MIGRAINE TREATMENT UPDATE: CURRENT AND PIPELINE

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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 in 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
MIGRAINE Aura

- .........................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.

Headache: The Journal of Head and Face Pain, Volume: 58, Issue: S1, Pages: 4-16, First published: 26 April 2018, DOI: (10.1111/head.13300)
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

### Acute/Abortive Examples

<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/aspiron/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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<td>Diclofenac</td>
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<td>Frovatriptan</td>
<td>Butalbital/aspiron/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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</table>
Proposed Mechanisms for Triptan Effect on Migraine

Trigeminal nerve

Inhibition of NT release

5-HT\textsubscript{1D}

5-HT\textsubscript{1F}

Nociceptive & Inflammatory Neurotransmitters: CGRP, NKA, Substance P

Triptans

5-HT\textsubscript{1B}

Vasoconstriction

Keck Medicine of USC
<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>
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<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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<td>Citalopram</td>
<td>Gabapentin</td>
<td>Metoprolol</td>
<td>Nifedipine</td>
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<td>Emgality®</td>
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<td>Doxepin</td>
<td>Topiramate</td>
<td>Nadolol</td>
<td>Nimodipine</td>
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<td>Fluoxetine</td>
<td>Valproic acid</td>
<td>Propranolol</td>
<td>Verapamil</td>
<td>Lisinopril</td>
<td>Vyepti™</td>
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<td>Losartan</td>
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<td>Mirtazapine</td>
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<td>Ramipril</td>
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<td>Protriptyline</td>
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<td>Sertraline</td>
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<td>Venlafaxine</td>
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</table>
Preventative treatment

**Neuronal membrane Stabilizers**

Prevent spontaneous depolarization

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Antidepressants</th>
<th>Antihypertensives</th>
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</thead>
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<tr>
<td>Valproic Acid</td>
<td>Amitriptyline</td>
<td>Beta-blockers:</td>
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<td>Topiramide</td>
<td>Nortriptyline</td>
<td>Propranolol</td>
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<tr>
<td>Zonisamide</td>
<td>SNRIs</td>
<td>Timolol</td>
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<tr>
<td>Lamotrigine</td>
<td><em>SNRIs</em></td>
<td>Calcium channel blockers</td>
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<td></td>
<td><em>Muscle relaxants</em></td>
<td>ACE inhibitors/ARBs</td>
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<tr>
<td></td>
<td>Tizanidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baclofen</td>
<td><strong>Botulinum toxin type A injection</strong></td>
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<tr>
<td></td>
<td></td>
<td>CGRP MABs</td>
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<tr>
<td></td>
<td></td>
<td>Erenumab (Aimovig)</td>
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<td></td>
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<td>Fremanezumab (Ajovy)</td>
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<td></td>
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<td>Galcanezumab (Emgality)</td>
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<td></td>
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<td>Eptinezumab (V)</td>
</tr>
</tbody>
</table>
Preventative treatment

**NEUTRATEUTICALS**

**ALTERNATIVE MED**

<table>
<thead>
<tr>
<th><strong>MAGNESIUM</strong></th>
<th><strong>YOGA</strong></th>
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<tbody>
<tr>
<td>VITAMIN B2</td>
<td>BIOFEEDBACK</td>
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<tr>
<td>COENZYME Q10</td>
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<tr>
<td>BUTTERBUR</td>
<td>ACUPUNCTURE</td>
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<tr>
<td>FEVERFEW</td>
<td>MEDITATION</td>
</tr>
<tr>
<td><strong>MELATONIN</strong></td>
<td></td>
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<tr>
<td>TURMERIC</td>
<td></td>
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</tbody>
</table>

Keck School of Medicine of USC
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**

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

- **Galcanezumab**
  - CGRP ligand antagonist
  - Monthly SQ
  - Prevention episodic chronic migraines
  - Cluster

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

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

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

Timeline Tagline

2020 Feb

Eptinezumab
- CGRP ligand antagonist
- Quarterly IV
- Prevention episodic and chronic migraines

2020 February

Rimegepant
- Small molecule CGRP receptor antagonist
- Acute migraine treatment

2020
<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, STRIVE 70 mg, 140 mg</td>
<td>- Runny/stuffy nose, - Upper respiratory tract infection, - 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, - Upper respiratory tract infection, - 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, - 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
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>Details</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>
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<tr>
<td>Stress management</td>
<td>Stressor identification and remediation, coping strategies</td>
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<tr>
<td>Medication management</td>
<td>Medication overuse headache prevention, compliance</td>
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<td>Weight management</td>
<td>Weight loss or weight gain</td>
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<tr>
<td>Ergonomics</td>
<td>Limit physical or environmental triggers, prescribe work 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

<table>
<thead>
<tr>
<th>Measure</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>General Health*</td>
<td>&lt;.0001</td>
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<tr>
<td>Pain*</td>
<td>&lt;.0001</td>
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<tr>
<td>Social functioning*</td>
<td>&lt;.0001</td>
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<tr>
<td>Emotional well-being*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Energy/fatigue*</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Role limitations due to emotional problems*</td>
<td>.0178</td>
</tr>
<tr>
<td>Role limitations due to physical health*</td>
<td>.0002</td>
</tr>
<tr>
<td>Physical functioning*</td>
<td>.0002</td>
</tr>
</tbody>
</table>

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

![Schematic of scalp block nerves in a pediatric patient.](image-url)

**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
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>
<thead>
<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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<td>DHE45</td>
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<td>Depacon</td>
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<td>Propofol</td>
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<td>Lidocaine</td>
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<td>Levetiracetam</td>
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<td>Tramadol</td>
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<tr>
<td>Ketamine</td>
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<tr>
<td>Methocarbamol</td>
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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
NEUROLOGY (Headache Division):
Soma Sahai, M.D (Division Chief)
Lauren Green, D.O
Paul Henri Cesar, M.D.
Sandhya Ravikumar, M.D
Ana Gjurjevich, 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: Active 66.7%, Sham 38.8%, P < .0001
- Pain Free: Active 37.4%, Sham 18.4%, P < .005
- MBS Relief: Active 46.3%, Sham 22.2%, P < .001

Sustained response at 48 hours post-treatment

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