The Diagnosis and Management of Adult Migraine

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Disclosures

• None personally
• I will be discussing some off-label treatments for migraine
Objectives

- What are the different types of migraines?
- What types of pharmacologic treatments are there for migraine abortive treatment?
- What types of pharmacologic treatments are there for migraine preventative treatment?
- What types of non-pharmacologic treatments are there for migraine treatment?

So You’ve Decided It’s a Migraine

- What type IS it?
### Migraine without Aura

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  1. unilateral location
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following:
  1. nausea and/or vomiting
  2. photophobia and phonophobia

Source: ichd-3.org

### Migraine with Aura

- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
  1. visual
  2. sensory
  3. speech and/or language
  4. motor
  5. brainstem
  6. retinal
- C. At least two of the following four characteristics:
  1. at least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
  2. each individual aura symptom lasts 5-60 min
  3. at least one aura symptom is unilateral
  4. the aura is accompanied, or followed within 60 min, by headache

Source: ichd-3.org
Complicated Migraine or Atypical Migraine

- Don’t exist!
- “Probable” = all but one criteria

Emergency Management
Emergency Management

- Should offer (Level B) – IV metoclopramide, IV prochlorperazine, subQ sumatriptan
- May offer (Level C) – IV acetaminophen, IV chlorpromazine, IV dexketoprofen, IV diclofenac, IV dipyrone (not available here), IV droperidol, IV haloperidol, IV ketorolac, IV valproate
- AVOID – IV Benadryl (although the paper commented that use of benadryl in regard to treatment of potential akathisia was outside the scope of the paper’s work), hydromorphone, lidocaine, octreotide (can be used as abortive in cluster)
- No recommendation – DHE, ergotamine, lysine, magnesium (could be beneficial for those with migraine with aura), meperidine, nalbuphine, propofol, promethazine, tramadol, trimethobenzamide

Prevention of Migraine Recurrence

- Should offer (Level B) – IV dexamethasone (10 mg in one study, 20 mg in another, 24 mg in the third). Avoid in diabetics or those with other contraindications (steroid psychosis history, etc.). Risk of avascular necrosis after one dose of dexamethasone is “exceedingly low.”
Home Options for Rescue Therapy

- Acetaminophen
- NSAIDs, including prescription indomethacin, diclofenac, etodolac, etc.
- Combination analgesics (acetaminophen/caffeine/ aspirin). Midrin (isometheptene/dichloralphenazone/acetaminophen). AVOID butalbital-containing compounds due to risk of medication overuse headaches
- Triptans
  - Longer-acting: frovatriptan, zolmitriptan (pill and nasal spray), naratriptan
  - Shorter-acting: sumatriptan (pill, nasal powder, injectable, nasal spray), almotriptan, rizatriptan, eletriptan
- Ergots
  - DHE (subcutaneous or nasal spray)
- Anti-emetics
  - Prochlorperazine (rectal, oral, injectable), metoclopramide (oral or injectable), promethazine (rectal, oral, injectable)


Clinical Pearls for Rescue Treatment

- Avoid triptans, ergots, acetaminophen/dichloralphenazone/isometheptene in patients with coronary artery disease, peripheral vascular disease, hemiplegic migraine, or stroke.
- These are technically contraindicated in migraine with brainstem aura as well.
- Avoid medication overuse headaches. Limit all abortive use to 10 days/month or less. Exception is muscle relaxants and anti-emetics.
- Oral steroid tapers can break migraine cycles. I usually use a three day course of dexamethasone (4 mg TID day 1, 4 mg BID day 2, 4 mg once day 3) or prednisone (60 mg daily for 5 days and then taper by 10 mg per day until off). Add PPI/H2 blocker if not already on one, and avoid this in patients with poorly controlled diabetes.
- Another option is chlorzoxazone 500 mg every 6 hours for 5 days
- Sometimes infusion therapy is warranted.
• 67 patients with migraine with brainstem aura
• 13 with hemiplegic migraine
• Treated with triptans or DHE
• No adverse cardiovascular or neurovascular events
• Risk is theoretical

Preventative Treatments

Research Submissions

The 2012 AHS/AAN Guidelines for Prevention of Episodic Migraine: A Summary and Comparison With Other Recent Clinical Practice Guidelines

