MIGRAINE TREATMENT UPDATE: CURRENT AND PIPELINE

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Director, Neurology Clinics
Program Director, Headache Fellowship
Division Chief, Headache and Neuralgia

Keck School of Medicine of USC
Disclosures

Previously:
Consultant for Amgen, Allergan
Speaker Bureau for Teva and Eli Lilly
Outline

1. Recognize the global disability from migraine
2. Understand that migraine is a brain disorder
3. Learn about the current and future abortive treatments for Migraine headache
4. Recognize current and future preventative treatments for migraine

GBD 2015 Neurological Disorders Collaborator Group

Summary

Background Comparable data on the global and country-specific burden of neurological disorders and their trends are crucial for health care planning and resource allocation. The Global Burden of Disease, Injuries, and Risk Factors...
Figure 1: Global DALYs by age and neurological disorder in 2015
DALYs = disability-adjusted life-years.
The Migraine Attack

Intensity of Symptoms or Phases

Prodrome | Aura | Headache | Postdrome

Associated Features

Time
• Migraine is not “just a headache”.
• Migraine is an inherited neurological disorder characterized by an underlying state of increased responsiveness of cortical and subcortical networks that amplify the intensity of sensory stimuli.
• It is a “syndrome” characterized by disturbances of sensory function, affect, cognitive and autonomic function.
Why is Migraine a brain disorder?

Neurovascular

Neuronal hyperexcitability, esp. occipital cortex... → ...makes brain susceptible to migraine attacks
• is an electrical event in the brain

• This event is called *Cortical spreading depression*, a wave that spreads at the rate of 2-6 mm/min on the surface of the brain

• There is change in chemical flow within the neurons---resulting in changes in electrical signaling---which leads to change in local blood flow.
CNS Activation During Migraine

Dysfunction of brain stem pain and vascular control centers

Pain Perception*
- Anterior cingulate cortex

“Migraine Generator”*
- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

*Areas of red indicate cerebral blood flow increases (P < 0.001).
(Weiller et al. 1995)
PET scan in experimentally induced pain
Phase 1: prior to migraine attack

- Upto 3 days prior to migraine
- Fatigue, mood changes, food cravings, yawning, muscle tenderness.
- Points to involvement of Hypothalamus as a potential origin of migraine attack.
- Other areas of activation include brainstem, limbic (emotional) system and cortical (executive, speech, language) areas.
A Phase-by-Phase Review of Migraine Pathophysiology

1. Multiple afferents carry parasympathetic signals to the SSN

2. Signals from the SSN activate postganglionic parasympathetic neurons in the SPG, projecting to the meninges

3. Increased parasympathetic tone activates meningeal nociceptors and the trigeminovascular pathway

4. Intracranial vasodilation and local release of inflammatory molecules in the meninges
Multiple mechanisms of Migraine:
Many pathways/receptors and chemicals
Migraine headaches: Acute abortive treatment

Which is the best treatment to stop an acute migraine attack?

1. to decrease pain intensity by 50% or more
2. to stop or decrease nausea/vomiting
3. to stop or decrease other symptoms (light or noise sensitivity)
Migraine headaches: Acute abortive treatment

<table>
<thead>
<tr>
<th>NSAIDs/Analgesics</th>
<th>Ergot Alkaloid Derivative</th>
<th>Triptans</th>
<th>Combination/Other</th>
<th>Calcitonin Gene-Related Peptide Antagonists (small molecules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Ergotamine</td>
<td>Almotriptan</td>
<td>Acetaminophen/aspirin/caffeine</td>
<td>UBRELVY™</td>
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<tr>
<td>Aspirin</td>
<td>Dihydroergotamine (DHE)</td>
<td>Eletriptan</td>
<td>Butalbital/acetaminophen/caffeine</td>
<td>Nurtec™</td>
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<tr>
<td>Diclofenac</td>
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<td>Frovatriptan</td>
<td>Butalbital/aspirin/caffeine</td>
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<tr>
<td>Ibuprofen</td>
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<td>Naratriptan</td>
<td>Butorphanol</td>
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<td>Naproxen</td>
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<td>Rizatriptan</td>
<td>Ergotamine/caffeine</td>
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<td>Sumatriptan</td>
<td>Sumatriptan/naproxen</td>
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<td></td>
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<td>Zolmitriptan</td>
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</tbody>
</table>
Proposed Mechanisms for Triptan Effect on Migraine

