Treatment Update in Migraine

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DISCLOSURES

I have no relevant financial relationships to disclose.
Objectives

• Basic approach to treatment
• Migraine abortive treatments
• Migraine preventive treatments
• The pipeline
Headache Epidemiology

- Global Burden of Disease Study, headache disorders collectively third leading cause worldwide of years lost due to disability (YLD).
- Chronic headache on 15 or more days every month affects 1.7–4% of the world’s adult population.
Introduction to Acute Migraine Treatments

• Center around individual migraine sufferers
• Contextualized by comorbidities and daily activities
• Understanding individual wants and expectations
• Meeting the challenge with compassion and an earnest desire to achieve pain freedom
• Interconnect concepts with measurable terms (quality of life, impact)
Introduction to Acute Migraine Treatments

# GOALS

• Alleviate suffering
• Provide fast relief of pain and associated migraine related symptoms
• Restore function
• Reduce disability
• Optimize self-care
• Minimize side-effects
Patient preferences for acute migraine treatment

Proportion of migraine sufferers reporting reasons for dissatisfaction with acute migraine treatments

- Pain relief takes too long: 87%
- Doesn't relieve all pain: 84%
- Doesn't always work: 84%
- Headache comes back: 71%
- Too many side effects: 35%

Proportion of migraine sufferers reporting attributes of acute migraine treatment as important

- Complete pain relief: 87%
- No recurrence: 86%
- Rapid onset: 83%
- No side effects: 79%
- Relief of associated symptoms: 76%
- Route of administration: 56%

*Complete, rapid relief without recurrence*

Lipton and Stewart. Headache 1999;39[suppl 2]:S20-S26
Migraine treatments

• Abortive or acute treatment
  ✓ Used to alleviate the pain when it starts
  ✓ Think of these as pain killers
  ✓ Should be used as needed
  ✓ Should not be overused

• Preventive treatment
  ✓ 4 to 6 headache days per month
  ✓ Infrequent but severe/disability attacks
  ✓ Used to decrease headache frequency
  ✓ Daily medications
  ✓ Can take time to become effective
Principles in treating migraine attacks

- Treat attacks early
- Choose treatment based on attack severity
- Combine acute treatments when needed (triptan + antinausea medication)
- Consider preventive strategies (medication and non-medication) when headache days per month are increasing or infrequent attacks are very disabling

Lipton et al JAMA. 2000; 284(20):2599-2605
Migraine treatment – what are we targeting

- Brain excitability
- Neurotransmitters and areas of the brain that may be activated during migraine
- Activation nerves that signal pain from the head and neck
- Inflammation around the coverings of the brain
- Release of pain signaling proteins like Calcitonin Gene Related Peptide or CGRP
Acute Migraine Treatments

Less specific
• NSAIDs
• Combination meds
• Anti-nausea meds (Reglan, Zofran etc)
• Antihistamines

More Specific
• DHE
• Triptans
• Ditans
• Gepants
Nonsteroidal Anti-inflammatory Drugs

- Reduce inflammation
- Can cause stomach irritation, bleeding, and kidney dysfunction if used too much
- Some are over the counter
- Can be used in combination with triptans
  - Naproxen sodium 500-550mg, tablet
  - Diclofenac potassium 50mg, tablet, sachet
  - Ibuprofen 400mg, tablet, solubilized
  - Indomethacin 25mg, tablet, PR
  - Flurbiprofen 100mg
  - Ketoprofen 100mg
  - Acetylsalicylic Acid 975-1000mg, effervescent and tablet
Triptans

- Core of acute migraine treatment
- Migraine-specific medications
- Multiple clinical trials demonstrate effectiveness
- Differences in how fast and long they act
- Differences in the formulation (pill, injection, nasal spray)
## Triptans

### vs Sumatriptan 100mg

<table>
<thead>
<tr>
<th></th>
<th>2Hr Relief</th>
<th>Sustained Pain-free</th>
<th>Consistency 2 of 3</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan (50 mg)</td>
<td>=</td>
<td>=</td>
<td>=/−</td>
<td>=</td>
</tr>
<tr>
<td>Zolmitriptan (2.5 mg)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Naratriptan (2.5 mg)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Rizatriptan (10 mg)</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>=</td>
</tr>
<tr>
<td>Eletriptan (80 mg)</td>
<td>+(+)</td>
<td>+</td>
<td>=</td>
<td>−</td>
</tr>
<tr>
<td>Almotriptan (12.5 mg)</td>
<td>=</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

- inferior, =/- possibly inferior, = no difference, + better, +(+) possibly much better, ++ much better compared to 100 mg sumatriptan

Lasmiditan (Reyvow) controlled substance option for people with vascular disease

- Dosing: 50, 100mg tablets Q24Hr PRN
- Centrally-penetrant, highly selective 5-HT1F receptor agonist without vasoconstrictive activity
- Serotonin syndrome were reported in patients treated with REYVOW
- Has abuse potential
- CNS depression, sedation, driving impairment
Small molecule CGRP Receptor Blockers

- Rimegepant (Nurtec) 75mg Q24 hr PRN
- Ubrogepant (Ubrelvy) 50mg and 100mg, PRN pain, can re-dose in 2 hours

- Increased freedom from pain at 2 hours
- Increased pain relief at 2 hours
- Improvement in most bothersome accompanying symptom
- Continued 24 hours relief

Graphs showing:
- Freedom from Pain over time for Rimegepant and Placebo
- Percentage of participants with freedom from pain over time for Ubrogepant and Placebo
The other options

