Acute Treatment of Migraine: Now and in the Future

Learning Objective

After completing this activity, the participant should be better able to:

- Explain pharmacologic approaches to acute migraine treatment
Outline for Acute Treatment of Migraine

1. What do we hope to accomplish with acute treatment of migraine? Patient and Provider Goals
2. What does optimal acute treatment yield?
3. Migraine Pathophysiology and Acute Medication Targets
4. Triptans, Ergots, NSAIDs
5. New Devices for Delivering Current Medications
6. The Future Medications: Ditans and Gepants
7. Noninvasive Neuromodulation

NSAIDs=nonsteroidal anti-inflammatory drugs.

Goals of Acute Migraine Treatment

- 2-hour Pain Freedom (PF) is one FDA criterion for approval of new acute migraine medications
- 2-hour relief of Most Bothersome Symptom (MBS), chosen at onset (nausea, photophobia, or phonophobia)
  - Most patients choose photophobia
- 2- to 24-hour sustained pain freedom (SPF): 2-hour headache freedom, no recurrence, repeat dosing, or rescue medication
What Do Patients Want Most From An Acute Treatment?

- Attributes of acute migraine treatments rated as important by persons with migraineurs in the general population


Migraine-ACT/ Migraine Treatment Optimization Questionnaire (mTOQ)-4

<table>
<thead>
<tr>
<th>Question</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>When you take your treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Does your migraine medication work consistently, in the majority of your attacks? (Q 2, mTOQ-4)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>When you take your treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Does the headache pain disappear within 2 hours? (Q 1, mTOQ-4)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>When you take your treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Are you able to function normally within 2 hours? (Q 4, mTOQ-4)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>When you take your treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Are you comfortable enough with your medication to be able to plan your daily activities? (Q 3, mTOQ-4)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Migraine-ACT Score

An increasing number of ‘no’ answers indicates increasing treatment needs. A score of at ≤ 2 indicates the need to change treatment.

ACT=Assessment of Current Therapy.
Poor Acute Treatment Associated With Chronic Migraine Risk

American Migraine Prevalence and Prevention (AMPP)
- 3.1% of episodic migraine (EM) progressed to chronic migraine (CM) in 1 year (N=5681)
- Efficacy of acute treatment evaluated with mTOQ-4
  - 1.9% of the group with maximum acute treatment efficacy developed CM
  - New onset CM with moderate treatment efficacy (2.7%), poor treatment efficacy (4.4%), and very poor acute treatment efficacy (6.8%)
  - Very poor acute treatment group had ≥2X increased risk of new onset CM (OR=2.55)

Conclusions From AMPP:
- Inadequate acute treatment increased risk of new onset CM over 1 year
- Optimal acute treatment might prevent progression (not yet proven)

OR=odds ratio.

Pathophysiology

Cutaneous allodynia
Throbbing pain
Sensitized peripheral neuron (trigeminal ganglion)
Meningeal blood vessel
Activated central neuron (Thalamus)
Dura
Central generator?
Thalamus
Periperal pain mechanisms: CGRP release
Pain perception
Pain processing: Sensitized central neuron (trigeminal cervical complex)
Muscle tenderness

Tepper SJ. Presented at: American Academy of Neurology 2017 Annual Meeting; April 22-28, 2017; Boston, MA. Adapted from C79.
Migraine Pathophysiology

Trigeminovascular System

- Calcitonin gene-related peptide (CGRP) → Vasodilation and Neurogenic Inflammation
Calcitonin Gene-related Peptide: CGRP

- Neuropeptide belonging to calcitonin family
  - Calcitonin
  - Amylin
  - Adrenomedullin
  - Intermedin

- Present at all migraine pathogenesis sites
- Increases in migraine, decreases with treatment

\[ cAMP = \text{cyclic adenosine monophosphate; CLR=calcitonin receptor-like receptor; DRG=dorsal root ganglion; elPB=external part of the pontine lateral parabrachial nucleus; emPB=external medial pontine lateral parabrachial nucleus; NS=nervous system; RAMP=receptor activity modifying protein; RCP=receptor component protein; Vmpo=ventromedial posterior nucleus; VPpc=ventral posterior parvicellular nucleus.} \]


Effects of Neuropeptide Release on Blood Vessels
Arachidonic Cascade Results in Prostaglandins

