Review of migraine treatment and new and emerging therapies

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disclosures

- None

- I will be discussing off-label uses of medications

- Remember: Guidelines are based on available evidence
objectives

- Review guidelines for acute and Preventive migraine treatment
- Discuss recently FDA-approved therapies and devices for migraine
- Discuss Future developing treatments for migraine
Get to know the audience questions

- Who here treats migraine patients?
  - 1) Yes
  - 2) No
Get to know the audience questions

- Who likes treating migraine patients?
  - 1) Yes
  - 2) No
Get to know the audience questions

- Who uses published guidelines for acute and preventive migraine therapy?
  - 1) Yes
  - 2) No
Abortive treatments
2015 American Headache Society Evidence Assessment

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<th>Level A = Effective</th>
<th>Analgesic and Combination medications</th>
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### Abortive treatments

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## Triptans Tips

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<tr>
<th>Triptan</th>
<th>Route</th>
<th>Dose/max dose</th>
<th>Onset</th>
<th>Half-life</th>
<th>OK with MAOI?</th>
<th>Approx. Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>SQ</td>
<td>1-6 mg/12 mg</td>
<td>10-15 minutes</td>
<td>115 min</td>
<td>No</td>
<td>$90 (6 mg Statdose pen, generic)</td>
</tr>
<tr>
<td></td>
<td>Oral tablet</td>
<td>25, 50, 100mg/200 mg</td>
<td>20-30 minutes</td>
<td>2.5 hours</td>
<td>No</td>
<td>$1-3 (generic)</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>5, 10, 20 mg/40 mg</td>
<td>15 minutes</td>
<td>2 hours</td>
<td>No</td>
<td>$40 (20 mg, generic)</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Oral</td>
<td>1, 2.5 mg/5 mg</td>
<td>1-3 hours</td>
<td>6 hours</td>
<td></td>
<td>~$11 (generic)</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Oral</td>
<td>6.25, 12.5/25 mg</td>
<td>30 min-2 hrs</td>
<td>3-4 hours</td>
<td></td>
<td>$35 (generic)</td>
</tr>
</tbody>
</table>

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<tr>
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<th>Route</th>
<th>Dose/max dose</th>
<th>Onset</th>
<th>Half-life</th>
<th>OK with MAOI?</th>
<th>Approx. Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frovatriptan</td>
<td>Oral</td>
<td>2.5 mg/7.5 mg</td>
<td>2-3 hours</td>
<td>26 hours</td>
<td></td>
<td>~$55 (generic)</td>
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<tr>
<td>Rizatriptan</td>
<td>Oral</td>
<td>5,10 mg/30 mg</td>
<td>30 min-2 hrs</td>
<td>1-1.5 hrs</td>
<td>No</td>
<td>~$2 (10 mg, generic)</td>
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<tr>
<td>Eletriptan</td>
<td>Oral</td>
<td>20, 40mg/80 mg</td>
<td>30 minutes</td>
<td>4 hours</td>
<td></td>
<td>~$50</td>
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<tr>
<td>Zolmitriptan</td>
<td>Oral</td>
<td>1.25, 2.5, 5mg/10 mg</td>
<td>45 minutes</td>
<td>3 hours</td>
<td>No</td>
<td>$42 (2.5mg, generic)</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>2.5, 5mg/10 mg</td>
<td>15 minutes</td>
<td>3 Hours</td>
<td>No</td>
<td>$60</td>
</tr>
</tbody>
</table>