• Opioids and barbiturates can cause sedation, respiratory and cardiac depression, opioid induced hyperalgesia, and dependency

• Considering opioid induced hyperalgesia, abuse/addiction issues, and some evidence that opioids render migraine-specific abortive medications less effective, it is recommended that opiates/opioids **not be used as first-line therapy for migraine pain**
Influences on preventive therapy

Patients
- Balancing for and against:
  - Expectation of effect / efficacy
  - Fear of side effects / drug dependency
  - Negative health feeling when daily use
  - Pressure of others
  - Ease of administration
- Perceived burden of migraine:
  - Frequency and severity attacks (impact)
  - Ability to cope with the attacks
  - Effect of attack treatment
  - Too much attack medication
- Earlier interventions:
  - Behavioral / dietary interventions
  - Complementary medicine
- Autonomy / self-determination:
  - Bearing responsibility on self
  - Availability of (conflicting) information
  - Fear becoming 'chronic patient'
  - Being able to take care of others

Physician
- Active approach
- Taking initiative
- Positive interaction
- Providing relevant information
- Acknowledgement of suffering/impact

Process
- Complex / time consuming decision
- Offer at right moment
- Keeping of diary
- Impact personal / social functioning

Acceptance

Preventive therapy
“There is rarely a single, immediate remedy, she said, whether it was a drug or a change in diet or an exercise regimen. Nonetheless, she wanted her patients to trust her. Things would take a while—months, sometimes longer. Success would be incremental.”
• Diet, exercise, adequate hydration
• Sleep hygiene
• Avoiding triggers if present (typically stress reduction techniques and sleep management)
• Food diaries can be tedious
• Unclear if specialized diets (including modified Atkins) help
• Mindfulness based meditation
• Cranial sacral massage
• Can start with nutritional supplements
  - Magnesium
  - Riboflavin
  - Feverfew
  - Avoid Butterbur
<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Medication</th>
<th>Usual Daily Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Atenolol</td>
<td>50-100 mg</td>
<td>? Avoid in migraine w aura</td>
</tr>
<tr>
<td>A</td>
<td>Propranolol</td>
<td>✔ 80-240 mg</td>
<td>✔ Avoid in migraine w aura</td>
</tr>
<tr>
<td>A</td>
<td>Metoprolol</td>
<td>50-150 mg</td>
<td>✔ Avoid in migraine w aura</td>
</tr>
<tr>
<td>U</td>
<td>Verapamil</td>
<td>180-480 mg</td>
<td>Cluster, migraine w prolonged aura, vestibular migraine</td>
</tr>
<tr>
<td>A</td>
<td>Divalproex sodium</td>
<td>✔ 250-1500 mg</td>
<td>FDA pregnancy category D</td>
</tr>
<tr>
<td>U</td>
<td>Gabapentin</td>
<td>300-1800 mg</td>
<td>Downgraded, favorable AE profile</td>
</tr>
<tr>
<td>A</td>
<td>Topiramate</td>
<td>✔ 25-150 mg</td>
<td>FDA pregnancy category D</td>
</tr>
<tr>
<td>B</td>
<td>Amitriptyline</td>
<td>10-150 mg</td>
<td>Downgraded but clinically strong</td>
</tr>
<tr>
<td>B</td>
<td>Venlafaxine</td>
<td>37.5-150 mg</td>
<td>Well tolerated, not sedating</td>
</tr>
<tr>
<td>C</td>
<td>Cyproheptadine</td>
<td>2-8 mg</td>
<td>Pediatric population, sedating</td>
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Non-prescription (magnesium, COQ10, feverfew, riboflavin), Lisinopril, Candesartan, Lamotrigine (migraine aura), devices, biofeedback and behavioral therapies
Onabotulinum Toxin A is the only FDA approved medication for the treatment of chronic migraine – PREEMPT trials

Chronic migraine = 15 or more headache days per month for 3 or more months

155 Units, 31 injection sites
CGRP Antibodies for the treatment of episodic and chronic migraine

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab ALD 403</th>
<th>Galcanezumab LY29517542</th>
<th>Erenumab AMG 334</th>
<th>Fremanezumab TEV-49125</th>
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</thead>
<tbody>
<tr>
<td><strong>CGRP Target &amp; IgG</strong></td>
<td>Ligand(α&amp;β) (-90% humanized) IgG1/kappa9east</td>
<td>Ligand(α&amp;β) (-90% humanized) IgG4a</td>
<td>Receptor (human) IgG2/kappa6 XenoMouse®</td>
<td>Ligand(α&amp;β) (fully humanized) IgG2/kappa6</td>
</tr>
<tr>
<td><strong>T1/2</strong></td>
<td>~32 days</td>
<td>25-30 days</td>
<td>21 days³ PK modeling for 70mg/70kg</td>
<td>~45 days¹</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>IV Q 3 months (SQ monthly)</td>
<td>SQ monthly</td>
<td>SQ monthly 70mg dose levels detectable ≥100 days³</td>
<td>SQ monthly</td>
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<tr>
<td><strong>Median Tmax</strong></td>
<td>3-14 days throughout dose range &amp; all cohorts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CGRP receptor binding</strong></td>
<td>5000 fold &gt; AMY, AM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P for both vs Placebo<0.001

Placebo (-2.2 days)
Quarterly (-3.4 days)
Monthly (-3.7 days)

Visit: Baseline Week 1 Week 2 Week 3 Month 1 Month 2 Month 3

Migraine treatment – what are we targeting

- PACAP
- Insulin like growth factor 1 nasal spray
- CGRP blocker nasal spray (Zavegepant)
- Neuromodulation
Thank you