Migraine Diagnosis and Treatment

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Disclosure: Merle L. Diamond, MD

| Consultant | • Alder BioPharmaceuticals  
| • Allergan  
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Background

Treatment guidelines recommend preventive treatments for people with frequent and disabling headaches.

Only one-third of people with migraine who meet guidelines for preventive treatments receive them\(^1\).

Of those who start preventive treatment, 80% lapse over the course of 1 year\(^2\).

- Why aren’t preventive treatments being more widely utilized?
- How can we optimize the appropriate use of preventive treatments?

Migraine Is a Global Problem

Affects >10% of population (959 million globally)\(^1\)

>44 million individuals affected in the United States\(^2\)

30 to 39 years\(^3\)
Prevalence peaks in middle life during prime years\(^3\)

\(~20\%\) to 35\% of people with migraine have \(\geq 4\) days per month\(^3\)

2 to 3x more common in women vs men\(^5-7\)

Global prevalence\(^4\) 15-25\%

Lifetime prevalence\(^4\) 43\%

6-8\%

18\%

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Migraine Frequency Exists on a Spectrum

• One-third of people with migraine have headache on ≥4 days per month, and 6% have headache on 15 or more days per month

• Traditional criteria for preventive treatment are defined in part by headache days

Frequency of Headache Days in Migraine (N=8281)

Migraine Frequency Is Dynamic

- Migraine frequency can increase over time and may transition from episodic to chronic, a process termed “chronification”\(^2\)
- Migraine can also transition from chronic to episodic\(^2\)

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Migraine Is Usually Associated With Severe Impairment or Need for Bed Rest

Migraine-related impairment was common in the American Migraine Prevalence and Prevention (AMPP) study of >18,000 individuals with migraine.\textsuperscript{1}

Respondents were asked how they are “usually affected by severe headaches” with the following response options:\textsuperscript{2}

\begin{itemize}
  \item Able to work/function normally
  \item Working ability or activity impaired to some degree
  \item Working ability or activity severely impaired
  \item Bed rest required
\end{itemize}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{migraine_impairment_chart.png}
\caption{Percentage of respondents affected by severe impairment or bed rest required.}
\end{figure}

Disability Increases Progressively With Increasing Number of Headache Days

International Burden of Migraine Study (N=8281)

<15 headache days/month (n=7812)
≥15 headache days/month (n=469)

Level of disability based on Migraine Disability Assessment (MIDAS) score
- Little or no disability (score 0-5)
- Mild disability (score 6-10)
- Moderate disability (score 11-20)
- Severe disability (score 21-40)
- Very severe disability (score 41-270)

What Can We Offer This Patient?

Abortive Medical Toolbox

Real case.
NSAIDs (nonsteroidal anti-inflammatory drugs)

- Block cyclooxygenase (COX) enzymes
- Reduce prostaglandins

1899 (introduced in)
1926 (introduced in)

Ergots

- 5-HT$_{1B/1D}$ agonist
- Prolonged interaction with 5-HT$_{1A}$, 5-HT$_{5}$, 5-HT$_{2}$, 5-HT$_{7}$, α-adrenoceptors, and dopamine (DA) D2 receptors
Triptans

• 5-HT$_{1B/1D}$ agonist
• 5-HT$_{2A}$ receptors in peripheral arteries

1992 (FDA approval)
Triptan/NSAID

- $5\text{-HT}_{1\text{B}}$ agonist + NSAID

2008 (FDA approval)
Neuromodulatory devices

- Transcranial magnetic stimulation (sTMS, eNeura)
- Supraorbital external trigeminal nerve stimulation (TENS, Cefaly)
- Noninvasive vagus nerve stimulator (nVNS, gammaCore)
Consider Prevention When...

<table>
<thead>
<tr>
<th>Significant Interference</th>
<th>Attack Frequency</th>
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<tbody>
<tr>
<td>With routine activities— despite use of acute treatment</td>
<td>&gt; 1/week</td>
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<tr>
<th>Elevated Risk</th>
<th>Acute Medications</th>
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<tr>
<td>Medication overuse</td>
<td>Ineffective, Contraindicated, Troublesome AEs, Overused</td>
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<table>
<thead>
<tr>
<th>Uncommon Subtypes Present</th>
<th>Patient Preference</th>
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<tbody>
<tr>
<td>Hemiplegic, Brainstem, Prolonged aura, Migrainous infarction</td>
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Informed choice
Migraine Prevention Is Underused

The AMPP study surveyed 18,968 individuals with migraine and found that

- ~39% were candidates for or should be considered for prophylactic treatment
- ~29% had received prophylactic medication for migraine in the past but discontinued treatment
- ~12% were current users of prophylactic medication for the treatment of migraine

Data from the AMPP study suggest that approximately two-thirds of individuals with migraine who qualify for prophylaxis do not receive it.