Abortive treatments  
2015 American Headache Society Evidence Assessment

<table>
<thead>
<tr>
<th>Level B = Probably effective</th>
<th>Antiemetics</th>
<th>Ergots</th>
<th>NSAIDs</th>
<th>Others</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorpromazine IV 12.5 mg</td>
<td>DHE IV, IM, SC 1 mg</td>
<td>Flurbiprofen 100 mg</td>
<td>MgSO4 IV (migraine with aura) 1-2 g</td>
<td>Codeine/acetaminophen 25/400 mg</td>
</tr>
<tr>
<td></td>
<td>Droperidol IV 2.75 mg*</td>
<td>Ergotamine/caffeine 1/100 mg</td>
<td>Ketoprofen 100 mg</td>
<td>Isometheptene 65 mg</td>
<td>Tramadol/acetaminophen 75/650 mg</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide IV 10 mg</td>
<td></td>
<td>Ketorolac IV/IM 30-60 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine IV/IM 10 mg; PR 25 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Black Box Warning: QTc prolongation and Torsades

Choosing symptomatic treatments
2015 American Headache Society Evidence Assessment

<table>
<thead>
<tr>
<th>Level C = Probably effective</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic</td>
<td>Valproate IV 400-1000 mg</td>
</tr>
<tr>
<td>Ergot</td>
<td>Ergotamine 1-2 mg</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Phenazone 1000 mg</td>
</tr>
<tr>
<td>Opioids</td>
<td>Butorphanol IM 2 mg</td>
</tr>
<tr>
<td></td>
<td>Codeine 30 mg PO</td>
</tr>
<tr>
<td></td>
<td>Meperidine IM 75 mg</td>
</tr>
<tr>
<td></td>
<td>Methadone IM 10 mg</td>
</tr>
<tr>
<td></td>
<td>Tramadol IV 100 mg</td>
</tr>
<tr>
<td>Steroid</td>
<td>Dexamethasone IV 4-16 mg</td>
</tr>
<tr>
<td>Others</td>
<td>Butalbital 50 mg</td>
</tr>
<tr>
<td></td>
<td>Lidocaine intranasal</td>
</tr>
<tr>
<td>Combinations</td>
<td>Butalbital/acetaminophen/caffeine/codeine 50/325/40 mg</td>
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Abortive treatment tips/pearls

- Choose specific therapies based on effectiveness, contraindications, side effect profile, patient preference
- Use an adequate dose
- Treat early (<60 minutes from onset) and when pain is still mild
- Stratified care approach to treatment
  - Match treatment to attack characteristics - mild/moderate/severe, nausea/vomiting
- Consider route of administration
  - Sumatriptan SQ or Nasal, Zolmitriptan nasal
- Although opioids are probably effective, not recommended for regular use
- Avoid medication overuse
  - Simple analgesics, Triptans, opioids, bultalbital
- Rizatriptan = 5 mg if patient on Propranolol
- OK with MAOI = Naratriptan, Almotriptan, Frovatriptan, Eletriptan
- Naratriptan, Almotriptan - better tolerated than Sumatriptan
- Frovatriptan - lowest recurrence rate
- Rizatriptan - best efficacy at 2 hours for orals, but high recurrence rate
- Zolmitriptan nasal spray - rapid acting alternative to injection
- Eletriptan - ½ dose with potent CYP3A4 inhibitors (clarithromycin, ritonavir, nelfinavir, itraconazole)
Which of the following medications are FDA approved for prevention of migraine?

- 1) Valproic acid, Topiramate, propranolol
- 2) Topiramate, propranolol, amitriptyline, Lisinopril
- 3) Valproic acid, topiramate, propranolol, timolol, atenolol
- 4) Valproic acid, topiramate, propranolol, timolol
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- 3) Valproic acid, topiramate, propranolol, timolol, atenolol
- 4) Valproic acid, topiramate, propranolol, timolol
Preventive treatment goals

- Decrease attack frequency, intensity, duration
- Improve responsiveness to acute treatment
- Improve function and quality of life
- Reduce need for acute treatment, reduce/eliminate medication overuse
- Not “no headaches”
When to start a migraine preventive

  - “Migraineurs with six or more headache days per month
  - four or more headache days with some degree of functional disability
  - three or more headache days per month resulting in severe disability requiring bed rest

