2008 Migraine Update

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2008 Migraine Update

Epidemiology

2008 Migraine Update

• Epidemiology
• Abortive Treatment
• Prophylactic Treatment
• Emerging New Treatments

Headache Classification and Diagnosis

Primary Headaches
• Migraine
• Tension-type
• Cluster headache

Secondary Headaches
• Tumor
• Meningitis
• Giant cell arteritis

Primary Headache 90%

Adapted from Headache Classification Committee of the IHS, Cephalalgia, 1988
Diagnostic Criteria For Migraine Without Aura

A. At least 5 attacks fulfilling B-D
B. Migraine is defined as episodic attacks of headache lasting 4 to 72 hours.
C. With 2 of the following symptoms:
   - Unilateral location
   - Pulsating quality
   - Aggravation by or causing avoidance from physical activity
   - Moderate or severe pain intensity

Summary

- Primary headache syndromes are diagnosed by defining the clinical features of an individual’s attacks and applying them to established definitions
- The majority of headaches seen in primary care will be one of the primary headache disorders
- If care is taken to identify warning signs and symptoms, the chances of missing a secondary headache is greatly diminished
Diagnostic Criteria For Migraine Without Aura

D. And 1 of the following symptoms:
   - Nausea and/or vomiting
   - Photophobia and phonophobia

Diagnostic Criteria For Migraine Aura

A. At least 2 attacks fulfilling B and C
B. At least three of the following four characteristics:
   1. Fully reversible aura symptoms explained by focal brain dysfunction
   2. At least one aura symptom evolves gradually over at least 4 minutes or two or more symptoms evolve in succession.
   3. Each symptom lasts <60 minutes.
   4. Headache begins during the aura or more frequently follows aura with a symptom-free interval of less than 60 minutes.
C. Not attributed to another disorder

Characteristic Migraine Features

- Frequent temporal association with menstrual cycle
- Characteristic triggers
- Paradoxical relationship to sleep – frequently occur during sleep or upon awakening but also abated by sleep
- Family history of migraine
- Reversible attack-related cognitive impairment
- Dizziness, vertigo

Premonitory Symptoms

**Excitatory**
- Irritability
- Elation
- Physical hyperactivity
- Yawning
- Food craving
- Photophobia/phonophobia
- Increased bowel and/or bladder activity

**Inhibitory**
- Mental/physical slowing
- Poor concentration
- Word finding difficulty
- Weakness/fatigue
- Chills, anorexia, constipation, abdominal bloating

**Migraine Aura**
- Neurologic symptoms / signs reflecting cortical or brainstem dysfunction
- Visual and somatosensory most common
- Speech / language, motor, or brainstem deficits may also occur, often in combination with visual aura
- Symptoms evolve slowly and persist for up to 20-60 minutes
- Aura usually precedes and terminates before headache, but may persist or begin during headache phase

**The Migraine Attack Headache**
- Moderate to severe unilateral, throbbing pain aggravated by normal physical activity
- Associated symptoms: nausea, vomiting, photophobia, phonophobia, osmophobia
- Resolution with sleep

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**Visual Aura**

1 Minute | 5 Minutes | 15 Minutes
--- | --- | ---

Adapted from Lashley KS. Arch Neurol Psychiatry. 1941;46:331-339.

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**Migraine Is a Highly Prevalent Medical Disorder**

28 million US migraine sufferers

- 12.6% Overall
- 18.2% Females
- 6.5% Males

Adapted from Lipton et al. Headache. 2001.
Migraine Affects Individuals During their Most Productive Years

28 million US migraine sufferers

Migraine Patients Suffer From Pain and Symptoms

Adapted from Lipton RB et al. Headache. 2001;41:646-657.
Migraine Is Disabling

Percentage of Migraine Sufferers Reporting Impairment

Unable to Do Household Work: 75%
Household Productivity Reduced \( \geq 50\% \): 67%
Missed Family/Social Activity: 59%
Work/School Productivity Reduced \( \geq 50\% \): 51%

