The Importance of Non-Oral Therapies for Acute Migraine: Addressing Patient Needs

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Presentation Objectives

• Describe the rationale for the use of non-oral drug therapies for the acute treatment of migraine

• Define the clinical circumstances where a non-oral drug therapy would be indicated for the acute treatment of migraine

What Do Patients Want Most From An Acute Treatment?

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

Many Patients Are Dissatisfied and Willing to Try Something New

Areas of Dissatisfaction With Current Acute Therapies

- Inadequate pain relief: 42%
- Slow onset of action: 37%
- Recurrence/worsening of pain: 50%
- Inability to function/work quickly after taking medication: 48%
- Undesirable adverse events: 39%
- Would be willing to try another acute medication to treat the headache: 79%

Adapted from Bigal ME et al. Headache. 2007;47:475-479.

Need for Fast Pain Relief Persists

- Oral administrations have slow onset of pain relief
  - Result in 9% to 12% pain relief at 30 minutes
- Injections have illustrated relatively faster pain relief
  - However, 50% of migraine patients experience needlephobia

“. . . route of administration depends on the intensity and how quickly the pain peaks, the timing and intensity of gastrointestinal symptoms . . .”

Factors That Determine Drug Selection and Route of Administration

- For patients whose usual pain intensity/functional impairment is moderate-severe, it’s about **TIME**
  - Time of onset (sleep, upon awakening, during day)
  - Time to peak intensity
  - Timing and severity of nausea/vomiting
Morning Migraine: Occurs Often, Difficult to Treat

- 48% of migraine attacks occur in early morning (4 AM – 9 AM) and are already full-blown on awakening

Migraine Headache Onset and Severity Most Common Between 4:00-8:00 AM

### Time to Peak Intensity of Migraine Headache Pain

- **60% to 80% of migraine headaches peak within 60 minutes**

  - **Migraine with aura**
    - 11 cases
    - 19 cases
  - **Migraine without aura**
    - 48 cases
    - 60 cases
    - 28 cases
    - 14 cases

  - **P<.002**

  **Adapted from Pryse-Phillips AW et al. Headache. 2006;46(10):1480-1486.**

### Migraine: Timing of Onset and Peak Intensity

<table>
<thead>
<tr>
<th>How often did your severe headaches...</th>
<th>Men N=1334 (%)</th>
<th>Women N=3367 (%)</th>
<th>Total N=4701 (%)</th>
<th>Chi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Come on very rapidly</td>
<td>56.3</td>
<td>53.4</td>
<td>54.2</td>
<td>3.16</td>
<td>NS</td>
</tr>
<tr>
<td>Reach peak intensity in &lt;30 minutes</td>
<td>54.3</td>
<td>50.3</td>
<td>51.5</td>
<td>6.23</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Awaken you from sleep</td>
<td>31.0</td>
<td>31.5</td>
<td>31.4</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Present at normal time of awakening</td>
<td>34.0</td>
<td>44.1</td>
<td>41.2</td>
<td>40.82</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Courtesy of RB Lipton, MD**

Migraine: Nausea and Gastric Dysmotility

Presence of nausea at baseline is among the most powerful predictors of failure to achieve pain relief or pain-free response to triptans


Frequency of Most Bothersome Associated Symptom Among Persons With EM and CM

- Photophobia
- Phonophobia
- Nausea

CM=chronic migraine; EM=episodic migraine.

Nausea Is Substantial Barrier to and Consequence of Taking Oral Acute Therapies

<table>
<thead>
<tr>
<th>How often did...</th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>Total (%)</th>
<th>Chi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea make it difficult/impossible to take oral medication</td>
<td>21.0</td>
<td>18.6</td>
<td>19.2</td>
<td>3.52</td>
<td>NS</td>
</tr>
<tr>
<td>Taking oral medication cause nausea</td>
<td>17.1</td>
<td>13.4</td>
<td>14.5</td>
<td>10.16</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Taking oral medication worsen nausea</td>
<td>19.5</td>
<td>13.3</td>
<td>15.1</td>
<td>27.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>You find oral medication less effective when taken with nausea</td>
<td>22.3</td>
<td>18.8</td>
<td>19.8</td>
<td>6.56</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Migraine: Gastric Stasis

- Gastric stasis has been associated with migraine
- Gastric stasis may delay absorption of oral medications used for the treatment of migraine and negatively impact treatment efficacy