- Failure, contraindication to, or troublesome side-effects from acute medications
- Overuse of acute medications
- Increased frequency of attacks

Silberstein SD *et al.*, *Neurology* 2000
Comparison to other guidelines

- AHS/AAN
  - Level of evidence -> treatments graded A/B/C/U based on efficacy alone
- Canadian Headache Society
  - Level of evidence -> treatments graded strong or weak based on balance of benefits and harms
- European Federation of Neurological Societies (EFNS)
  - Broader inclusion criteria
    - Graded A,B,C based on evidence base and expert opinion

Areas of agreement: Highest level in all 3 guidelines:
- Divalproex
- Metoprolol
- Propranolol
- Topiramate
2012 AAN/AHS Guidelines Ratings for Preventive therapies

- **Level A**: established efficacy (at least two Class I trials)
- **Level B**: probably effective (one Class I or at least two Class II studies)
- **Level C**: possibly effective (at least one Class II study)
- **Level U**: inadequate or conflicting data to support or refute use
- **Level A-, B-, C-**: treatments that are established as possibly or probably ineffective
Preventive therapy
American Headache Society - American Academy of Neurology
Guidelines 2012

<table>
<thead>
<tr>
<th>Level A: Effective</th>
<th>Medication</th>
<th>Studied and/or Target doses</th>
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</thead>
</table>
| Antiepileptic drugs | Divalproex sodium  
Sodium valproate  
Topiramate | 1000 mg/d  
50 mg twice a day |
| Beta Blockers | Timolol  
Propranolol  
Metoprolol | 20 mg/d  
120-160 mg/d  
50-100 mg/d |

Shapiro. *Headache*, 2012  
Evans R et al, *Headache* 2006  
Young WB. In: Robbins MS et al, *Neurology In Practice: Headache*, 2013
Preventive therapy

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<th>Level B: Probably Effective</th>
<th>Medication</th>
<th>Studied and/or Target doses</th>
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<tbody>
<tr>
<td>Antidepressants/SSRI/SNRI/TCA</td>
<td>Amitriptyline</td>
<td>50-75 mg/d</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>150-300 mg/d</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>Atenolol</td>
<td>50-100 mg/d</td>
</tr>
<tr>
<td></td>
<td>Nadolol</td>
<td>20-120 mg/d</td>
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Silberstein et al. Neurology, 2012
Shapiro. *Headache*, 2012
Evans R et al, *Headache* 2006
Young WB. In: Robbins MS et al, *Neurology In Practice: Headache*, 2013
Preventive therapy  

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<th>Level C: Possibly Effective</th>
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<tr>
<td>ACE inhibitors</td>
<td>Lisinopril</td>
<td>10-20 mg/d</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Candesartan *</td>
<td>16 mg/d</td>
</tr>
<tr>
<td>Alpha-Agonists</td>
<td>Clonidine</td>
<td>0.75-0.15 mg/d</td>
</tr>
<tr>
<td></td>
<td>Guanfacine</td>
<td>0.5-1 mg/d</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Carbamazepine</td>
<td>600 mg/d</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Nebivolol</td>
<td>5 mg/d</td>
</tr>
<tr>
<td></td>
<td>Pindolol</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Cyproheptadine</td>
<td>4-12 mg/d</td>
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Shapiro. Headache, 2012  
Evans R et al, Headache 2006  
Young WB. In: Robbins MS et al, Neurology In Practice: Headache, 2013  
Stovner et al. Cephalalgia. 2014
Which of the following are FDA approved for prevention of chronic migraine?

- 1) Topiramate
- 2) Propranolol
- 3) Onabotulinum toxin A (Botox)
- 4) Valproic acid
- 5) Topiramate and Onabotulinum toxin A (Botox)
- 6) Topiramate, Propranolol and Onabotulinum toxin A (botox)
Which of the following are FDA approved for prevention of chronic migraine?