Trigeminal nerve

Inhibition of NT release

5-HT1D

5-HT1F

Nociceptive & Inflammatory Neurotransmitters:
CGRP
NKA
Substance P

Triptans

5-HT1B

Vasoconstriction
## Prophylactic Examples

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Antiepileptics/Anticonvulsants</th>
<th>Beta-blockers</th>
<th>Calcium Channel Blockers</th>
<th>Angiotensin-Converting Enzyme (ACE) Inhibitors/Angiotensin II Receptor Blockers (ARB)</th>
<th>Calcitonin Gene-Related Peptide Antagonists (mAbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Divalproex sodium</td>
<td>Atenolol</td>
<td>Diltiazem</td>
<td>Candesartan</td>
<td>Aimovig®</td>
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<tr>
<td>Citalopram</td>
<td>Gabapentin</td>
<td>Metoprolol</td>
<td>Nifedipine</td>
<td>Enalapril</td>
<td>Emgality®</td>
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<tr>
<td>Doxepin</td>
<td>Topiramate</td>
<td>Nadolol</td>
<td>Nimodipine</td>
<td>Irbesartan</td>
<td>Ajovy®</td>
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<tr>
<td>Fluoxetine</td>
<td>Valproic acid</td>
<td>Propranolol</td>
<td>Verapamil</td>
<td>Lisinopril</td>
<td>Vyepti™</td>
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<tr>
<td>Fluvoxamine</td>
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<td>Timolol</td>
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<td>Losartan</td>
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<tr>
<td>Mirtazapine</td>
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<td>Olmesartan</td>
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<td>Nortriptyline</td>
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<td>Ramipril</td>
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<td>Paroxetine</td>
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<td>Valsartan</td>
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<td>Protriptyline</td>
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<td>Valsartan</td>
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<tr>
<td>Sertraline</td>
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<td></td>
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<td>Valsartan</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
<td></td>
<td></td>
<td>Valsartan</td>
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</tr>
</tbody>
</table>
# Preventative treatment

## Neuronal membrane Stabilizers

Prevent spontaneous depolarization

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>Beta-blockers:</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Propranolol</td>
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<tr>
<td>Zonisamide</td>
<td>Timolol</td>
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<tr>
<td>Lamotrigine</td>
<td>Calcium channel blockers</td>
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**Antidepressants**

<table>
<thead>
<tr>
<th>Beta-blockers:</th>
<th>Calcium channel blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>ACE inhibitors/ARBs</td>
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<tr>
<td>Timolol</td>
<td></td>
</tr>
</tbody>
</table>

**SNRIs**

<table>
<thead>
<tr>
<th>ACE inhibitors/ARBs</th>
<th>Botulinum toxin type A injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>Erenumab (Aimovig)</td>
</tr>
<tr>
<td>Wellbutrin</td>
<td>Fremanezumab (Ajovy)</td>
</tr>
</tbody>
</table>

**Muscle relaxants**

<table>
<thead>
<tr>
<th>Erenumab (Aimovig)</th>
<th>Fremanezumab (Ajovy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galcanezumab (Emgality)</td>
<td>Eptinezumab (V)</td>
</tr>
</tbody>
</table>

### Keck School of Medicine of USC
Preventative treatment

<table>
<thead>
<tr>
<th>NEUTRACEUTICALS</th>
<th>ALTERNATIVE MED</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGNESIUM</td>
<td>YOGA</td>
</tr>
<tr>
<td>VITAMIN B2</td>
<td>BIOFEEDBACK</td>
</tr>
<tr>
<td>COENZYME Q10</td>
<td>ACUPUNCTURE</td>
</tr>
<tr>
<td>BUTTERBUR</td>
<td>MEDITATION</td>
</tr>
<tr>
<td>FEVERFEW</td>
<td></td>
</tr>
<tr>
<td>MELATONIN</td>
<td></td>
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<tr>
<td>TURMERIC</td>
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CALCITONIN GENE-RELATED PEPTIDE (CGRP): EFFECTS ON THE BODY

Locally
- Thermal, mechanical and chemical stimuli
- CGRP
- Increased blood flow, potentially long lasting
- Promotes wound healing
- Modulates inflammation

Systemically
- Released in response to endogenous stresses
- Heart
- Aorta
- Kidney
- Protection against hypertension, hypertrophy and inflammation
Figure 3

Published in Annual review of pharmacology and toxicology 2015
Calcitonin gene-related peptide (CGRP): a new target for migraine.
Andrew F Russo
Migraine bonanza

