New Medications for Migraine

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Conventional Migraine Treatments

Preventatives
• Antidepressants
  – TCA, SSRI, SNRI
• Beta Blockers
• Antiepileptic medications
  – Valproic acid, topiramate (FDA approval)
  – Gabapentin, lamotrigine
• Calcium channel blockers

Abortives
• Migraine-specific
  – Ergots, Triptans
• Non-specific analgesics
Targets for Migraine Therapy

- Normalization of neuronal hyperexcitability
- Ion channel modulation
- Neurotransmitter modulation
- Blockade of cortical spreading depression
- Prevention of peripheral and/or central sensitization
- Promote degradation of pro-inflammatory factors
- Modulate vasoreactivity
- Normalization of brainstem function

Emerging Therapies for Acute Migraine

- Goal: Pain free at 2 hours, with no use of rescue meds or HA recurrence within 24 h and no adverse events
- Desire for a compound which is not vasoactive
- Current areas of research
  - Serotonin receptor agonists
  - Calcitonin gene-related (CGRP) receptor antagonist
  - Transient receptor potential vanilloid (TRPV1) receptor antagonist
  - Nitric oxide synthesis inhibition peptide
  - Prostanoid receptor antagonists
### Traditional New Oral Non-vasoactive Oral Acute Drugs

- 5-HT$_{1F}$ agonist Lasmiditan COL-144 completed Phase II – central side effects
- CGRP receptor antagonist #5 going into Phase II: BMS-927711
- Neuronal Nitric Oxide synthase (nNOS) antagonist (NeurAxon) done with Phase II

### Emerging Acute Migraine Therapies

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Treatment Class</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL-144</td>
<td>5-HT1F receptor agonist</td>
<td>Phase II – complete</td>
</tr>
<tr>
<td>Telcagepant (MK-0974)</td>
<td>CGRP receptor antagonist</td>
<td>Phase III–complete</td>
</tr>
<tr>
<td>BI 44370</td>
<td>CGRP receptor antagonist</td>
<td>Phase II – complete</td>
</tr>
<tr>
<td>BGG492</td>
<td>AMPA receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>Tezampanel (LY-293558)</td>
<td>AMPA and kainate receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>LY466195*</td>
<td>GLUK5 kainate receptor antagonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>SB-705498</td>
<td>TRPV1 receptor antagonist</td>
<td>Phase II – complete</td>
</tr>
<tr>
<td>NXXN-188</td>
<td>Neuronal nitric oxide synthase (nNOS) inhibition &amp; 5-HT1B/D agonist</td>
<td>Phase II</td>
</tr>
<tr>
<td>GW274150</td>
<td>Inducible nitric oxide synthase inhibition</td>
<td>Phase II – complete</td>
</tr>
<tr>
<td>BGC20-1531</td>
<td>Prostanoid EP4 receptor antagonist</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*Not yet listed on the ClinicalTrials.gov website

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, CGRP calcitonin gene-related peptide, TRPV1 transient receptor potential vanilloid subfamily member 1
Calcitonin gene-related peptide (CGRP)

- CGRP antagonist: Most promising acute migraine treatment
- Most potent naturally occurring human vasodilator
- Rises correlate with migraine attacks
- Falls or blockade correlate with successful acute treatment of migraine

News of anti-CGRP receptor compounds

- Telagepant (Merck)
  - Worked about the same as a triptan with better tolerability
  - Elevated liver transaminases led to discontinuation of development July 2011
- Back up compound Merck has also been dropped
- Is the liver problem a class effect?
- A third Merck compound is in very early development (# 6)
- Boehringer Ingelheim
  - Olcegepant, the first tried in humans, but only intravenous was effective and well tolerated
  - BI 44370 TA oral compound was effective but dropped
- BMS: CGRP antagonist going into Phase II: BMS-927711
Gastric Stasis Limits Oral Delivery

- Gastric emptying was evaluated with scintigraphy in 3 migraineurs versus normative data.

![Gastric Half-Emptying Time and % Radioactive Material Remaining](image)

Traditional Versus Novel Delivery

- Acute-migraine drugs need rapid onset
- Patients often prefer oral therapies, but efficacy is limited by gastric absorption and emptying.