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Which have the best evidence for efficacy for prevention of chronic migraine?

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- 5) Topiramate and Onabotulinum toxin A
- 6) Topiramate, Propranolol and Onabotulinum toxin A

Deiner et al. 2007
PREEMPT 1 and 2
Preempt 1 and 2 Pooled Analysis

Aurora et al. Headache. 2011
Onabotulinum toxin a Injection sites

155 units
31 injection sites
Every 12 weeks
Prevention tips

- Start low and go slow
- Titrate up until therapeutic response achieved, target dose is achieved, or side effects are experienced
- Adequate duration
- Try to get “two-fer”
- Topiramate >200 mg/day can decrease OCP levels
- Zonisamide if intolerant of topiramate
New and emerging therapies

- Thanks to Stew Tepper, MD

- Current treatments delivered differently - “old wine in new bottles”
- Devices
- Future drugs
  - Monoclonal antibodies
  - Ubrogepant and other “gepants”
  - Lasmiditan
Emerging Treatments for Migraine

- Current treatments delivered differently
  - Sumatriptan: new injection devices, new breath powered dry nasal powder, patch in development
  - Zolmitriptan: patch and inhaler in development
  - Rizatriptan: oral dissolvable film in development
  - DHE: inhaler in development
- Devices
  - Neuromodulation- devices boldly go where no medications have gone before: tSNS, sTMS, and in development nVNS and CVS
  - Other devices: Skin patch zolmi & suma, suma oral spray, inhaled zolmi
- Future drugs
  - Acute: ubrogepant, lasmiditan
  - Preventive: Atogepant, monoclonal antibodies
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 specs, and drugs or modulation delivered reliably in consistent aliquots
- The FDA has been updating CMC regulations as recently as April 22, 2016
- Almost all of the devices have had holdups in CMC, and some have current delays (e.g. inhalable DHE)
Current Treatments Delivered Differently “Old Wine in New Bottles”

• FDA approved:
  ▶ Sumatriptan needle-free injection (Brand name SUMAVEL) - available
  ▶ Sumatriptan epipen-like injection (Brand name ALSUMA) - not available
  ▶ Sumatriptan auto-injectors (Dr. Reddy’s, Sun, generic) - available
  ▶ Breath-powered powder sumatriptan intranasal treatment (Brand name ONZETRA, AVP-825, formerly OPTINOSE)
  ▶ Sumatriptan iontophoretic patch (Brand name ZECUITY) - off the market

• Before the FDA:
  - Rizatriptan dissolvable film (RHB-103, VersaFilm)
  - Dihydroergotamine (DHE) oral inhalation (Brand name SEMPRANA, iDHE, MAP0004, formerly LEVADEX)
Sumatriptan auto-injectors

Needle-free

4 & 6 mg

Epipen-like

Currently facing prolonged out-of-stock situation

Prefilled Auto-injectors

6 mg

6 mg

These work differently, so watch the online videos or get practice devices to show your patients!
Removal of sumatriptan iontophoretic patch (Zecuity) from market

Safety Announcement

- **[06-02-2016]** The FDA is investigating…serious burns and potential permanent scarring reported with Zecuity (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

- **[06-10-2016]** Zecuity manufacturer Teva Pharmaceuticals has decided to temporarily suspend sales, marketing, and distribution to investigate the cause of burns and scars associated with the Zecuity patch. Health care professionals should discontinue prescribing Zecuity, and patients should stop using any remaining patches and contact their prescribers for an alternative migraine medicine.