Migraine Headache Attacks Last Most of the Day

Duration of Untreated or Unsuccessfully Treated Migraine Headache Attacks

- > 2 Days: 4
- 1-2 Days: 8
- 5-24 Hours: 49
- \( \leq 4 \) Hours: 39

Economic Burden of Migraine in the US

A recent study by Hu and colleagues reported:

- Total cost >$14 billion
- Direct medical costs = $1 billion
  - Inpatient
  - Physician visits
  - Prescriptions
- Indirect cost = $13 billion
  - Missed workdays
  - Reduced productivity

Migraine Remains Underdiagnosed and Undertreated

- Most migraine sufferers have 1 to 2 attacks per month that can last 24 hours or more if untreated
- 25% have 4 or more attacks per month
- 75% are unable to work due to their headaches (on average 3 workday equivalents per 3-month period)
- 91% report functional impairment
- 53% report severe functional impairment
- Migraine is costly because it is a direct cause of lost productive time


2008 Migraine Update

Abortive Treatment

Migraine Remains Underdiagnosed and Undertreated

General Principles of Management

- Establish a diagnosis
- Educate patients about their condition and its treatment
- Establish realistic expectations
- Encourage patients to participate in their own management
  - Discuss treatment / medication preferences

**General Principles of Management (cont.)**

- Individualize management (stratified care)
- Treatment choice depends on
  - Attack frequency and severity
  - Presence and degree of disability
  - Associated symptoms
  - Prior response to medications
  - Comorbid and coexistent conditions

Adapted from US Headache Consortium Headache Guidelines, [www.aan.com](http://www.aan.com), 2010

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**Recommendations for Acute Migraine Management (cont.)**

- Select a nonoral route of administration for migraine associated with severe nausea or vomiting
- Consider a self-administered rescue medication for severe migraine that fails to respond to other treatments
- Guard against medication-overuse headache

Adapted from US Headache Consortium Headache Guidelines, [www.aan.com](http://www.aan.com), 2010

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**The Ideal Acute Therapy**

- Treat attacks rapidly and consistently
- Restore patient's ability to function
- Minimize use of backup and rescue medication
- Optimize self care
- Minimal or no adverse events

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**Educate Employees Regarding Self-Treatment Options**

- Migraines may be triggered
  - Triggers vary from individual to individual
  - Triggers often can be managed
- Common triggers include
  - Stress
  - Menstruation
  - Diet
    - Alcohol
    - Caffeine
    - Cheese
    - Nitrites
  - Irregular sleep
  - Fasting
  - Strong odors
  - Loud noise
  - Bright or flickering lights, glare
  - Weather

Martin VT, BenbAKER VM. Med Clin N Am. 2001;85:911-941
Nausea Treatment Options

- Metochlopramide
- Prochorperazine

Treatment of Acute Migraine Attacks

US Headache Consortium Guidelines:

- Serotonin Receptor Agonists (Triptans) are useful choices for patients who have moderate to severe migraine or no relief from NSAIDS [Grade A]

- All Triptans share the same mechanism of action: promote vasoconstriction and block pain pathways at Brainstem level.

Treatment of Acute Migraine Attacks

US Headache Consortium Guidelines:

- Non-steroidal Anti-inflammatory Agents and non-opiate analgesics (Ibuprofen, Naproxen, and Aspirin) for patients with mild to moderate migraine pain [Grade A]

- Triptans
  - Sumatriptan (Imitrex)
  - Zolmitriptan (Zomig)
  - Naratriptan (Amerge)
  - Rizatriptan (Maxalt)
  - Eletriptan (Relpax)
  - Almotriptan (Axert)
  - Frovatriptan (Frova)
Treatment of Acute Migraine Attacks

- Ergot Alkaloids and Derivatives: DHE and Ergotamine for patients with severe to moderate migraine pain [Grade B and C].
- Opioid Analgesics: For patients with moderate to severe attacks. Efficacy must be balanced against the risks of sedation and dependency [Grade A and B].
- Barbiturate Hypnotics: Same as Opioids. [Grade B].