- Kinins facilitate the production of cyclooxygenases
- Cyclooxygenases convert arachidonic acid to prostaglandins

Neurogenic Inflammation and Vasodilation

- Calcitonin gene-related peptide (CGRP) and prostaglandins cause vasodilation and neurogenic inflammation of cerebral and meningeal blood vessels as well as surrounding tissues
Targeting Acute Migraine Treatments

Serotonin (5-HT) Mechanisms in Migraine

- Anti-migraine agonist targets:
  - 5-HT₁B receptors:
    - Vasoconstrict
  - 5-HT₁D receptors:
    - Prevent peripheral CGRP release
    - Prevent signal to brainstem
  - 5-HT₁F receptors:
    - May also prevent peripheral CGRP release
    - Central inhibition

Triptans, Ergots, NSAIDs

**Triptans and Ergots**

- Are 5-HT$_{1B/D}$ agonists
- Some, such as frovatriptan, have some 5-HT$_{1F}$ agonist activity
- Ergots also have non-serotonin activity
- All inhibit release of CGRP via presynaptic 5-HT$_{1D}$ action
- All vasoconstrict via 5-HT$_{1B}$ agonism
- All prevent transduction of signal via nociceptive afferents to brainstem via 5-HT$_{1D}$ action
Triptan Groups

Group 1
- Faster onset, high potency
  - Sumatriptan
  - Zolmitriptan
  - Rizatriptan
  - Almotriptan
  - Eletriptan
  - Sumatriptan/Naproxen

Group 2
- Slower onset, lower potency
  - Naratriptan
  - Frovatriptan

Formulations and Doses of Triptans, Ergots

Triptans Group 1
Fast onset, high potency
- Sumatriptan
  - Subcutaneous 3, 4, 6 mg
  - Oral 25, 50, 100 mg
  - Nasal spray 5, 20 mg
  - Nasal powder 22 mg
- Zolmitriptan
  - Oral & ODT 2.5, 5 mg
  - Nasal 2.5, 5 mg
- Rizatriptan
  - Oral & ODT 5, 10 mg
- Almotriptan
  - Oral 6.25, 12.5 mg
- Eletriptan
  - Oral 20, 40 mg
- Sumatriptan and Naproxen Sodium
  - Oral sumatriptan 85 mg, naproxen sodium 500 mg

Triptans Group 2
Slower onset, lower potency
- Naratriptan
  - Oral 1.25, 2.5 mg
- Frovatriptan
  - Oral 2.5 mg

Ergots
- Dihydroergotamine (DHE)
  - Injectable subcutaneous, IM, IV 1 mg
  - Liquid Nasal 4 mg
- Ergotamine Tartrate
  - Oral 2 mg

ODT=orally dissolving tablet.
NSAIDs, NSAIDs + Triptans

- **NSAIDs**
  - Inhibit the peripheral arachidonic acid cascade
  - Prevent or reverse central sensitization
    - FDA approved prescription NSAID for acute treatment of migraine:
      - Diclofenac potassium for oral solution 50 mg
      - Ketorolac: oral, injectable, nasal (not FDA approved for migraine)
    - In development: DFN-15, liquid celecoxib

- **NSAIDs + Triptans**
  - Address both peripheral sets of actions, CGRP-mediated vasodilation and neurogenic inflammation, and can prevent or reverse central sensitization
  - FDA-approved combination tablet triptan + NSAID for acute treatment of migraine: sumatriptan 85 mg/naproxen sodium 500 mg
  - In development: rizatriptan/meloxicam (AXS -07)

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New Devices for Delivering These Currently Approved Medications
Devices for Delivering Medications

FDA-approved and available
- Sumatriptan autoinjectors
- Sumatriptan breath-powered nasal powder

In development
- Phase 3 RCTs completed
  - Zolmitriptan skin patch (ADAM)
  - DFN-02 sumatriptan nasal spray

In development
- DHE HFA propellant nasal spray
- DHE powder nasal spray
- Sumatriptan skin patch

ADAM=adhesive dermally applied microarray; HFA=hydrofluoroalkanes; RCTs=randomized, controlled trials.