Sumatriptan breath powered dry nasal powder, onzetra exsail

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

Current treatments delivered differently

• FDA APPROVED:
  • SUMATRIPTAN NEEDLE-FREE INJECTION (BRAND NAME SUMAVEL) - AVAILABLE
  • SUMATRIPTAN EPIPEN-LIKE INJECTION (BRAND NAME ALSUMA) - NOT AVAILABLE
  • SUMATRIPTAN AUTO-INJECTOR (SUN, GENERIC) - AVAILABLE
  • SUMATRIPTAN IONTOPHORETIC PATCH (BRAND NAME ZECUITY) – NOT AVAILABLE

• BEFORE THE FDA:
  - RIZATRIPTAN DISSOLVABLE FILM (RHB-103, VERSAFILM)
  - DIHYDROERGOTAMINE (DHE) ORAL INHALATION (IDHE, MAP0004)
RHB-103, fast dissolving thin film orally dissolvable formulation of rizatriptan

- Dissolves in mouth but absorbed in GI tract
- March 2014, response to Feb '14 FDA questions related to 3rd party Chemistry, Manufacturing and Controls (CMC), packaging, and labeling
Orally inhaled dihydroergotamine (IDHE), semprana inhaler

Phase 3 Pivotal RCT

- No pain or mild pain: 58% (iDHE) vs 34% (Placebo)
- No photophobia: 46% (iDHE) vs 27% (Placebo)
- No phonophobia: 52% (iDHE) vs 34% (Placebo)
- No nausea: 67% (iDHE) vs 59% (Placebo)

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

Tepper SJ. Headache 2013;53;S2:43-53.
New medication devices in development

- ZP-Zolmitriptan Skin Patch
- Sumatriptan Sofusa DoseDisc System Skin Patch
- Zolmitriptan Oral Inhalation, CVT-427
- Sumatriptan Oral Spray, SUD-001
Microneedle array skin deliveries

1. ZOLMITRIPTAN, ZP ZOLMITRIPTAN (ZOSANO) - PHASE 2

   A (0.48 mg)  B (0.48 mg x 2)  C (1.9 mg)  F (1.9 mg x 2)  G (3.8 mg)  D (2.5 mg oral)

2. Sumatriptan Sofusa DoseDisc System (Kimberly-Clark) [no images or data]
Inhaled zolmitriptan cvt-427

Clinical testing ~2017

Photos of prototypes of CVT-301, levodopa inhalers
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 (20mg and 30mg) with 50mg sumatriptan tablet showed faster absorption rate with SUD-001 than tablets and up to 50% increase in relative bioavailability of sumatriptan
- Open label dose ranging migraine study: up to 5 treatments, sumatriptan 50mg and 100mg tablets, and SUD-001 20mg, 30mg, 40mg oral spray
- 1 hour Headache relief:
  - SUD-001 30mg - 42%
  - SUD-001 40mg - 46%
  - 50 mg sumatriptan tablet - 12%
  - 100 mg sumatriptan tablet - 42%

Which neuromodulation device is FDA approved for the prevention of migraine?

1) Single-pulse transcranial magnetic stimulator for acute treatment of migraine w/aura (sTMS, SpringTMS)

2) Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEFALY)

3) Noninvasive vagal nerve stimulator (nVNS, gammaCore, ElectroCore)

4) Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Neuromodulation devices

- Single-pulse transcranial magnetic stimulator for acute treatment of migraine w/aura (sTMS, SpringTMS) - UK and US FDA approved, available in selected US and UK centers
- Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEFALY) - Health Canada and EU approved with 3 settings, US FDA approved with 1 setting
- Noninvasive vagal nerve stimulator (nVNS, gammaCore, ElectroCore) - Health Canada approved, CE Mark EU, UK NICE approved, currently before the FDA
- Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Single-pulse transcranial magnetic stimulator for acute treatment of migraine w/aura (sTMS, SpringTMS) - UK and US FDA approved, available in selected US and UK centers

Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEFALY) - Health Canada and EU approved with 3 settings, US FDA approved with 1 setting

Noninvasive vagal nerve stimulator (nVNS, gammaCore, ElectroCore) - Health Canada approved, CE Mark EU, UK NICE approved

Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Single Pulse Transcranial Magnetic Stimulator sTMS [SpringTMS] (eNeura)