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Novel</th>
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</thead>
<tbody>
<tr>
<td>- Injections</td>
<td>- Needle-free injections</td>
</tr>
<tr>
<td>- Intranasal</td>
<td>- Inhalation</td>
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<tr>
<td>- Oral</td>
<td>- Intranasal Dry Powder</td>
</tr>
<tr>
<td>- Sublingual</td>
<td>- Lingual Spray/Transmucosal</td>
</tr>
<tr>
<td>- Rectal</td>
<td>- Topical/Transdermal</td>
</tr>
<tr>
<td></td>
<td>- Novel oral formulations</td>
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<td></td>
<td>- Stimulators</td>
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</tbody>
</table>
Approved Novel Agents in US

- Needle-free injectable sumatriptan (SUMAVEL)
- Epi-pen of sumatriptan (ALSUMA)
- Diclofenac:
  - Sachets of diclofenac dissolve in water (CAMBIA): migraine
  - Liquid gel caps with ProSorb® (ZIPSOR): headache
- Iontophoretic dermal patch of sumatriptan (ZELRIX)
- Intranasal ketoralac (SPRIX): moderately severe pain

New Formulations of Sumatriptan
Injectable: **SUMAVEL DOSE-PRO**  
Needle-Free Sumatriptan

- Advantage: improved patient acceptance over injection with needles
- Needle-free injectable sumatriptan  
  - Approved for acute migraine and cluster headache  
  - SC delivery of sumatriptan 6 mg  
  - Compressed nitrogen gas pushes sumatriptan subcutaneously

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Transdermal: **ZELRIX**  
Sumatriptan Iontophoresis

- Advantages: avoids GI; sustained delivery  
- Sumatriptan iontophoresis patch  
  - Low electrical current facilitates transdermal delivery  
  - Linear relationship between applied current and sumatriptan delivery  
  - PK data  
    - AUC = SC suma  
    - C<sub>Cmax</sub> < SC suma  
    - Consistent and predictable PK  
  - Efficacy = suma po  
    - SPF: 34% vs 21%  
    - 2 h pain relief: 53% vs 29%  
    - 2 h pain free: 18%

Intranasal Dry Powder: **OPTINOSE**

**Sumatriptan – Phase II**

- Nasal drug delivery device
  - Delivers sumatriptan powder
  - $T_{max} = 20$ minutes: faster than traditional NS
  - Most common AE
    - Bitter/ metallic taste
  - Sustained pain-free (SPF) AND no AEs (SNAE)
    
    $$\text{SNAE} = \text{SPF} \times (1 - \text{AE})$$

- 37% (15 mg) and 39% (7.5 mg) with sumatriptan powder
- 6% to 22% with oral triptans
- 18% with sumatriptan plus naproxen
- 13% with oral CGRP antagonist

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**Lingual Spray: Sumatriptan – Phase II**

- Sumatriptan lingual spray (LS)
  - Advantages: rapid absorption and avoids GI system
  - Sprayed over the tongue
  - PK in 10 normal males
  - Crossover comparison with sumatriptan 50-mg tablets
  - Sumatriptan LS absorption was biphasic
    - Lower mean peak concentration compared with oral sumatriptan tablets
  - There were no reports of unpleasant taste
Oral Inhalational Delivery

• Alveoli provide a large, absorptive surface
  – Advantages\textsuperscript{1,2}
    – Painless
    – High permeability
    – Rapid access to systemic circulation
  – Lung deposition of drug depends on particle size and properties and the health of the respiratory system\textsuperscript{1}
  – Small, lipophilic molecules delivered to the deep lung affords rapid onset of action\textsuperscript{1}

• Advantages of inhalation administration\textsuperscript{3}
  – Noninvasive systemic drug delivery
  – Fast, predictable, effective plasma concentration

Orally Inhaled DHE (MAP0004): LEVADEX
Submitted to FDA June 2011

Significant IV plasma 'spike' - ↑ Potential for side effects

suppress inhaled plasma Cmax - ↓ Potential for side effects

Cook. Presented at: European Headache and Migraine Trust International Congress (EHMTIC); September 4-7, 2008; London, UK.

Orally Inhaled DHE (MAP0004) Phase IIIA

MAP0004 (n = 395) ▪ Placebo (n = 397)

Significant difference from placebo:
↓ P < .05.
↑ P < .0001.