Rescue Treatment

- Hydration
- Antiemetics
- Steroids
- Dihydroergotamine
- Occipital Nerve Blocks
- IV Steroids, Thorazine, Valproate, Magnesium, Ketorolac
- “Raskin” protocol

Treatment of Acute Migraine Attacks

- Antiemetics: Intravenous Metoclopramide and IV or IM Prochlorperazine have pain relieving properties [Grade B]

- Other Agents:
  - Isometheptene for mild to moderate pain [Grade B]
  - Corticosteroids for status migrainous.

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Prophylactic Treatment
Who Needs Migraine Prevention?

- Frequent migraines
- Significant disability despite abortive treatment
- Poor response to abortive treatment
- Complicated migraine
- Patient preference

Migraine Prevention

- Effective management of chronic migraine involves the treatment of acute attacks plus the initiation and use of strategies to prevent or minimize new episodes from recurring

Goals of Treatment

- Decrease headache frequency by 50%
- Decrease disability
- Improve function
- Improve response to abortive therapy

Consider Physical/Behavioral Therapy

- Patient preference
- Poor tolerance or contraindication to pharmacologic treatments
- Pregnancy or nursing
- Cervicogenic trigger
- Anxiety/depression
### Migraine Prevention

**US Headache Consortium Guidelines**

- Non-Pharmacologic Interventions may be provided before or in conjunction with traditional anti-migraine prophylaxis:
  - Behavioral Treatment
  - Physical Treatment

### Preventive Treatment of Migraine

**Physical Treatments**

(No recommendation by the US Headache Consortium)

- Acupuncture
- Transcutaneous electrical nerve stimulation
- Cervical Manipulation
- Mobilization Therapy

### What Can You Do to Manage Your Migraines?

**Behavioral Treatments (Grade A and B)**

- Relaxation Training
- Biofeedback Therapy
- Cognitive-Behavioral
- Stress Management training

**Lifestyle**

- Identify and then avoid your triggers
  - Write down what you were eating, drinking, and doing as well as what was happening around you when a migraine attack began
- Follow a regular sleep routine
- Eat meals at regular times each day
What Can You Do to Manage Your Migraines?

- Avoid eating foods and beverages that may trigger migraine
  - Foods containing nitrites or monosodium glutamate (MSG)
  - Foods and beverages containing the artificial sweetener aspartame
  - Chocolate
  - Aged cheeses
  - Alcohol
- Exercise often

Migraine Prevention

Pharmacological Approach

- The agent should be chosen from one of the major categories based on side effects profile, and coexistent co-morbid conditions
- Preventive medications should be started at a low dose and increased slowly until therapeutic effect develop, side effects develop, or the ceiling dose for the agent is reached
- A full trial may take 2-6 months

What Can You Do to Manage Your Migraines?

- Reduce stress
- Relaxation exercise
  - Tense muscles are a sign of stress, which can trigger a migraine
  - Deep-breathing exercise
    - Sit in a quiet place
    - Close your eyes and inhale slowly and deeply through the nose to the count of 10
    - Expand your stomach and abdomen but do not let your chest rise
    - Exhale through the nose to the count of 10
    - Focus on your breathing and counting; clear your mind of other thoughts
    - Repeat 5-10 times
Preventive Medications: Drug Classes

- Anticonvulsants
- Antidepressants
- Beta adrenergic blockers
- Calcium channel antagonists
- NSAIDs
- Serotonin antagonists
- Neuroleptics
- Others (including riboflavin, co-enzyme Q10, minerals, herbs, & botulinum toxin-A)