- RCT OF STMS FOR ACUTE TREATMENT MIGRAINE W/AURA, 2 PULSES VS SHAM WITHIN 1 H OF AURA ONSET, N=164\(^1\)

Open label UK study, 29 patients pulsed sTMS BID and acutely prn\(^2\)

<table>
<thead>
<tr>
<th>Hours after treatment</th>
<th>Proportion of patients pain free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>p = 0.0179</td>
</tr>
<tr>
<td>24 h</td>
<td>p = 0.0405</td>
</tr>
<tr>
<td>48 h</td>
<td>p = 0.0327</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduction of acute treatment meds</th>
<th>Reduction of migraine days</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>27.5</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>28</td>
<td>18</td>
</tr>
</tbody>
</table>


sTranscranial Magnetic Stimulation
Acute Level of Evidence is B, Prevention U

- For **acute** treatment:
  - **Level B**, Probably Effective, based on one Class 1 study, *but it is FDA approved already*
  - It is FDA approved as a minimal risk device
- For **prevention** of migraine, **Level U**, 4 RCTs with conflicting data:
  - 1 positive RCT (Misra et al), 3 negative RCTs
  - Future RCTs need to be on dose ranging, MO, prevention, and AEs
  - Device is available by prescription at selected centers in US and UK
Single-pulse transcranial magnetic stimulator for acute treatment of migraine w/aura (sTMS, SpringTMS) - UK and US FDA approved, available in selected US and UK centers

Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEFALY) - Health Canada and EU approved with 3 settings, US FDA approved with 1 setting

Noninvasive vagal nerve stimulator (nVNS, gammaCore, ElectroCore) - Health Canada approved, CE Mark EU, UK NICE approved

Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Transcutaneous supraorbital neurostimulation for prevention of migraine (Cefaly)

- One 67 patient RCT; Turn it on and wear it 20 minutes/day
- Migraine d/mo 3rd mo: NS ; ≥ 50% reduction in migraine d/mo: (+) for 38.2%
- Cost: $349 US + $35 shipping +3 electrodes/$30, each lasting ≈ 20 sessions
- It can be returned within 60 days
- tSNS received US FDA approval March 2014 as minimal risk device
- Canada & EU: 3 settings, acute, preventive, relaxation; US just prevention
- Level of Evidence: Level B, probably effective, based on 1 RCT

Change in HA days (NS) P = 0.054
50% Responder Rates P = 0.023

nVNS

- Single-pulse transcranial magnetic stimulator for acute treatment of migraine w/aura (sTMS, SpringTMS) - UK and US FDA approved, available in selected US and UK centers
- Transcutaneous supraorbital neurostimulation (tSNS) for prevention of migraine (CEFALY) - Health Canada and EU approved with 3 settings, US FDA approved with 1 setting

- **Noninvasive vagal nerve stimulator (nVNS, gammaCore, ElectroCore)** - Health Canada approved, EU CE Mark, UK NICE approved, currently before the FDA

- Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Noninvasive vagal nerve stimulator (nVNS, gammacore, electrocore), before the fda

- Handheld, patient-controlled device
- Definitely stimulate the vagus

- CM RCT: TWO 90 SEC PULSES TID
- NS AT 2 MONTHS
- ↓HA DAYS DURING OLE


Mean Change in Number of Headache Days per 28 Days By Duration of nVNS Treatment

Noninvasive caloric vestibular stimulation (CVS, Scion NeuroStim)
Noninvasive caloric vestibular stimulation (cvs, scion neurostim)

- 6 SITE, PLACEBO-CONTROLLED, BLINDED, HOME-USE PROTOCOL
- 4-14 HA DAYS/MONTH
- 1° ENDPOINT: ↓ MIGRAINE D, 3RD MO
- 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)
- ITT: ACTIVE (N = 34); PBO (N = 18)
- ACTIVE: -3.2 HA DAYS VS. BASELINE (P < 0.0001)
- ACTIVE VS. SHAM: -2.4 HA DAYS (P = 0.034)

