in monthly migraine days
     -2.1 vs 0.3, \( p=0.054 \) \( \leftarrow \) did NOT meet endpoint
  2) 50% responder rate
     38.2% vs 12.1%, \( p=0.02 \)

Survey study
15% I cannot bear the feeling during an attack
49% It does not provide sufficient relief

Chou et al., Proceedings of the IHC of the HSt, Vancouver, BC, Canada. HSt;2017
Penning et al., ActaNeurol Belg 2017 117(2):547-549
Schoenen et al., Neurology 2013;80:697-704
Tepper D. Headache 2014;54:1415-6
Vagus Nerve Stimulator

- Only FDA approved device for cluster headaches
- Reduction in cortical spreading depression
- Reduce glutamate in the trigeminal nucleus
- Bilateral inhibitory effect, used abortively / preventatively
- Up to 40% receive 50% reduction in attacks
- AE: burning / tingling soreness / stinging at application site, lip or facial pulling
- Not studied with pacemaker, hearing aid, cardiovascular disease, pregnancy

de Coo IF, Marin J, Silberstein SD, et al. Non-invasive vagus nerve stimulation (nVNS): acute treatment of episodic and chronic cluster headache: pooled analysis of ACT1 and ACT2 studies
Thank you for your attention!
Any Questions?