Elizabeth Loder, MD, MPH; Rebecca Burch, MD; Paul Rizzoli, MD
Preventative Treatments

- Level A Evidence: valproic acid, metoprolol, propranolol, topiramate
- Level B Evidence: amitriptyline, venlafaxine
- Likely to be higher level of evidence next round: candesartan

Clinical Pearls for Preventative Treatments

- For now, tailor treatments to patient’s other comorbidities.
- Consider topiramate for an obese patient, venlafaxine for a patient with anxiety, amitriptyline for a patient with poor sleep, beta blocker for patient with high blood pressure, etc.
- Onabotulinumtoxin A is the main treatment approved for chronic migraine, although there is some evidence for topiramate as well.
What’s new?

- Single pulse transcranial magnetic stimulation
- Transcutaneous supraorbital neurostimulation
- Noninvasive vagal nerve stimulation
  - Approved for episodic cluster and episodic migraine abortive treatment, as well as the adjunctive preventative treatment of cluster headache
- Caloric vestibular stimulation
  - Not yet FDA approved
- Calcitonin gene-related peptide antibodies
- Serotonin (5-HT)\textsubscript{1F} agonists
  - Triptan without vasoactive properties
  - Not yet FDA approved
- Calcitonin gene-related peptide antagonists
  - Not yet FDA approved

Spring TMS

- Approved for acute and prophylactic treatment of migraine by FDA
- For prevention, somewhat conflicting data
- Most insurances don’t cover, large upfront out of pocket expense.
- Thought to inhibit cortical spreading depression, proposed mechanism of migraine with aura.

# Spring TMS

Source for image: Wikipedia.org

<table>
<thead>
<tr>
<th><strong>Cefaly</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supraorbital nerve stimulation, device applied by sticker to forehead.</td>
</tr>
<tr>
<td>• Wear 20 minutes a day for prevention, 60 minutes for rescue treatment</td>
</tr>
<tr>
<td>• Approved by FDA for migraine treatment</td>
</tr>
<tr>
<td>• Cost: $349 US + shipping one time ($500 for both rescue and preventative treatment)</td>
</tr>
<tr>
<td>• Also need to buy electrodes at $25 a pop, each lasting about 20 sessions.</td>
</tr>
<tr>
<td>• 50% responder rate, but not headache days/month reduction, was significant vs. sham</td>
</tr>
</tbody>
</table>

Cefaly

Source: Wikipedia.org

CGRP (calcitonin gene-related peptide)

- There are currently four CGRP antibodies who have completed phase III study, three approved by FDA so far
- Three are to the peptide itself, one is to the receptor
- Thought to act at the trigeminal ganglion, do not cross blood-brain barrier.
- Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) approved by the FDA for preventative treatment of migraine
- Three are subcutaneous, one is intravenous
- Studied in chronic and episodic migraine as well as cluster
- Promising results so far with few side effects
**CGRP**

Image Source: Wikipedia.org

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**Simvastatin + Vitamin D**

- Simvastatin 20 mg BID
- Vitamin D3 1000U BID
Memantine

• Level B pregnancy!

Alternative Treatments

<table>
<thead>
<tr>
<th>Herbs Preparations, Vitamins, Minerals, and Other Interventions</th>
<th>Strong evidence</th>
<th>Moderate evidence</th>
<th>Weak evidence</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes (butterbur) is established as effective and should be offered for migraine prevention</td>
<td>Level A.</td>
<td>Riboflavin, magnesium, and MIG-99 (levelev) are probably effective and should be considered for migraine prevention</td>
<td>Level B.</td>
<td>Coenzyme Q10 and estrogen are possibly effective and may be considered for migraine prevention</td>
</tr>
<tr>
<td>Evidence is inadequate or conflicting to support or refute the use of omega 3 or hyperbaric oxygen therapy for migraine prevention</td>
<td>Level U.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: aan.com
• Small effect of true acupuncture over sham
• May be at least similarly effective to prophylactic drugs

Behavioral Treatments

• Level A Evidence for: Biofeedback (EMG and thermal combined with relaxation training), cognitive behavioral therapy, relaxation therapy effective for migraine prevention

Photo Source: flickr.com
**General Pearls**

- Headache lifestyle is very important: keep caffeine intake steady, hydration, exercise, sleep, regular meals, mood.
- Many patients, especially with chronic migraine for many years, may require a multidisciplinary approach including physicians, physical therapists (a cervical component of migraine is often under diagnosed), and psychologists.