AEs >1 patient: nausea, dizziness, ear sx, tinnitus
Placebo dizziness = Active dizziness (4 in each)

Levels of Evidence and Summary

- **sTMS (SpringTMS):**
  - Level B for Acute Treatment Episodic Migraine with Aura, US FDA and NICE UK approved
  - Level U for Prevention of Migraine, NICE UK approved

- **tSNS (Cefaly):** Level B for Preventive Treatment Episodic Migraine, Health Canada, US FDA approved, EU CE Mark

- **nVNS (gammaCore):** [CE mark EU, NICE & Canada approved, currently before the US FDA]
  - Level U for Migraine

- **CVS (Scion):** Level B for Prevention of Migraine, no regulatory approval
Future Drugs

- **Acute Drugs**
  - CGRP Antagonist small molecule gepants: ubrogepant, BMS-927711
  - 5HT1F Agonist: Lasmiditan
- **Preventive medications**
  - Anti-CGRP monoclonal antibodies: ALD-403, galcanezumab, TEV-48125
  - Anti-CGRP receptor monoclonal antibody: Erenumab
  - Gepant: Atogepant
Future *Acute* Drugs
Future Drugs: *Acute* Medications for migraine

- Calcitonin gene-related peptide (CGRP) release leads to vasodilation and neurogenic inflammation
- Serotonin:
  - $1_B$ agonists: vasoconstriction
  - $1_D$ agonists: Inhibition of neuropeptide release and of afferent limb meninges to brainstem
  - $1_F$ agonists: central inhibition

**Gepants: CGRP Receptor Antagonist small molecules**

- CGRP is the most potent endogenous vasodilator
  - BMS-927711: blocks receptor; completed & published Phase 2, being shopped
  - Ubrogepant completed and published Phase 2, entering Phase 3
  - Seven have been tried in humans, all worked, at least two had liver toxicity

**Serotonin (5-HT)$_F$ agonist**

- Terminates migraine without vasoactive properties
  - Lasmiditan has reported a positive Phase 3
Ubrogepant Phase 2 Acute Treatment of Episodic Migraine

- Typical single attack Phase 2 dose-ranging study with ubrogepant 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, or placebo in a 1:1 ratio
- The co-primary endpoints were pain freedom and headache response at two hours
- Ubrogepant 100 mg was significantly superior to placebo for two-hour pain freedom (25.5% vs 8.9%) but not for two-hour headache response
- Per the prespecified multiplicity strategy, this nonsignificant result precluded further formal hypothesis testing
- On to Phase 3

Lasmiditan Phase 3 for the Acute Treatment of Episodic Migraine

- Lasmiditan 100 mg or 200 mg or placebo
- Primary endpoint, 2 hour pain free
- Secondary endpoint, 2 hour freedom from the most bothersome associated symptom (MBS) of migraine (nausea, phonophobia or photophobia)
- Both doses worked for 2h PF: 100 mg 28.2%; 200 mg 32.3%; Placebo 15.30%, p<0.001
- Both doses worked for 2h MBS: 100 mg 40.9%; 200 mg 40.7%; Placebo 29.5%, p<0.001
- Dizziness + vertigo= 100 mg 12.9%; 200 mg 15.7%
- Somnolence + fatigue + lethargy= 100 mg 10.9%, 200 mg 10.6%
- For comparison, Rizatriptan 10 mg PI:
  - Dizziness 20%; Somnolence + fatigue 15%