Adherence to Current Migraine Preventives Is Poor

Retrospective Claims Database Analysis:
Insured Patients With Migraine and ≥15 Headache Days/Month (N=8688)*

83% of people with migraine discontinue preventive treatment over 1 year

*Oral prophylactic medications analyzed in this retrospective study were limited to specific antidepressants, β-blockers, and anticonvulsants. Adherence rates were reported as the proportion of patients with a proportion of days covered ≥80%.

Patient-Reported Reasons for Discontinuation of Prophylactic Medication

Lack of efficacy and medication side effects are the most common reasons for discontinuation of prophylactic medications.
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<tr>
<td><strong>1.</strong> Standard definition of success is a 50% headache response rate (50% reduction in migraine days from baseline to weeks 9 to 12 or later).</td>
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<td><strong>2.</strong> This definition is predicated on the art of the possible or on what available treatments deliver.</td>
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<td><strong>3.</strong> Patients would prefer greater reductions in migraine days that would be achieved more quickly.</td>
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<td><strong>4.</strong> High discontinuation rates on current therapies may reflect unmet and inadequately managed patient expectations.</td>
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What Can We Offer This Patient?

Preventive Medical Toolbox

Real case.
Tricyclic antidepressants

- Increase levels of norepinephrine (NE) and 5-HT
- Block histaminic, cholinergic, and α1-adrenergic receptor sites

mid-1960s
(case reports showing benefit)
Beta blockers

- Noradrenergic receptor antagonists

1979 (FDA approval)
Antiepileptics

- Enhance gamma-aminobutyric acid (GABAergic) inhibitory neurotransmission
- Decrease glutamatergic excitatory neurotransmission

1996 (FDA approval)
OnabotulinumtoxinA

- Block acetylcholine release
- May act in part through blocking CGRP release

2010
(FDA approval)
Neuromodulatory devices

- Supraorbital external trigeminal nerve stimulation (TENS, Cefaly)
- Transcranial magnetic stimulation (sTMS, eNeura)
- Caloric vestibular stimulation (CVS, Scion NeuroStim)
2018 (FDA approval)

anti-CGRP MAB therapy
Targets the CGRP receptor
Addressing the Unmet Need in Preventive Treatment

- Approximately 80% of patients discontinue oral preventive therapy after 1 year of treatment\(^1\)
- More than 40% of patients receiving therapy still experience at least one migraine-related issue, including headache-related disability, treatment dissatisfaction, and/or excessive opioid use\(^2\)
- Up to 13% of patients with migraine receiving acute or preventive therapy still have at least 1 emergency department visit a year\(^3\)

All Approved Oral Drugs Share Similar Efficacy to Prevent Migraine

215 publications of RCTs provided mostly low-strength evidence because of the risk of bias and imprecision

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<thead>
<tr>
<th>Approved Drugs</th>
<th>Off-Label Drugs</th>
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<tr>
<td>Topiramate (9 RCTs)</td>
<td>Metoprolol (4 RCTs)</td>
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<tr>
<td>Divalproex (3 RCTs)</td>
<td>Atenolol (1 RCT)</td>
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<td>Timolol (3 RCTs)</td>
<td>Nadolol (1 RCT)</td>
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<td>Propranolol (4 RCTs)</td>
<td>Captopril (1 RCT)</td>
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- Topiramate and antidepressants result in more adverse events
- No significant differences in treatment discontinuation due to adverse events between labeled drugs
- Angiotensin-converting enzyme inhibitors and beta blockers most tolerable and effective
- Long-term evidence is lacking (>3-month duration)

RCTs=randomized, controlled trials.
Communication

Establish goals

Headache toolbox

Check in

Calendar/diary
New and Emerging Headache Therapies

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Professor of Neurology,
Geisel School of Medicine at Dartmouth
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## Disclosures 2017-2018 Stewart J. Tepper, MD