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**New Therapies in Pediatric Migraine**

Ann Pakalnis, MD  
Director  
Headache Clinic at Nationwide Children’s Hospital  
Clinical Assistant Professor of Neurology  
Department of Neurology  
The Ohio State University Wexner Medical Center
Migraines

• Recurrent and unpredictable
• Can have significant negative impact on family dynamics, school attendance, and parental work schedules
• Prevalence ~ 10-15% of older school-aged children and adolescents
• Slightly more common in boys 1.5-1 below age of 9 yr; than increasing prevalence in girls (similar to adults)

Making the diagnosis of migraine

• History, including family history ~ 80% of pediatric migraineurs have positive family history
• Headache diary, I Headache, Migraine buddy apps.
• Thorough physical and neurologic examination
Criteria for Diagnosis of Migraine
ICHD-3

• Migraine Without Aura
  – Headache lasting 4-72 hours (2-72 hrs in children)
  – At least five attacks fulfilling criteria below.
  – Headache characterized by at least two of the following:
    • Unilateral/Bilateral location
    • Pulsating quality
    • Moderate or severe intensity (inhibits or prohibits daily activities)
    • Aggravated by climbing stairs or similar routine physical activity
  – During headache at least one of following:
    • Nausea and/or vomiting
    • Photophobia and phonophobia (can be inferred in children)
    (Cephalalgia, 2013)

Criteria for Diagnosis of Migraine
(International Headache Society)

• Migraine With Aura
  – At least two attacks fulfilling criteria below.
  – Presence of at least 3 of the following:
    • One or more fully reversible aura symptoms indicating focal cerebral cortical dysfunction or brainstem dysfunction, or both.
    • At least one aura symptom develops gradually over more than four minutes or two or more symptoms occur in succession.
    • No aura symptom lasts more than 60 minutes. When more than one aura symptom is present, accepted duration is proportionally increased.
    • Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with aura)
PLAN OF TREATMENT

- Minimize exacerbating factors
  - Fatigue, stressors, dietary
- Fluids, Fluids, Fluids!
  - 8-10 glasses/day
  - Water, juices, sports drinks
  - Coke/Pepsi don’t count
- Tylenol 15mg/kg q 4hr
- Ibuprofen 10mg/kg q 6 hr
- Psych Factors
  - Biofeedback/relaxation therapy

Importance of lifestyle issues

- Adequate hydration (dehydration depletes central serotonin, migraine is a hyposerotonergic state
- Sleep deprivation
- STRESS (School and over-scheduled adolescents)
- Skipping meals (hypoglycemia increases headaches
- Hormonal changes in adolescent girls
## Biofeedback/Relaxation Therapy Stress Counseling

- Children 8 years or older can participate
- Studies suggest significant benefits in migraine (Hershey, 2002)
- Go to school; keep regular schedule

## Ibuprofen vs Acetaminophen

<table>
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<tbody>
<tr>
<td>- Ibuprofen had best overall pain relief</td>
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<tr>
<td>- Double-blind with placebo controlled study</td>
</tr>
<tr>
<td>- Both were effective and well-tolerated</td>
</tr>
<tr>
<td>- 10mg/kg Ibuprofen</td>
</tr>
<tr>
<td>- 15mg/kg Acetaminophen</td>
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</tbody>
</table>
### OTC’s


- Double blind study with ibuprofen
- Dose 7.5 mg/kg in 84 children
- Decreased headache pain in 76%, but all positive responders were boys
- Placebo responder rate of 53%

### Triptans

- Almotriptan, Zolmitriptan, rizatriptan, and treximet has adolescent FDA indication

- Oral rizatriptan down to age of 6 years.
- Sumatriptan nasal spray and zolmitriptan nasal spray have shown more favorable results. Significant placebo responder rate present
The Triptans: Pharmacokinetic Profiles*

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Oral Bioavailability</th>
<th>t 1/2, h</th>
<th>Active Metabolites</th>
<th>Sulfonamide Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>2 - 3</td>
<td>14</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>1.5 - 2</td>
<td>40 - 46</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2 - 3</td>
<td>74 (F)</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>1 - 1.5</td>
<td>40 - 45</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>1.5 - 2</td>
<td>70</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>1 - 1.5</td>
<td>50</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2 - 3</td>
<td>25</td>
<td>26</td>
<td>No</td>
</tr>
</tbody>
</table>

*Tₚₘₐₓ indicates time to maximum concentration; t½, half-life; F, females; M, males.