Timeline Tagline

**2018-April**

**Erenumab**
CGRP receptor antagonist
Monthly SQ
Prevention episodic and chronic migraines

**2018-June**

**Galacanezumab**
CGRP ligand antagonist
Monthly SQ
Prevention episodic chronic migraines
Cluster

**2018-sept**

**Fremazenumab**
CGRP ligand antagonist
Monthly SQ or quarterly
Prevention episodic and chronic migraines

**2019-oct**

**Lasmitidan**
Ditan
Acute treatment
Schedule V.
Driving advisory

**2019-dec**

**Ubrogepant**
Small molecule
CGRP receptor antagonist
Acute treatment
50, or 100mg prn
Migraine bonanza

Timeline Tagline

2020
February
Eptinezumab
CGRP ligand antagonist
Quarterly IV Prevention episodic and chronic migraines

Rimegepant
Small molecule CGRP receptor antagonist

2020
Ubrogepant
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<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>DOSING</th>
<th>FREQUENCY</th>
<th>TRIAL</th>
<th>COMMON SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab (AMG 334)</td>
<td>Subcutaneous injection</td>
<td>Monthly</td>
<td>ARISE 70 mg</td>
<td>• Runny/stuffy nose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>STRIVE 70 mg 140 mg</td>
<td>• Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Injection site pain</td>
</tr>
<tr>
<td>Galcanezumab (LY2951742)</td>
<td>Subcutaneous injection</td>
<td>Monthly</td>
<td>EVOLVE-1 120 mg 240 mg</td>
<td>• Injection-site reaction and pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EVOLVE-2 120 mg 240 mg</td>
<td>• Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Abdominal pain</td>
</tr>
<tr>
<td>Fremanezumab (TEV-48125)</td>
<td>Subcutaneous injection</td>
<td>Monthly or quarterly</td>
<td>HALO EM 225 mg (monthly) 675 mg (quarterly)</td>
<td>• Injection site pain</td>
</tr>
<tr>
<td>Eptinezumab (ALD403)</td>
<td>Intravenous infusion</td>
<td>Every 12 weeks</td>
<td>PROMISE 1 100 mg</td>
<td>• Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Urinary tract infection</td>
</tr>
</tbody>
</table>
Figure 3 Reduction in MHDs at each month

Holland C. Detke et al. Neurology 2018;91:e2211-e2221
A. Corrugator  
5 U each side

B. Procerus  
5 U (one site)

C. Frontalis  
10 U each side

D. Temporalis  
20 U each side

E. Occipitalis  
15 U each side

F. Cervical paraspinal  
10 U each side

G. Trapezius  
15 U each side
Multidisciplinary Team Treatment Approaches to Chronic Daily Headaches

Soma Sahai-Srivastava, MD; Erica Sigman, DPT; Ashley Uyeshiro Simon, OTD, OTR/L, MSCS; Lyssa Cleary, DPT; Lori Ginoza, DPT
<table>
<thead>
<tr>
<th>Topics</th>
<th>Methods/Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache self-management</td>
<td>Logs, journals, increasing patient self-efficacy&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exercise routines</td>
<td>Frequency, type, and duration of exercise&lt;sup&gt;p&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eating routines</td>
<td>Regularity, blood sugar management, dietary H/A</td>
</tr>
<tr>
<td>Sleep routines</td>
<td>Regularity, quantity, and quality; sleep hygiene; health</td>
</tr>
<tr>
<td>Stress management</td>
<td>Stressor identification and remediation, coping strategies</td>
</tr>
<tr>
<td>Medication management</td>
<td>Medication overuse headache prevention, compliance</td>
</tr>
<tr>
<td>Weight management</td>
<td>Weight loss or weight gain</td>
</tr>
<tr>
<td>Ergonomics</td>
<td>Limit physical or environmental triggers, prescribe schedules&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body mechanics</td>
<td>Posture, proper mechanics for activities&lt;sup&gt;l,m&lt;/sup&gt;</td>
</tr>
<tr>
<td>Activity pacing &amp; energy conservation</td>
<td>Taking breaks, preventing flare-ups&lt;sup&gt;n,o&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lifestyle balance</td>
<td>Preventing overexertion throughout the day/week&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cognition</td>
<td>Memory, concentration, focus&lt;sup&gt;n,p&lt;/sup&gt;</td>
</tr>
<tr>
<td>Communication</td>
<td>Assertiveness, communication strategies&lt;sup&gt;n,p&lt;/sup&gt;</td>
</tr>
<tr>
<td>Community integration</td>
<td>Minimize triggers in the community, socialization,</td>
</tr>
</tbody>
</table>
Outcomes of the program development study for quality improvement:

N= 322 patients

Completers = 157 patients (met the inclusion criteria of completing 4 or more OT sessions.