5-HT\textsubscript{1F} Agonists:
Lasmiditan In Development

HEADACHE MEDICINE
5-HT$_{1F}$ Agonist for Acute Migraine Treatment In Development: Lasmiditan

Central 5-HT$_{1F}$ agonist effects: no vasoconstriction, but central adverse events

- **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 MBS 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%**

- Conclusions for lasmiditan acute treatment:
  - Central adverse events probably due to central 5-HT$_{1F}$ activity and likely no vasoconstrictive effects

- Submitted to FDA in Nov 2018

MBS=most bothersome symptom.


Tepper et al. Presented at: 60th Annual Scientific Meeting of the American Headache Society; June 28–July 1, 2018; San Francisco, CA. Abstract PS038.
Gepants: Small-Molecule CGRP Receptor Antagonists In Development

**Acute Treatment of EM**
- 6 gepants effective in acute migraine treatment: olcegepant, BI 44370 TA, telcagepant, MK-3207, rimegepant, ubrogepant
- BI 44370 TA, telcagepant, and MK-3207 all reportedly liver toxic
  - Conclusions for ubrogepant and rimegepant phase 3 for acute treatment:
  - Tolerability is excellent
  - No conclusive evidence of liver toxicity to date
  - Prevent vasodilation; no expectation of vasoconstriction

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

# Ubrogepant Two Phase 3 Acute Treatment of Migraine Trials

## End Points Statistics

### Co-Primary End Point 1: Pain Freedom 2 Hours After Initial Dose

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Placebo (N=456)</th>
<th>Ubro 50mg (N=435)</th>
<th>Ubro 100mg (N=444)</th>
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<tbody>
<tr>
<td>Pain Free at 2 Hours, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>.0023</td>
<td>.0001</td>
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### Co-Primary End Point 2: Absence of Most Bothersome Symptom 2 Hours After Initial Dose

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<tr>
<th>Statistics</th>
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<th>Ubro 50mg (N=435)</th>
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<tbody>
<tr>
<td>Absence of MBS1, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>.0023</td>
<td>.0023</td>
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<tr>
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<td>.0385</td>
<td>.0129</td>
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### Co-Primary End Point 2: Absence of Most Bothersome Symptom 2 Hours After Initial Dose

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### Primary End Points

1. Most Bothersome Symptoms of photophobia, phonophobia, or nausea

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## Successful Achievement of Both Co-Primary Regulatory End Points in 2 Pivotal Phase 3 Trials of Rimegepant

### Study 302

<table>
<thead>
<tr>
<th>2 hour Endpoint</th>
<th>Rimegepant (n=537)</th>
<th>Placebo (n=535)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Freedom</td>
<td>19.6%</td>
<td>12.0%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Freedom from MBS1</td>
<td>37.6%</td>
<td>25.2%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

### Study 301

<table>
<thead>
<tr>
<th>2 hour Endpoint</th>
<th>Rimegepant (n=543)</th>
<th>Placebo (n=541)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Freedom</td>
<td>19.2%</td>
<td>14.2%</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Freedom from MBS1</td>
<td>36.6%</td>
<td>27.7%</td>
<td>&lt; 0.002</td>
</tr>
</tbody>
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1. Most Bothersome Symptoms of photophobia, phonophobia, or nausea
Noninvasive Neuromodulation
FDA-Approved for Acute Migraine Treatment

Noninvasive Neuromodulation for Acute Migraine Treatment: FDA-Approved

1. Transcutaneous supraorbital neurostimulation (tSNS, s-TNS)
2. Single pulse transcranial magnetic stimulator (sTMS)
3. Noninvasive vagal nerve stimulator (nVNS)
Noninvasive Neuromodulation for Acute Migraine Treatment In Development

Remote, nonpainful stimulation for acute treatment of migraine

Combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS)

Summary

Acute Treatment of Migraine

1. What do we hope to accomplish with acute treatment of migraine? Patient and Provider Goals:
   - Sustained Pain Free, One-and-Done response, MigraineAct, mTOQ-4

2. What does optimal acute treatment yield?
   - Probably reduced risk of transformation to chronic migraine

3. Migraine Pathophysiology and Acute Medication Targets
   - 5-HT1b/d/f agonists
   - Anti-inflammatories
   - CGRP antagonists

4. Triptans, Ergots, NSAIDs
5. New Devices for Delivering Current Medications
6. The Future Medications: Ditans and gepants
7. Noninvasive Neuromodulation