Poster presentation EHMTIC meeting, Glasgow, Sept 2016.
Future *Preventive* Drugs
<table>
<thead>
<tr>
<th>Episodic vs Chronic Migraine</th>
<th>Erenumab (Amgen 334)</th>
<th>ALD403</th>
<th>Galcanezumab (LY2951742)</th>
<th>Fremanezumab (TEV48125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic vs Chronic Migraine</td>
<td>Episodic Chronic</td>
<td>Episodic, Chronic</td>
<td>Episodic Migraine, Episodic and Chronic Cluster</td>
<td>Episodic Chronic</td>
</tr>
<tr>
<td>Phase 2 Administration</td>
<td>Subcutaneous</td>
<td>Intravenous</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Phase 2 Dosing Frequency</td>
<td>Once a month</td>
<td>One treatment</td>
<td>Twice a month</td>
<td>Monthly, or Q 3 months</td>
</tr>
<tr>
<td>Target (peripheral)</td>
<td>CGRP receptor</td>
<td>CGRP peptide</td>
<td>CGRP peptide</td>
<td>CGRP peptide</td>
</tr>
</tbody>
</table>

Future Drugs: *Preventive* Drugs for Migraine

Four injectable *monoclonal antibodies* to CGRP or its receptor
Two Phase 2 Trials of CGRP monoclonal antibodies for Episodic migraine (5-14 days/month):
Reduction in migraine days/month

ALD403

Galcanezumab (LY2951742)

Chronic Migraine/MOH Fremanezumab (TEV-48125) CGRP mAB: ↓# HA Hours Relative to Baseline, Positive at 4 days

Erenumab (amgen) Chronic Migraine + RCT

Presented at EHMTIC meeting, Glasgow, Sept 2016.
Representative Safety Data: Serious Adverse Events (SAE) with Erenumab

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N = 282)</th>
<th>Erenumab 70 mg (N = 190)</th>
<th>Erenumab 140 mg (N = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>7 (2.5)</td>
<td>6 (3.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Abdominal adhesions</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Cartilage injury</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Intervertebral disc protrusion</td>
<td>1 (0.4)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Costochondritis</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fibroma</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Radius fracture</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Migraine</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Parotitis</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Atogepant (AGN-241689, MK-8031) For Episodic Migraine Prevention

- “A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study To Evaluate The Efficacy, Safety, And Tolerability Of Multiple Dosing Regimens Of Oral AGN-241689 In Episodic Migraine Prevention”

- Doses: 10 mg PO QD, 30 mg QD, 30 mg BID, 60 mg QD, 60 mg BID and placebo

- To start in 2016

Final question...

- Will everyone with migraine in the audience please raise their hands?
Congratulations!!

- “Migraine, like gout, attacks more wise men (and even more women!) than fools.”
  - Sydenham
Thank you for your attention!
<table>
<thead>
<tr>
<th><strong>Level U = Conflicting or Inadequate Evidence</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Celecoxib 400 mg</td>
</tr>
<tr>
<td>Others</td>
<td>Lidocaine IV Hydrocortisone IV 50 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Level B Negative = Probably Ineffective</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Octreotide SC 100g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Level C Negative = Possibly Ineffective</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetics</td>
<td>Chlorpromazine IM 1 mg/kg Granisetron IV 40-80 g/kg</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ketorolac tromethamine nasal spray</td>
</tr>
<tr>
<td>Analgesic</td>
<td>Acetaminophen IV 1000 mg</td>
</tr>
<tr>
<td>Level U: Inadequate or Conflicting data</td>
<td>Medication</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>Acenocoumarol</td>
</tr>
<tr>
<td></td>
<td>Coumadin</td>
</tr>
<tr>
<td></td>
<td>Picotamide</td>
</tr>
<tr>
<td>Antidepressants/SSRI/SNRI/TCA</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Protriptyline</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Bisoprolol</td>
</tr>
</tbody>
</table>
Preventive therapy

<table>
<thead>
<tr>
<th>Other: Possibly or Probably ineffective</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not effective</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Probably not effective</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Possibly not effective</td>
<td>Acebutolol Clonazepam Nabumetone Oxcarbazepine Telmisartan</td>
</tr>
</tbody>
</table>