Silberstein, 1997

Evidence-Based Guideline Key

Clinical Impression

0  Ineffective, most people get no improvement
+  Somewhat effective, few people with clinically sig. improvement
++ Effective, some people with clinically sig. improvement
+++ Very effective, most people with clinically sig. improvement

Evidence-Based Guideline Key

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Evidence Quality</th>
<th>Scientific Effect</th>
<th>Clinical Impression</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>30-150 mg</td>
<td>A</td>
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<td>Nortriptyline</td>
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<td>Protriptyline</td>
<td>C</td>
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<td>++</td>
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<tr>
<td>Doxepin</td>
<td>C</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>C</td>
<td>?</td>
<td>+</td>
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### Selective Serotonin Reuptake Inhibitors

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<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
<td>C</td>
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### Beta Blockers

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<td>Metoprolol</td>
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<td>Nadolol</td>
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<td>+++</td>
</tr>
<tr>
<td>Propranolol</td>
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<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Timolol</td>
<td>20-30 mg</td>
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### Other Antidepressants

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<td>Bupropion</td>
<td>C</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mirtazepine</td>
<td>C</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Trazadone</td>
<td>C</td>
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<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>C</td>
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### Calcium Channel Blockers

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<tbody>
<tr>
<td>Cyclandelate</td>
<td>1200-1600 mg</td>
<td>B</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Diltiazem</td>
<td>C</td>
<td>?</td>
<td>0</td>
<td></td>
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<tr>
<td>Flunarizine</td>
<td>10 mg</td>
<td>B</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>120 mg</td>
<td>B</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Verapamil</td>
<td>240 mg</td>
<td>B</td>
<td>+</td>
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Antiepileptics

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<th>Medication</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>600 mg</td>
<td>B</td>
<td>++</td>
<td>0</td>
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<tr>
<td>Divalproex</td>
<td>500-1500 mg</td>
<td>A</td>
<td>###</td>
<td>###</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900-2400 mg</td>
<td>B</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>C</td>
<td>?</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Topamax</td>
<td>C</td>
<td>?</td>
<td>++</td>
<td>++</td>
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</table>

- Drugs with documented high efficacy and mild to moderate adverse effects (AEs) include β-blockers, amitriptyline, divalproex, and topiramate.
- Drugs with lower documented efficacy and mild to moderate AEs include SSRIs, calcium channel antagonists, gabapentin, and riboflavin.
- Drug use based on opinion include many antidepressant medications like doxepin, sertraline, trazodone etc.

Migraine Prevention

- Drugs with documented high efficacy that have significant AEs include methysergide.
- Drugs with proven limited or no efficacy include cyproheptadine, lithium and phenytoin.
- The older patient with cardiac disease or patients with significant hypotension may not be able to use TCAs or calcium channel or β-blockers but could easily use divalproex.
- In the athletic patient, β-blockers should be used with caution.
- Tertiary TCAs that have a sedating effect would be useful at bedtime for patients with insomnia.
Migraine Prevention

Choose a drug based on its proven efficacy, drug’s side effects and the presence or absence of coexisting or co-morbid disease

- An underweight patient would be a candidate for TCA. In contrast, one would try to avoid these drugs in the overweight patient
- An obese or overweight patient would be a good candidate for topiramate because weight loss is a common adverse reaction for this agent

- Migraine headache may improve with time. A drug holiday should be attempted every few months
- A woman of childbearing potential should be on adequate contraception before starting migraine medications

Migraine Prevention

- When migraine and hypertension and/or angina occur together, β-blockers or calcium-channel blockers is effective for all conditions
- For patients with migraine and depression, TCAs or SSRIs may be especially useful
- For the patient with migraine and epilepsy or migraine and manic depressive illness, divalproex sodium, gabapentin, or topiramate are the drugs of choice

Botulinum toxin type A (Botox)

- In a large placebo controlled trial, injection of Botox into glabellar, frontalis, and temporalis muscles significantly reduced the frequency of migraine attacks.
- It is not FDA approved and further studies of the agent are indicated.
Migraine Prevention