Thermally Generated–Aerosol (TGA) Prochlorperazine – Phase II

<table>
<thead>
<tr>
<th>Route</th>
<th>$T_{\text{max}}$ (minutes)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Over 5 Seconds</td>
<td>3.50 ± 2.88</td>
<td>1.06 ± 0.84</td>
</tr>
<tr>
<td>Single-Breath Inhalation</td>
<td>2.00 ± 0.76</td>
<td>1.38 ± 0.56</td>
</tr>
<tr>
<td>Between-Treatment Difference ($P$ value)$^a$</td>
<td>.13</td>
<td>.30</td>
</tr>
</tbody>
</table>

Data are listed as mean ± SD (n = 8).

$^a$ Difference between IV and aerosol by paired t test.

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TGA Prochlorperazine in Migraine

- Phase 2b, randomized study
- Single migraine
  - 3 doses: 5 mg; 7.5 mg; 10 mg
  - Placebo
- N = 400
- Aerosol prochlorperazine better than placebo after
  - 15 minutes with 7.5 mg ($P = .02$)
  - 30 minutes with 5 and 10 mg ($P = .006$)
- Phase 2b migraine trial with loxapine has been initiated

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Cassella et al. Presented at: 59th Annual Meeting of the American Academy of Neurology; April 28-May 5, 2007; Boston, MA.
Liquid

Dissolvable Diclofenac

- More rapid absorption than traditional pills with 30-min Tmax
- Onset of analgesia 15 min for powder vs 60 min for tablets

- Adverse events (AEs) were typical of those seen with oral diclofenac

Other Intranasal Delivery Systems

Intranasal Ketorolac for pain (SPRIX)
FDA Approved

- Phase 3 clinical trials
  - Postoperative pain
  - N = 300
  - Greater pain reduction with ketorolac
  - Morphine use reduced by 34% with ketorolac versus placebo
  - AEs were typical of those seen with oral ketorolac; nasal irritation occurred for 24% with intranasal ketorolac versus 2% with placebo

Intranasal: Carbon Dioxide (CO₂) Phase II

- CO₂ inhibits sensory nerve activation and neuropeptide release
- Intranasal CO₂ in migraine pilot study
  - Randomized, double-blind, placebo-controlled, parallel-group
  - N = 132
  - 2-hour pain free in 9% with placebo versus 30% with intranasal CO₂ ($P < .01$)
- Phase 2 trials are ongoing

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Other Transdermal Delivery Systems
Transdermal: Liposomal Formulations

- **Traditional liposomes are vesicles made with phospholipid membranes**
  - May be filled with drugs for drug delivery
- **Drug carrier:** elastic liposomes
  - Noninvasive drug delivery across skin
  - Highly deformable to permit squeezing through pores smaller than own diameter
  - Achieves more rapid onset and sustained effect
- **Migraine**
  - Diclofenac\(^1\)
  - Rizatriptan\(^2\)


Pediatric Considerations

- Options have been to use simple analgesics and sleep
- **Adolescents (12-17 yrs):**
  - Almotriptan (FDA approved)
  - Sumatriptan NS
  - Zolmitriptan NS
- **Adolescents and Children (6 yrs+):**
  - Rizatriptan
Stimulators

Occipital Nerve Stimulation (ONS)

- Approval for the Genesis neurostimulator for ONS for the treatment of intractable chronic migraine in Europe
- Their CM study, an RCT was reported by Silberstein et al at IHC Berlin 2009 (not published in peer reviewed journal yet)
- Statistical significance was demonstrated across most measures.
- 157 patients the active group showed a 41% improvement after 12 weeks of stimulation vs 13% improvement in the control group
Occipital Nerve Stimulation