TRIPTANS

- Ueberall & Wenzel (1998)
  - Intranal sumatriptan effective compared to placebo
  - Pakalnis, et al 2003
- Doses used:
  - <30 Kg - 5 mg intranal
  - 30-50Kg - 10mg
  - >50Kg - 20 mg
Rizatriptan

(Winner, 2002)
• 5 mg dose (12-17 yr)
• n=296 double-blind, placebo-controlled
• Insignificant efficacy, prominent placebo response depended on whether teenager treated weekday versus weekend

(Ahonner, 2006)
• 5 or 10 mg dose
• 147 patients (6-17 yrs)
• Positive response compared to placebo

Abortive or Prophylactic Medication

• > 3 or more headaches a month is time to consider prophylactic Rx
• Assess headache disability
• Homeopathic Routes
  – Riboflavin 400mg/d (Neurology, 1998) - adults
  – Magnesium oxide 9mg/kg (Headache, 2003) – pediatrics
### Drugs Approved by U.S. FDA for Prophylaxis of Adult Migraine

- Timolol
- Propranolol
- Divalproex sodium
- Topiramate-approved in adolescents

### Propranolol

Ludvigsson, 1974 study, open label
- 28 patients – 0.5 to 1 mg/kg/day
- 71% of patients had complete headache response
- Side-effects – exacerbation of asthma, decreased exercise tolerance
<table>
<thead>
<tr>
<th>Cyproheptadine</th>
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<tbody>
<tr>
<td><strong>Lewis, et al – 2004</strong></td>
</tr>
<tr>
<td>• Open label study</td>
</tr>
<tr>
<td>• n=30</td>
</tr>
<tr>
<td>• Positive efficacy</td>
</tr>
<tr>
<td>• Weight gain and sedation were side-effects</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Amitriptyline</th>
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<tbody>
<tr>
<td><strong>Hershey, et al – 2000</strong></td>
</tr>
<tr>
<td>• Tri-cyclic antidepressant</td>
</tr>
<tr>
<td>• Depression/sleep disorders are common co-morbidities with migraine</td>
</tr>
<tr>
<td>• Doses up to 1 mg/kg/day</td>
</tr>
<tr>
<td>• Cardiac abnormalities, such as long Q-T, would contraindicate use</td>
</tr>
</tbody>
</table>
### Topiramate

**Hershey, 2002**
- Average dose 1.4 mg/kg/day

**Winner, 2005**
- Double-blind study, n=112
- Average dose of 2 mg/kg/day
- Side-effects: paresthesia, metabolic acidosis, kidney stone, possible cognitive issues

### Divalproex

**Apostol, 2009**
- n=112
- Well tolerated, no significant side-effects
- Side-effects: weight gain, somnolence, nausea
- Doses ~ 10-20 mg/kg/day in most studies (Caruso, et al; Pakalnis, et al)
Levetiracetam

- Anti-epileptic drug
- Doses generally 20-40 mg/kg/day
- Well tolerated
- Behavioral changes, sedation reported (Pakalnis, et al; Miller, et al)
- Positive treatment outcome in majority of patients – studies reported were open-label or retrospective

Hormones and Migraines

- Increased prevalence in adolescent girls associated with menarche
- with migraine with aura should never use COC’s (increased risk of CVA)
- Sequential use of COC’s may be helpful in some patients (ex. seasonal, avoiding placebo week)
Summary

1. Migraine is common in pediatric population
2. Evaluation for co-morbidities, such as sleep disorder and psychiatric issues, is important
3. Education in lifestyle issues
4. Selected triptans are FDA approved.
5. Recent AAN/AHS treatment guidelines published - emphasizes lifestyle modifications. Psychologic interventions such as cognitive behavioral therapy/biofeedback and addition of amitriptyline.

New therapies-CGRP antibodies

- Phase 2 and 3 studies in pediatrics are ongoing with the erenumab(Aimovig) at this time, no data published.
- Studies planned with Galcanezumab (Emgality) and Fremenazumab (Ajovy).