<table>
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<th>Grants/Research Support (No Personal Compensation)</th>
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New Horizons in Headache Treatment!
Overview

• New formulations of existing medications, FDA-approved and in development

• Pathophysiology leads to pharmacology and neuromodulation: translational research made real
  • New classes of acute medication in development
    • Gepants, serotonin (5-HT_{1F}) agonists [ditans]
  • New classes of preventive medication in development
    • Anti-calcitonin gene-related peptide (CGRP) or anti-CGRP receptor monoclonal antibodies (MABs)
  • Neuromodulation
    • Noninvasive, FDA approved: Transcutaneous supraorbital neurostimulation (tSNS), single pulse transcranial magnetic stimulation (sTMS), non-invasive vagal nerve stimulation (nVNS), and caloric vestibular stimulation (CVS)
    • Noninvasive in development: Remote nonpainful electrical upper arm skin stimulation and combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS)
    • Minimally invasive in development: Sphenopalatine ganglion stimulation (SPG)
Pathophysiology and Neurotransmitter Targets
Pathophysiology

Peripheral pain mechanisms:
CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP)

Meningeal blood vessel
Sensitized peripheral neuron (trigeminal ganglion)
Cutaneous allodynia
CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP)

Activated central neuron (thalamus)

Central generator?

Pain processing:
Sensitized central neuron (trigeminal cervical complex)

Neck muscle tenderness

Tepper SJ. Adapted from C79, Comprehensive Migraine Education Program 1 presented at AAN 2017; Boston.
New Devices for Delivering Medications
Devices for Delivering Medications

**FDA-approved and available**¹
- Sumatriptan autoinjectors (Sun Pharma, Dr. Reddy’s, Zembrace)
- Sumatriptan breath-powered dry nasal powder (ONZETRA Xsail)

**In development**²
- **Phase 3 RCTs completed**
  - Zolmitriptan skin patch (ADAM)
  - DFN-02 sumatriptan nasal spray
- **In development**
  - Oxytocin nasal spray, T1-001
  - Sumatriptan skin patch (Sofusa platform), KC5010
  - Zolmitriptan oral inhalation, CVT-427
  - Sumatriptan oral spray, SUD-001
  - DHE HFA nasal spray, powder nasal spray, novel autoinjectors

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¹ RCT=randomized, controlled trial.
New Acute Treatment Classes
Serotonin (5-HT) Mechanisms in Migraine

- Anti-migraine targets: $5\text{-HT}_{1B/1D}$ receptors
- $5\text{-HT}_{1F}$ receptors

Lasmiditan: A 5-HT\textsubscript{1F} Agonist (ditan)
Data From 2 Phase 3 Lasmiditan Trials for Acute Treatment of Episodic Migraine

- 2-Hour Pain Freedom:
  100 mg- 28.2-31.4%
  200 mg- 32.4-38.8%
  Placebo- 15.3%-21.3%

- Both doses also eliminated the Most Bothersome Symptom (MBS), chosen by the patient from nausea, photophobia, or phonophobia at 2 hours

- Adverse events in the Phase 3 RCTs:
  Dizziness + vertigo =100 mg average 15.5%
  200 mg average 16.8%

  Somnolence + fatigue + lethargy =100 mg average 10.4%
  200 mg average 12%

- For comparison, rizatriptan 10 mg prescribing information:
  Dizziness 20% greater than lasmiditan
  Somnolence + fatigue 15% greater than lasmiditan

- Conclusions for lasmiditan acute treatment:
  - Efficacy and side effects similar to rizatriptan
  - Central adverse events probably due to central 5-HT_{1F} activity and likely no vasoconstrictive effects
Gepants: Small-Molecule CGRP Receptor Antagonists
CGRP

- Neuropeptide belonging to calcitonin family
  - Calcitonin
  - Amylin
  - Adrenomedullin
  - Intermedin
- Present at all migraine pathogenesis sites
- Increases in migraine, decreases with treatment

CGRP = cyclic adenosine monophosphate. CLR = calcitonin receptor-like receptor. NS = nervous system. RAMP = receptor activity modifying protein. RCP = receptor component protein.