Faster Absorption ($T_{\text{max}}$) Correlates With Faster Onset of Pain Relief


Defeating Migraine Pain With Triptans: A Race Against the Development of Cutaneous Allodynia


Summary: Acute Migraine Treatment

- There remains a significant unmet need for migraine
- Patients most want complete and rapid pain relief
- Oral drugs have limitations, given the usual...
  - Time of attack onset (AM)
  - Rapid time to peak intensity (<60 minutes)
  - Nausea (attack-related and iatrogenic)
- Non-oral therapies with rapid absorption and high bioavailability should overcome some of these limitations

Non-Oral Treatment for Migraine: Current and Emerging Approaches

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### What Do We Have Now, and What Is In Development (Old and New)?

- Old wine in new bottles—current treatments delivered differently through devices
- FDA approved and in development
- Also, new delivery systems in development for currently FDA-approved medications being studied in new therapeutic areas

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### Devices for Delivering Medications
FDA-Approved Devices

New Devices for Currently Existing Medications: Old Wine in New Bottles

FDA-Approved Devices
- Sumatriptan 6-mg needle-free injection
- Sumatriptan 3-mg auto-injector
- Sumatriptan auto-injector
- Sumatriptan epipen-like auto-injector - not available
- Sumatriptan iontophoretic patch – withdrawn from market
- Sumatriptan breath-powered dry nasal powder
# Sumatriptan Auto-Injectors

- Statdose sumatriptan (generic): 4 mg, 6 mg
- Needle-free: 6 mg
- Epipen-like: Not available
- Prefilled Auto-Injectors: 3 mg, 6 mg
  - These work differently, so watch the online videos or get practice devices to show your patients!

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# The Removal of Iontophoretic Patch Sumatriptan From the Market

**Safety Announcement**

- **[06-02-2016]** The FDA is investigating serious burns and potential permanent scarring reported with sumatriptan iontophoretic transdermal system patch
- A large number of patients have reported burns or scars on the skin where the patch was worn. The reports included descriptions of severe redness, pain, skin discoloration, blistering, and cracked skin
- Product removed from the market June 2016

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**Sumatriptan Breath-Powered Dry Nasal Powder**

22 mg FDA-approved nominal sumatriptan dose delivers 16 mg in the nose.

![Diagram showing nasal delivery of sumatriptan](image)


### AVP-825 + placebo tablet (n=509 attacks) vs. Placebo delivery system + sumatriptan tablet (n=532 attacks)

<table>
<thead>
<tr>
<th>Time post-dose</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>1.24 (0.87, 1.77)</td>
<td>1.49 (1.12, 1.99)</td>
</tr>
<tr>
<td>15 min</td>
<td>1.94 (1.47, 2.56)</td>
<td>1.68 (1.26, 2.23)</td>
</tr>
<tr>
<td>30 min</td>
<td>1.60 (1.22, 2.11)</td>
<td>1.38 (1.04, 1.83)</td>
</tr>
<tr>
<td>45 min</td>
<td>1.37 (1.05, 1.80)</td>
<td>1.21 (0.89, 1.60)</td>
</tr>
<tr>
<td>60 min</td>
<td>1.21 (0.90, 1.60)</td>
<td>0.87 (0.69, 1.11)</td>
</tr>
<tr>
<td>90 min</td>
<td>0.97 (0.77, 1.23)</td>
<td>0.97 (0.77, 1.23)</td>
</tr>
</tbody>
</table>

**P** values: .24 .007 <.001 <.001 .03 .21 .27 .81

### Percentage of attacks achieving pain relief

![Graph showing percentage of attacks achieving pain relief](image)

### Percentage of attacks achieving pain freedom

![Graph showing percentage of attacks achieving pain freedom](image)

### FDA-Approved Sphenopalatine Ganglion/Maxillary Anesthetic/Block Devices

- **SphenoCath**
- **ChoanaCath**
- **Allevio**
- **Tx360**

SPG=sphenopalatine ganglion.


