

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

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Review Article

Management of Adults With Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies

Serena L. Orr, MD; Benjamin W. Friedman, MD, MS; Suzanne Christie, MD, FRCPC;
Mia T. Minen, MD; Cynthia Bamford, MD; Nancy E. Kelley, MD, PhD; Deborah Tepper, MD

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 dipyrrone (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)

Source: Becker, W. J. (2015) "Acute Migraine Treatment." *Continuum*; 21 (4): 953-972.

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.

A Retrospective Analysis of Triptan and DHE Use for Basilar and Hemiplegic Migraine

Paul G. Mathew, MD, FAHS; Regina Krel, MD; Bhuvn Buddhdev, MD; Hossein Ansari, MD; Shivang G. Joshi, MD, MPH, RPh; Warren D. Spinner, DO; Brad C. Klein, MD, MBA

- **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

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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

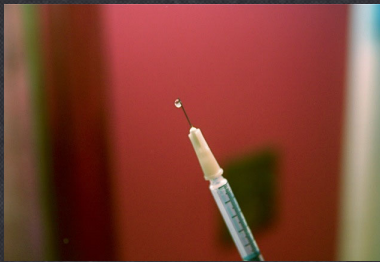
Preventative Treatments

- 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?

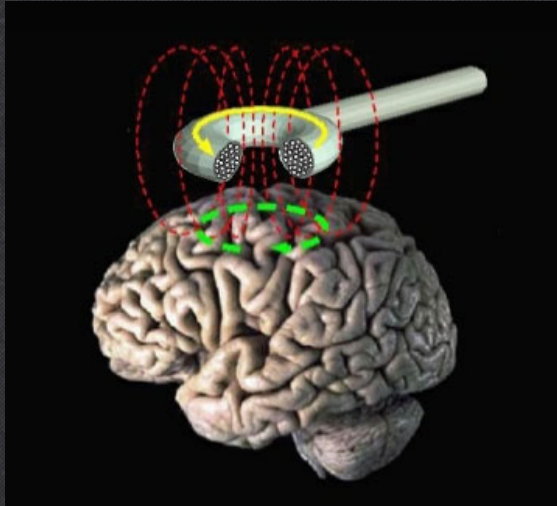
- Single pulse transcranial magnetic stimulation
- Transcutaneous supraorbital neurostimulation
- Noninvasive vagal nerve stimulation
 - Approved for episodic cluster and episodic migraine abortive treatment, as well as the adjunctive preventative treatment of cluster headache
- Caloric vestibular stimulation
 - Not yet FDA approved
- Calcitonin gene-related peptide antibodies
- Serotonin (5-HT)_{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.

- 1. Andreou et al. Brain. 2016;139(Pt 7):2002-14.
- 2. Lipton et al. Lancet Neurol.2010;9:373-80.
- 3. Bhola et al. J Headache and Pain 2016; DOI 10.1186/s10194-015-0535-3.

Spring TMS



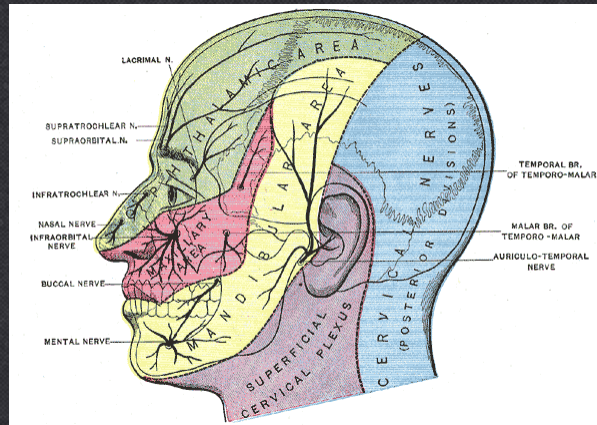
Source for image: Wikipedia.org

Cefaly

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

• Source: Schoenen et al. Neurology 2013;80;697-704.

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

Simvastatin + Vitamin D

Published in final edited form as:
Ann Neurol. 2015 December ; 78(6): 970-981. doi:10.1002/ana.24534.