**Gepants Are Small Molecule CGRP Receptor Antagonists: They Have Never Failed on Efficacy**

**Acute Treatment of Episodic Migraine**

- 6 gepants effective in acute migraine treatment: olcegepant, BI 44370 TA, telcagepant, MK-3207, rimegepant, and ubrogepant
- BI 44370 TA, telcagepant, and MK-3207 all reportedly liver toxic
- Efficacy: **Ubrogepant** Phase 3 acute treatment of episodic migraine:
  - 2-hour pain freedom: 50 mg 19.2%; 100 mg 21.2%; placebo 11.8%; Also relieved 2-hour MBS
- Efficacy: **Rimegepant** Phase 3 acute treatment of episodic migraine:
  - 2-hour pain freedom: 75 mg 19.2-19.6%; placebo 12%-14.2%; also relieved 2-hour MBS
- Adverse events
  1. Liver, **Ubrogepant**: 6 cases with ALT >3x ULN, one of which was 10X ULN; 1 case with placebo >3x ULN; **Rimegepant**: one case each from active and placebo with >3x ULN
  2. Tolerability, **Ubrogepant**: nausea, somnolence, dry mouth in <5% of patients; **Rimegepant**: nausea in <2% of patients

**Preventive Treatment of Episodic Migraine**

- Telcagepant had liver toxicity when given daily
- **Atogepant** vs placebo positive phase 2 for migraine prevention, no liver signal; **Rimegepant** to be tested

**Conclusions for gepants acute treatment:**

- Efficacy and side effects similar to naratriptan
- Tolerability is excellent
- Liver safety will still need to be explored
- Prevents vasodilation; no expectation of vasoconstriction

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Prevention: MABs
A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.
MABs to CGRP or the CGRP Receptor for Migraine Prevention

• How will they be different than what we have now?
  • MABs are big molecules that do not cross the blood brain barrier\(^1,2\)
  • MABs are eliminated by the reticuloendothelial system, so no risk for hepatotoxicity, as long as the gepant liver problem was metabolic degradation and not mechanism-based—so far, MABs are safe\(^1\)
  • Because they work, it means that peripheral, not central, CGRP action is sufficient to trigger migraine

• Will they be an improvement?\(^3\) All 4
  • Work to prevent episodic migraine, chronic migraine, and medication-overuse headache
  • Have quick onset, separating from placebo within 1 week
  • Show clinically meaningful response by 1 month
  • Have favorable responder rates for $\geq 50\%$ and higher
  • Have safety and tolerability similar to placebo
  • Decrease acute medication use days, and improve impact, disability, and/or quality of life

## 4 Injectable MABs to CGRP or Its Receptor in Development

**Terms:** N=neurologic; umab=fully human; zumab=humanized, 90-95% human

<table>
<thead>
<tr>
<th></th>
<th><strong>Erenumab-aooe</strong> (fully human)</th>
<th><strong>Galcanezumab</strong> (90% humanized)</th>
<th><strong>Fremanezumab</strong> (95% humanized)</th>
<th><strong>Eptinezumab</strong> (90% humanized)</th>
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<tbody>
<tr>
<td>Studied for</td>
<td>EM, CM</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM</td>
</tr>
<tr>
<td>Dosing</td>
<td>Monthly SC</td>
<td>Monthly SC</td>
<td>Monthly or quarterly SC; IV load for CH</td>
<td>Q3 month IV</td>
</tr>
<tr>
<td>Target</td>
<td>CGRP receptor</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
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<tr>
<td>Regulatory status</td>
<td>FDA approved May 17, 2018; EM &amp; CM registration studies fully published</td>
<td>Submitted to FDA for migraine prevention; Presented (+) phase 3 EM &amp; CM; One EM trial fully published; Announced (+) eCH trial, (-) cCH trial</td>
<td>Submitted to FDA for migraine prevention; Both pivotal trials (EM &amp; CM) fully published Announced (+) phase 3 EM &amp; CM RCTs</td>
<td>Presented (+) phase 3 EM &amp; CM RCTs</td>
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cCH=chronic cluster headache. CM=chronic migraine. eCH=episodic cluster headache. EM=episodic migraine. SC=subcutaneous. RCT=randomized controlled trial.