Natural Products

- Feverfew Tenacetum Parthenium: a medicinal herb used by some patients to self-treat migraine. However, its clinical effectiveness has not been established beyond reasonable doubt and more clinical trials are needed

- Riboflavin was found effective in reducing migraine attacks frequency in one placebo clinical trial

2008 Migraine Update

Emerging New Treatments for Acute Migraine Attacks

- Transcranial Magnetic Stimulation (TMS)
- Trexima (Sumatriptan plus Naproxen)

Natural Therapy

Emerging New Treatments for Acute Migraine Attacks

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Evidence Quality</th>
<th>Scientific Effect</th>
<th>Clinical Impression</th>
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<tr>
<td>Feverfew</td>
<td>50-82 mg</td>
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</tr>
<tr>
<td>Riboflavin (B2)</td>
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<td>+++</td>
<td>++</td>
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<tr>
<td>Magnesium</td>
<td>400-600 mg</td>
<td>B</td>
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## Emerging New Treatments for Acute Migraine Attacks

- Transcranial Magnetic Stimulation

## Background

**Neurovascular Theory:**
- Based on the trigeminal autonomic dysfunction theory, applying TMS pulses at the onset of migraine attack can deactivate the sensitization of the trigeminovascular afferents and hence relieve the headache
- Based on the CSD theory, applying TMS pulses during the aura phase can depolarize/deactivate the neurons and hence interrupt the cortical spreading depression activity and the headache

**Background**

- According to Faraday's law a fluctuating magnetic field (as applied by Transcranial Magnetic Stimulation-TMS) can induce current in a conductor
- We hypothesized that TMS might be effective in the acute treatment of migraine perhaps by disrupting cortical spreading depression or deactivating trigeminal vascular afferents

## Objective

- We sought this study to gather preliminary data on the safety and efficacy of two TMS pulses as an acute treatment of migraine.
Methods

• Two center, randomized double blind, parallel, placebo-controlled study on subjects 18 years of age or older, experiencing migraine with or without aura (meeting the IHS criteria)

• Subjects must complete a 2 months pre-enrollment diary to assess for eligibility in the study

Methods

• The magnetic stimulator will be applied by the subject over the area of maximal headache or over the occipital area (visual aura)

Methods

• Treatment was given during the aura or after moderate or severe pain developed

• Subjects completed a dairy at baseline and at 5, 15, 30, 45, 60 and 120 minutes post-treatment. Pain, functional status and associated symptoms were assessed on 4-point scales.

Methods

• All subjects will receive 2 TMS (1 Tesla) or placebo (0 Tesla) pulses delivered automatically 5 seconds apart after triggering the TMS device

Modified Magstim 200
Methods

Primary Efficacy Endpoint:

• Headache response (no or mild headache) at 2 hours post-treatment

Secondary Efficacy Endpoint:

• Functional disability score at 2 hours post-treatment

• Subject global rating of treatment at 2 hours post-treatment

Methods

• An audible buzzer will sound during the delivery of the active treatment and the placebo treatment to mask the active treatment stimulation

Secondary Efficacy Endpoint:

• Headache free at 2 hours post treatment

• Response of associated symptoms (photophobia, phonophobia, nausea, and vomiting) at 2 hours post-treatment

• Use of rescue medications at 2 hours post-treatment
Results

<table>
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<tr>
<th>Characteristics</th>
<th>Control</th>
<th>TMS</th>
<th>Total</th>
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<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>Males</td>
<td>2</td>
<td>2</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Females</td>
<td>18</td>
<td>21</td>
<td>39 (91%)</td>
</tr>
<tr>
<td>Mean age</td>
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<td>40.2</td>
<td>41.7</td>
</tr>
<tr>
<td>Caucasian</td>
<td>19</td>
<td>22</td>
<td>41 (95%)</td>
</tr>
<tr>
<td>Asian-Indian</td>
<td>1</td>
<td>1</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>18</td>
<td>30</td>
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<tr>
<td>Aura</td>
<td>8</td>
<td>5</td>
<td>13</td>
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Table 1. Patient Demographics and Characteristics