New Medication Devices in Development

Before the FDA:

- Dihydroergotamine (DHE) oral inhalation (iDHE, MAP0004)

Orally Inhaled Dihydroergotamine Inhaler

Phase 3 Pivotal RCT

- iDHE (n=397)
- Placebo (n=397)

No pain or mild pain
No photo-phobia
No phonophonia
No nausea

Commercial Inhaler

- Phase 3 regulatory RCT, 4 co-primary 2-hour end points all significant
- Works late in attacks with central sensitization
- FDA requested more actions on CMC 6/30/14


New Medication Devices in Development

• ZP-Zolmitriptan Skin Patch
• Sumatriptan Sofusa DoseDisc System Skin Patch
• DFN-02 Sumatriptan Nasal Spray
• Zolmitriptan Oral Inhalation, CVT-427
• Sumatriptan Oral Spray, SUD-001
• Oxytocin Nasal Spray T1-001

Microneedle Array Skin Deliveries

• Zolmitriptan ADAM – Registration RCT Reported

The Adhesive Dermally Applied Microarray (ADAM) Zolmitriptan System

- Hydrophilic drug formulation coated on tips of microneedles
- Microneedles are 200–350 microns long – close proximity to capillary bed
- Formulation quickly dissolved by interstitial fluid for short $T_{\text{max}}$


Primary End Point: 2-hour Pain Free (mITT)


Placebo ADAM Zolmitriptan ADAM Zolmitriptan ADAM Zolmitriptan

0 10 20 30 40 50 60
% Patients (95% CI)

14.3 30.4 27.7 41.5

P = .0001

P = .0351

P = .0149

mITT=modified intent-to-treat.
Co-Primary End Point: Freedom From Most Bothersome Symptom at 2 Hours (mITT)


Secondary End Point: Sustained Pain Freedom

DFN-02, Sumatriptan Nasal Spray

- DFN-02, an intranasal sumatriptan spray containing a permeation enhancer, 1-O-n-dodecyl-β-D-maltopyranoside (DDM)
- DDM is a nonionic surfactant, an alkylglycoside that is metabolized to simple carbohydrates, alcohols, and acids


- Primary Endpoint: 2-Hour Pain Freedom, DFN-02
- Secondary Endpoint: Sustained (2h - 24h) Pain Freedom
- Secondary Endpoint: Freedom from Patient Reported Most Bothersome Symptoms
Proprietary Technology – In Development
Sumatriptan Oral Spray

- SUD-001 (NVD-201) is a mint or honey-flavored oral sumatriptan spray
- Phase 1, 10 healthy male volunteers to determine absorption and PK
- 4-arm, crossover PK study comparing SUD-001 (20 mg and 30 mg) with 50-mg sumatriptan tablet: faster absorption rate with SUD-001 than with tablets and up to 50% increase in relative bioavailability of sumatriptan
- Open-label dose-ranging migraine study: up to 5 treatments, sumatriptan 50-mg and 100-mg tablets, and SUD-001 20-mg, 30-mg, 40-mg oral spray
- 1-hour headache relief:
  - SUD-001 30 mg – 42%
  - SUD-001 40 mg – 46%
  - 50-mg sumatriptan tablet – 12%
  - 100-mg sumatriptan tablet – 42%
- No photo available

PK=pharmacokinetics.

Nasal Oxytocin T1-001

Clinical Study for Migraine Headaches Not Responding to Treatment

T1-001 (oxitocina intranasal)
A Phase 2, Enriched-enrollment, Randomized-withdrawal Double-blinded, Placebo-Controlled Study to Assess the Efficacy, Tolerability, and Safety of Intranasal Oxytocin in Subjects With Chronic Migraine

Australian ad for T1-001 migraine study

Courtesy of Trigemina Inc
Three Letters to Remember on Regulatory Approval of Devices: CMC

- **CMC: Chemistry, Manufacturing, and Control**
- Companies must establish physicochemical properties of a new chemical entity
- Is the drug suitable to be made into specific current or new formulations?
- Devices must work according to specifications, and drugs or modulation delivered reliably in consistent aliquots
- The FDA has been updating CMC regulations, most recently April 22, 2016
- Almost all the devices have had holdups in CMC, and some have current delays (e.g., inhalable DHE)

What Do We Have Now, and What Is In Development (Old and New)?

- Current treatments delivered differently through devices
- FDA approved:
  - Sumatriptan SC auto-injectors
  - Sumatriptan breath-powered dry nasal powder
  - SPG/Maxillary block delivery devices
- In development:
  - DHE nasal spray
  - Microneedle array skin patch zolmitriptan, sumatriptan
  - Inhaled zolmitriptan
  - Sumatriptan oral spray
  - Sumatriptan + permeation enhancer nasal spray
  - Oxytocin nasal spray
- Remember, CMC is important

SC=subcutaneous.