Clinical Utility of the 4 MABs

- All data announced to date for EM and CM have shown a reduction in mean monthly migraine days (MMDs) with a magnitude of 1-3 days drop over placebo, similar to the registration studies for onabotulinumtoxinA
  - Using MMDs is necessary from a regulatory standpoint
  - However, MMDs are not a useful clinical endpoint for estimating value, as the clinical effect is underestimated due to inclusion of placebo
  - More useful is the drop from baseline and the secondary endpoints, such as responder rates

- Erenumab in CM prevention showed a 6.7-day reduction in MMDs in the pivotal trial, which would represent 79 fewer migraine days/year\(^1\); for eptinezumab, an 8-day reduction from baseline would be 96 fewer migraine days per year

- The \(\geq 50\%\) responder rates (secondary endpoints) in the galcanezumab EM registration studies were \(\geq 50\%\), in the eptinezumab CM study 61\%, and the \(\geq 75\%\) responder rates for both were about 1/3 of patients\(^2,3\)

- Erenumab 140 mg worked in patients who had failed 2-4 preventive medications in a prospective randomized placebo-controlled trial\(^4\)

How Are They Given?

- Erenumab and galcanezumab: Self-inject monthly
- Fremanezumab: Self-inject monthly or every 3 months
- Eptinezumab: Receive an IV infusion every 3 months

**Autoinjector**

Used for erenumab, etanercept for rheumatoid arthritis, and one of the generic sumatriptans.
How Could This Change the Future?

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<tr>
<th>Situation Before MABs</th>
<th>MABs Potential</th>
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<tr>
<td><strong>Current preventive medications</strong></td>
<td><strong>Specificity: designed for primary migraine prevention</strong></td>
</tr>
<tr>
<td>• Were designed for other therapeutic areas</td>
<td>• Wide therapeutic targets: EM, CM, MOH, and eCH</td>
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<tr>
<td>• Have numerous adverse events</td>
<td>• Speed—time to onset: &lt;1 week to 1 month</td>
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<tr>
<td>• Take 2-4 months to be effective</td>
<td>• Tolerability: similar to placebo</td>
</tr>
<tr>
<td>• Have ≥50% responder rates of &lt;50%</td>
<td>• Safety: no safety signal</td>
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<td>• May lose effectiveness in medication overuse headache (MOH)</td>
<td>• Improved responder rates, even at ≥75% or more</td>
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<td>• Sometimes don’t even lower acute medication use</td>
<td>• Lower acute medication use</td>
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If current safety is confirmed, one could potentially use these specific preventive biologics first line. The potential for this paradigm shift will depend on cost and access!
# Neuromodulation

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<thead>
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<th>FDA-approved</th>
<th>In development</th>
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<tr>
<td><strong>1</strong> Transcutaneous supraorbital neurostimulation (tSNS, e-TNS, Cefaly)</td>
<td><strong>5</strong> Remote, nonpainful stimulation for acute treatment of migraine (Nerivio Migra)</td>
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<tr>
<td><strong>2</strong> Single Pulse Transcranial Magnetic Stimulator (sTMS, SpringTMS)</td>
<td><strong>6</strong> Combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS, Relievion)</td>
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<td><strong>3</strong> Noninvasive vagal nerve stimulator (nVNS, gammaCore)</td>
<td><strong>7</strong> Sphenopalatine ganglion stimulation (SPGs, Pulsante)</td>
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<td><strong>4</strong> Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)</td>
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Transcutaneous Supraorbital Neurostimulation for Acute and Preventive Treatment of Migraine (tSNS, e-TNS, Cefaly)

- **Preventive RCT**: Turn it on and wear it 20 minutes/day; N=67
  - Migraine days/month in third month: not significant
  - ≥50% reduction in migraine days/month, 38.2% vs sham (P=0.023)

- **Acute RCT**: turn on in different setting for acute attack for 1 hour; N=57
  - Mean change in visual analog (VAS) 1-hour pain score reported as statistically significant in active vs placebo
  - FDA approved in 2017 for preventive and acute treatment of migraine as nonsignificant risk device
  - Cost: $550 (initial)
  - Cost: $25 (3 electrodes every 3 months)

HA=headache. NS=non-significant
Single Pulse Transcranial Magnetic Stimulation (sTMS, SpringTMS)