2 Hour Assessment: Headache Free

2 Hour Assessment: Pain Response

<table>
<thead>
<tr>
<th>TMS</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>74%</td>
<td>45%</td>
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P = 0.0531

P = 0.1141
In this small randomized Pilot trial:

- For the primary endpoint, 2 hour headache response differences were not significant but the trend was encouraging (74% vs. 45%, p = .0531)

- There were statistically significant differences in photophobia and phonophobia free

- Trends favored TMS for 2 hour pain free, nausea free, work function, and the global assessment but were not significant
Emerging New Treatments for Acute Migraine Attacks

- Trexima (Sumatriptan plus Naoroxen)

Trexima (Sumatriptan plus Naoroxen)

**BACKGROUND**
- Throbbing/Pulsating pain (vasodilation)
- Neurogenic Inflammation
- Pain Neuropeptides
- Central processing of trigemiovascular pain (Serotonin agonist).
- Central sensitization

Plans

- A portable device has been developed to facilitate early self-treatment at home.
- An adequately powered randomized trial focusing on treatment during the aura phase is complete.
- Future studies may focus on treatment during the premonitory or headache phase of migraine without aura.

Trexima (Sumatriptan plus Naproxen)

**BACKGROUND**
- Indirect evidence of relationship between Serotonin and migraine
- The pathogenesis of migraine involves multiple peripheral and central neural mechanisms that individually have been successful targets for acute treatment.
- Multiple mechanism therapy, which acts on multiple target sites, may confer improved efficacy and symptom relief for migraine patients
Trexima (Sumatriptan plus Naoroxen)

<table>
<thead>
<tr>
<th>Trexima 50+500</th>
<th>Sumatript. 50 mg</th>
<th>Naproxen 500 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained relief</td>
<td>46%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>Headache Response</td>
<td>65%</td>
<td>49%</td>
<td>46%</td>
</tr>
<tr>
<td>Headache recur</td>
<td>29%</td>
<td>41%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Smith et al. Headache 2005 Sep; 45(8):983-91

Emerging New Treatments for Migraine Prevention

- Patent Foramen Ovale (PFO) Closure
- Transcranial Direct Current Stimulation (tDCS)
- Occipital Nerve Stimulation (ONS).

Trexima (Sumatriptan plus Naoroxen)

<table>
<thead>
<tr>
<th>Trexima 85+500</th>
<th>Sumatript. 85 mg</th>
<th>Naproxen 500 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hr pain free</td>
<td>34%</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>2 hr relief</td>
<td>65%</td>
<td>55%</td>
<td>44%</td>
</tr>
<tr>
<td>Sust. relief</td>
<td>48%</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Brandes et al. JAMA. 2007 (n= 1677).
<table>
<thead>
<tr>
<th>PFO Closure</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>BACKGROUND</strong></td>
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</tr>
<tr>
<td>• PFO is a small flap-valve seen in the fetal circulation that disappear at birth and connects the right and left atria.</td>
<td>• PFO persists in 15-20% of the general population.</td>
</tr>
<tr>
<td></td>
<td>• PFO is more common in patients with migraine.</td>
</tr>
<tr>
<td></td>
<td>• PFO exits in 40-49% of migraine with aura patients (especially moderate to large size PFO).</td>
</tr>
<tr>
<td></td>
<td>• PFO exists in 20-25% of migraine without aura patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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</tr>
<tr>
<td>• Increases in intra-thoracic pressure can result in the valve opening and blood passing from the right to the left side of the circulation without being filtered by the lungs.</td>
<td>• There has been reports that migraine with aura in divers was significantly reduced when their PFO was closed, for decompressive purpose.</td>
</tr>
<tr>
<td></td>
<td>• There has been reports that migraine with aura, in stroke patients, was significantly reduced when their PFO was closed to prevent recurrent stroke.</td>
</tr>
</tbody>
</table>
PFO Closure