Non-completers= 165 did not meet this criteria ("non-completers").

average number of sessions attended 4.95
Figures 4-9: Outcome Measure Results

Health-Related Quality of Life (RAND SF-36)

Higher scores indicate better quality of life

- General Health*
- Pain*
- Social functioning*
- Emotional well-being*
- Energy/fatigue*
- Role limitations due to emotional problems*
- Role limitations due to physical health*
- Physical functioning*

Mean Difference (*indicates significant difference)
Physical Therapy Treatment

- Ergonomics and postural education
- Patient education
  - Strategies to manage musculoskeletal triggers
  - Strategies to modify response to headaches/pain
  - Sleep hygiene (sleep positions)

- Exercises to improve:
  - Muscle strength and endurance
    - Cervical muscles, scapula-thoracic muscles, abdominal muscles
  - Muscle-length deficits
  - Cervical spine ROM
  - Thoracic mobility
  - Postural deficits

- Modalities
  - TENS, Laser light, ice pack, moist heat

- Manual therapy
Peripheral nerve blocks

- Novacaine
- Low risk, quick, high yield
- Success depends on experience of injector
- Lasts 4-6 weeks
Peripheral nerve blocks

- Self-administration at home
- Battery powered, non-rechargeable
- Placed on upper arm and produces electrical signals to inhibit migraine pain
- An App is installed on a smartphone to control and monitor the treatment

The Use of “Scalp Block” in Pediatric Patients

Figure 1. Schematic of scalp block nerves in a pediatric patient.
Nerivio

• Self-administration at home
• Battery powered, non-rechargeable
• Placed on upper arm and produces electrical signals to inhibit migraine pain
• An App is installed on a smartphone to control and monitor the treatment
Refractory Headaches: innovative treatments

- Transcranial Magnetic stimulation

Fig. 1 Position of device for treatment
Refractory Headaches: innovative treatments

- Peripheral Neurostimulation nerve stimulators
- Cefaly acute, Cefaly prevent and Cefaly DUAL
Gammacore

1. Agonising headache

2. Gammacore device held firmly against the skin just below the chin
Refractory Headaches: innovative treatments

- Peripheral Neurostimulation implanted or percutaneous: Occipital, Supraorbital and Trigeminal nerve stimulators
Refractory Headaches: innovative treatments

- Sphenopalatine Ganglion blocks
Refractory Headaches: innovative treatments

- Radiofrequency ablation
Refractory Headaches: innovative treatments

- Occipital nerve decompression surgery
Infusion or injections for migraine

<table>
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<tr>
<th>Medication</th>
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<tbody>
<tr>
<td>MgSO4</td>
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<tr>
<td>Antinauseants</td>
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<tr>
<td>Steroids</td>
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<tr>
<td>DHE45</td>
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<td>Depacon</td>
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<td>Propofol</td>
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<tr>
<td>Lidocaine</td>
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<tr>
<td>Levetiracetam</td>
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<tr>
<td>Tramadol</td>
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<tr>
<td>Ketamine</td>
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<tr>
<td>Methocarbamil</td>
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</table>
SUMMARY

• EACH MIGRAINE IS AS DIFFERENT AS EACH INDIVIDUAL
• THERE IS NO ONE SIZE FITS ALL FOR MIGRAINE TREATMENT
• OFTEN A COMBINATION OF OPTIONS WORK FOR EACH
• FIND YOUR MIGRAINE VILLAGE
• DON’T GIVE UP
USC HEADACHE AND NEURALGIA CENTER

NEUROLOGY (Headache Division):
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Paul Henri Cesar, M.D.
Sandhya Ravikumar, M.D
Ana Gjurevich, NP
Hawa Mapara, NP

Neuroradiology
Alex Lerner

PHYSICAL THERAPY
Lori Ginoza
Erica Sigman
Max Borroso

OCCUPATIONAL THERAPY
Lindsey Reeves
Malia Sako

PAIN MANAGEMENT
Steven Richeimer, M.D.

PAIN PSYCHOLOGY
Susan Axtell
Faye Weinstein

NEUROSURGERY
Steven Gioannata, M.D.
Darrin Lee, M.D.
Dawn Fishback, PA
A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (Zavegepant*) Intranasal (IN) for the Acute Treatment of Migraine
Response at 2 hours post-treatment:

- Pain Relief: 66.7% (Active), 38.8% (Sham), P < .0001
- Pain Free: 37.4% (Active), 18.4% (Sham), P < .005
- MBS Relief: 46.3% (Active), 22.2% (Sham), P < .001

Sustained response at 48 hours post-treatment:

- Pain Relief: 39.1% (Active), 16.9% (Sham), P < .005
- Pain Free: 20.7% (Active), 7.9% (Sham), P < .05