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Number treated</th>
<th>Efficacy</th>
<th>Significant adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popeney et al.</td>
<td>CM</td>
<td>25</td>
<td>88% had &gt;50% decreased frequency or severity</td>
<td>36% had lead migration/ 12% had infection</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>CM</td>
<td>8</td>
<td>50% had &gt;50% decreased severity</td>
<td>20% had lead migration</td>
</tr>
<tr>
<td>Saper et al.</td>
<td>CM</td>
<td>29</td>
<td>39% had &gt;50% decreased frequency or severity</td>
<td>24% had lead migration/ 14% had infection</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>HC</td>
<td>2</td>
<td>100% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>HC</td>
<td>6</td>
<td>66% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Schwedt et al.</td>
<td>CCH</td>
<td>3</td>
<td>66% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Magnis et al.</td>
<td>CCH</td>
<td>8</td>
<td>63% had &gt;50% decreased frequency or severity</td>
<td>12% had unbearable paresthesia</td>
</tr>
<tr>
<td>Burns et al.</td>
<td>CCH</td>
<td>8</td>
<td>37% had &gt;50% decreased frequency or severity</td>
<td>62% had lead migraine or power loss</td>
</tr>
<tr>
<td>de Quintana et al.</td>
<td>CCH</td>
<td>4</td>
<td>50% had &gt;50% decreased frequency or severity</td>
<td>None reported</td>
</tr>
<tr>
<td>Goadsby et al.</td>
<td>PH</td>
<td>3</td>
<td>66% responded well</td>
<td>None reported</td>
</tr>
<tr>
<td>Goadsby et al.</td>
<td>SUNCT</td>
<td>2</td>
<td>50% had near complete resolution</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Total Number Treated Regardless of Condition: 98
Number Responding: 58
Percentage of Responders: 59%


Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM

- 3 month study
- 110 subjects, data from 66
- End point: 50% reduction in monthly HA days or a 3-point reduction in pain intensity
  - Stimulation group: 39%
  - Placebo: 6%
  - Medically managed group: 0%
- Lead migration: 24%

Saper JR. Cephalgia 2011;31:262-263
Transcranial Magnetic Stimulation (TMS)

- Aura is generated by cortical spreading activation, then cortical spreading depression (CSD)
- TMS blocks this CSD and can terminate migraine with aura
- Has not reached primary endpoint for migraine without aura


Transcranial Magnetic Stimulation (TMS)

- May interrupt cortical spreading depression
- 164 patients with migraine with aura (at least 30% of time) treated at least one attack with TMS (n=82) or sham stimulation (n=82)
- Pain-free response rates after 2 h were significantly higher with TMS (32/82 [39%]) than with sham stimulation (18/82 [22%]), for a therapeutic gain of 17% (95% CI 3-31%; p=0.0179)
- No device-related serious adverse

Background to sphenopalatine ganglion stimulator (SPG) studies

• Parasympathetic outflow may account for:
  – Autonomic Sx and vasodilation causing pain in *cluster headache*
  – Activation of meningeal neurogenic inflammation and vasodilation as peripheral pain mechanisms in *migraine*

• Parasympathetic outflow from the brainstem traverses the SPG

• SPG blocks and ablation can be useful in treating cluster, and perhaps migraine, by interrupting efferent pathways

• Oxygen works in cluster

Autonomic Technologies Inc (ATI) SPG Neurostimulation System
News on Preventive Migraine Treatments

• Mglu2 potentiator/Cys\lt1 antagonist LY2300559
  Phase II study for prevention - no data yet
• Tonabersat failed
• Gabapentin enacarbil failed
• OnabotulinumtoxinA (Botox) approved in the US Oct 2010

PREEMPT Study for Chronic Migraine
OnabotulinumtoxinA (Botox®)

• Chronic migraine ≥ 15 headache days/month for ≥ 4 hours/day
• Chronic migraine as classified by the FDA
• BOTOX® may act to down-regulate production of neuropeptides in the dorsal horn

   Diener HC. Cephalalgia. 2010;30(7):804-814
   Aurora SK. Cephalalgia. 2010;30(7):793-803
PREEMPT

• Fixed-site fixed-dose injection paradigm

• A total of 31 injections across seven specific head and neck muscles, with a minimum dose of 155 U of BOTOX® injected per patient


PREEMPT pooled analysis: mean change from baseline in frequency of headache days (primary)

• Patients treated with BOTOX® averaged of 8.2 fewer headache days/month at Week 24 compared with placebo (vs. 6.2 with placebo; p<0.001)1,2

Mean ± standard error.
The double-blind phase included 688 subjects in the BOTOX® group and 696 in the placebo group.
Headache days at baseline: 19.9 BOTOX® group vs 19.8 placebo group, p=0.498.

Summary

• Novel drug classes for acute migraine are in development
  — CGRP antagonists and 5-HT1F agonists are potentially promising agents
  — New formulations of older abortives may improve efficacy
• There is very limited promise of new preventative migraine therapy on the horizon
• Botulinum toxin is the one new treatment to show benefit for chronic migraine
• Neuromodulation (occipital nerve stimulation, transcranial magnetic stimulation and SPG stimulation) have shown promising results and may be valuable in the treatment of disabling migraine