Simvastatin and Vitamin D for Migraine Prevention: A Randomized Controlled Trial

Catherine Buettner, MD, MPH¹, Rony-Reuven Nir, PhD, BSc², Suzanne M. Bertisch, MD,
MPH¹, Carolyn Bernstein, MD³, Aaron Schain, PhD³, Murray A. Mittleman, MD, DrPH⁴, and
Rami Burstein, PhD³

- Simvastatin 20 mg BID
- Vitamin D3 1000U BID

Memantine

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Research Submission

Memantine for Prophylactic Treatment of Migraine Without Aura: A Randomized Double-Blind Placebo-Controlled Study

Rezvan Noruzzadeh, MD; Amirhossein Modabbernia, MD; Vajihah Aghamollai, MD;
Majid Ghaffarpour, MD; Mohammad Hossein Harirchian, MD; Sarvenaz Salahi; Nikta Nikbakht;
Nahid Noruzi; Abbas Tafakhori, MD

- Level B pregnancy!

Alternative Treatments

| Herbal Preparations, Vitamins, Minerals, and Other Interventions | |
|--|--|
| Strong evidence | Petasites (butterbur) is established as effective and should be offered for migraine prevention (Level A). |
| Moderate evidence | Riboflavin, magnesium, and MIG-99 (feverfew) are probably effective and should be considered for migraine prevention (Level B). |
| Weak evidence | Coenzyme Q10 and estrogen are possibly effective and may be considered for migraine prevention (Level C). |
| Insufficient evidence | Evidence is inadequate or conflicting to support or refute the use of omega 3 or hyperbaric oxygen therapy for migraine prevention (Level U). |

Source: aan.com



Cochrane Database of Systematic Reviews

Acupuncture for the prevention of episodic migraine (Review)

Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, Vickers A, White AR

- 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

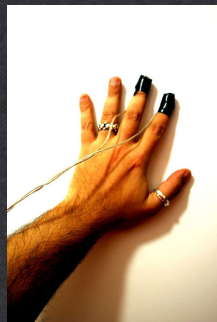


Photo Source: flickr.com

Source for information: Campbell JK, Penzien DB, Wall EM (2000). "Evidence-based guidelines for migraine headache: Behavioral and physical treatments." *US Headache Consortium*. Available at: <http://tools.aan.com/professionals/practice/pdfs/gl0089.pdf>

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.

New Therapies in Pediatric Migraine

Ann Pakalnis, MD
Director

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Clinical Assistant Professor of Neurology
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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

- **Hamalainen et al (1998, Neurology)**
 - Ibuprofen had best overall pain relief
 - Double-blind with placebo controlled study
 - Both were effective and well-tolerated
 - 10mg/kg Ibuprofen
 - 15mg/kg Acetaminophen

OTC's

Lewis, et al (2002)

- 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*

| Triptan Tablets | T _{max} , h | Oral Bioavailability, % | t 1/2, h | Active Metabolites | Sulfonamide Included |
|--------------------|----------------------|-------------------------------|----------|--------------------|-------------------------|
| Sumatriptan | 2 - 3 | 14 | 2 | No | Yes |
| Zolmitriptan | 1.5 - 2 | 40 - 46 | 3 | Yes | No |
| Naratriptan | 2 - 3 | 74 (F) 63 (M) | 6 | No | Yes |
| Rizatriptan | 1 - 1.5 | 40 - 45 | 2 | Yes | No |
| Almotriptan | 1.5 - 2 | 70 | 3 | No | Yes |
| Eletriptan | 1 - 1.5 | 50 | 4 | Yes | Yes |
| Frovatriptan | 2 - 3 | 25 | 26 | No | No |

*T_{max} indicates time to maximum concentration; t1/2, half-life; F, females; M, males.

TRIPTANS

- **Ueberall & Wenzel (1998)**
 - Intranasal sumatriptan effective compared to placebo
 - Pakalnis, et al 2003
 - Doses used:
 - <30 Kg - 5 mg intranasal
 - 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

(Ahoner, 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

Cyproheptadine

Lewis, et al – 2004

- Open label study
- n=30
- Positive efficacy
- Weight gain and sedation were side-effects

Amitriptyline

Hershey, et al – 2000

- Tri-cyclic antidepressant
- Depression/sleep disorders are common co-morbidities with migraine
- Doses up to 1 mg/kg/day
- Cardiac abnormalities, such as long Q-T, would contraindicate use

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 Fremenezumab (Ajovy).**