BACKGROUND

• PFO triggers migraine by allowing vasoactive substances, platelet emboli or paradoxical emboli to bypass the lung filter and trigger the cortical spreading depression of the aura

PFO Closure: BACKGROUND

MIST (Migraine Intervention with STARFlex Technology) trial

• Results:
  Only 4 of 74 patients in the PFO closure group and 4 of 73 patients in the sham group reported attack cessation.

42% of the patients receiving closure had 50% reduction in the number of headache days compared to 23% in the Placebo group

Ongoing Trial

MIST II: A Prospective Multi-Center, Double-Blinded, Placebo-Controlled Trial to Evaluate the effectiveness of PFO Closure with the BioSTAR Septal Repair Implant to Reduce Refractory Migraine Headache with aura.
PFO Closure

Ongoing Trial: MIST II

- NMT Medical Announces Termination of its MIST II Trial of PFO Closure for Migraine. The company’s decision to halt MIST II is due to difficulties enrolling patients in the trial and limitation in financial resources.

Emerging New Treatments for Migraine Prevention

- Occipital Nerve Stimulation (ONS).

Occipital Nerve Stimulation (ONS)

BACKGROUND

- Peripheral nerve stimulation leads to an inhibitory input within the pain pathways of the spinal cord (anti-nociceptive effect).
- It has been used for more than 30 years to relieve chronic pain.
- Recently, it has been used to treat pain in posttraumatic neuropathy, diabetic neuropathy, and reflex sympathetic dystrophy.

BACKGROUND

- The occipital nerve converges in the cervical spinal cord with the trigeminal system, which includes neurons and neural pathways responsible for conveying much of the throbbing pain associated with migraine to the thalamus.
- ONS can inhibit activity in the trigeminal system and hence reduce and prevent headache (anti-nociceptive effect).
**Occipital Nerve Stimulation (ONS)**

<table>
<thead>
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<tbody>
<tr>
<td>In 1999, Weiner reported cases of intractable occipital neuralgia responding to ONS.</td>
</tr>
<tr>
<td>PET studies demonstrated thalamic changes from ONS, especially in the patients with excellent therapeutic outcome.</td>
</tr>
</tbody>
</table>

**Occipital Nerve Stimulation (ONS)**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Using Peripheral Nerve Stimulation to Reduce the pain of C2-Mediated Occipital Headache.</td>
</tr>
<tr>
<td>Methods: 11 patients with occipital headache had implantation of PNS System.</td>
</tr>
<tr>
<td>Results: At 12 weeks post implantation, there was significant reduction in pain intensity and frequency.</td>
</tr>
</tbody>
</table>

**Occipital Nerve Stimulation (ONS)**

<p>| |</p>
<table>
<thead>
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<tbody>
<tr>
<td>ONS involves implanting a neuro-stimulator under the skin at the base of the head. The neuro-stimulator delivers electrical impulses near the occipital nerves via insulated lead wires tunneled under the skin.</td>
</tr>
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</table>

**Occipital Nerve Stimulation (ONS)**

<table>
<thead>
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<tr>
<td>Occipital nerve stimulation for chronic headache</td>
</tr>
<tr>
<td>Methods: 15 patients, eight had chronic migraine, with medically refractory headache underwent ONS.</td>
</tr>
<tr>
<td>Results: Both headache frequency and severity improved significantly at 5-42 months.</td>
</tr>
</tbody>
</table>
Occipital Nerve Stimulation (ONS)

- Randomized controlled trials of ONS in chronic migraine are now ongoing.

History of Migraine Treatment

- Migraine treatment has evolved from the witch magic and skull trepanation, in the ancient ages.

To

- Electrical and magnetic stimulation, in the cyber age.