- Magnetic pulses disrupt cortical spreading depression (CSD), the basis for aura, and down-regulate thalamocortical pain pathways
- 1 RCT for acute treatment of migraine with aura, N=167
  - 2 hours pain-free: 39% sTMS vs 22% sham ($P=0.0179$)
- 2 studies for prevention of migraine with prn extra pulses, N=249
  - 4-25 headache days for inclusion; 4 pulses BID with extra prn up to 17 pulses per day
- FDA-approved in 2017 as nonsignificant risk device for preventive and acute treatment of migraine
- Rental cost $225/month

Noninvasive Vagal Nerve Stimulator (nVNS, gammaCore)

- Handheld, patient-controlled device, which preferentially activates afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction\(^1\)
  - Inhibits CSD\(^2\) and central trigeminovascular and thalamocortical pathways\(^3,4\)
- 2 RCTs showed effectiveness in terminating attacks of episodic cluster headache, but not chronic cluster headache\(^5,6\)
- 2 RCTs failed primary endpoints in prevention and acute treatment of migraine, but showed suggestive secondary endpoints\(^7,8\)
- FDA-approved as nonsignificant risk device for acute treatment of episodic cluster headache attacks and acute treatment of migraine
- $575/month for loaded stimulation package

Caloric Vestibular Stimulation (CVS, Scion NeuroStim) Prevention RCT: Significantly ↓ Migraine Frequency

- 6-site, placebo-controlled, blinded, home-use protocol
- 4-14 HA days/month
- 1° endpoint: ↓ migraine d, 3rd month
- 2°: RR, acute meds, mood, cognition, balance
- Per protocol: active (n=28); placebo (n=18)
- Active: -3.6 HA days vs baseline ($P<0.0001$)
- Active vs sham: -2.7 HA days ($P=0.012$)
- 2° endpoints also positive
- Approved by FDA in March 2018 for prevention of EM ages 12 and above; not commercially available yet

AEs >1 patient: nausea, dizziness, ear sx, tinnitus.
Placebo dizziness= Active dizziness (4 in each).
Remote Nonpainful Electrical Upper Arm Skin Stimulation for Acute Migraine Treatment (Nerivio Migra)

- Prospective, double-blinded, randomized, crossover, sham-controlled trial
- Migraineurs applied electrical patch to upper arm soon after attack onset for 20 minutes, at various pulse widths, for up to 20 attacks
- 50% pain reduction for 64% of participants based on best of 3-pulse width stimuli per individual vs 26% sham, N=71 patients, 299 treatments
- Second study underway in US
Combined Occipital and Supraorbital Transcutaneous Nerve Stimulation (OS-TNS, Relievion)

• Randomized, sham-controlled trial for acute treatment of migraine attack, N=30, treatment duration 45 minutes

• Decreased pain VAS score in the treatment group vs increased pain VAS score in the control group (-79.2% vs + 14.9%, \(P=0.0002\))

• 2-hour pain-free: active OS-TNS vs sham (\(P=0.0031\))
Sphenopalatine Ganglion Stimulation (SPGs, Pulsante)

- The SPG is the final switching station for cluster and migraine
- The SPG is a wireless device with a minimally invasive oral procedure
- The device is powered by a programmable remote control
- 1 RCT showed efficacy for acute and preventive treatment of chronic cluster headache
- Around 2/3 of cluster patients have relief after stimulation within 15 minutes and/or at least a 50% reduction in cluster attack frequency
- The US randomized controlled trial for acute treatment of chronic cluster headache was announced as positive in 6/18

Summary

• New formulations of existing medications, FDA-approved, and in development
• Pathophysiology leads to pharmacology and neuromodulation: translational research made real
  • New classes of acute medication in development
    • Gepants, serotonin (5-HT\textsubscript{1F}) agonists [ditans]
  • New classes of preventive medication in development
    • Anti-CGRP or CGRP receptor MABs
• Neuromodulation
  • Noninvasive, FDA-approved: Transcutaneous supraorbital neurostimulation (tSNS, e-TNS, Cefaly), single pulse transcranial magnetic stimulation (sTMS, SpringTMS), noninvasive vagal nerve stimulation (nVNS, gammaCore), Caloric vestibular stimulation (CVS, Scion NeuroStim)
  • Noninvasive, in development: Remote nonpainful stimulation (Nerivio Migra), combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS, Relievion)
  • Minimally invasive, in development: Sphenopalatine ganglion stimulation (SPGs, Pulsante)
Q & A Session

For valuable resources related to this activity, please visit forefrontcollabactivities.com/Diamond2018