MIGRAINE
Updates in Diagnosis & Treatment

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Disclosures
Speakers bureau Allergan Pharmaceuticals

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Objectives
• Identify current diagnostic criteria for diagnosis of migraine headache.
• Based on current evidence, choose the most appropriate pharmacological treatments while evaluating side effects and efficacy.
• Evaluate non-pharmacological options available for treatment.
Migraine Defined
International Classification of Headache Disorders 3rd edition (beta version)
(IHCD-3β)

Primary Headache Disorders
Migraine
Tension-type headache
Trigeminal autonomic cephalalgias
Other primary headache disorders

Secondary Headache Disorders
Medication overuse headache
Post-traumatic headaches
Metabolic headaches (associated with hormonal/metabolic disorders)
Vascular/infection/withdrawal/psychosomatic
Cranial Neuralgias, Central & Primary Facial Pain, Other Headaches

ICHDI-III-β

Primary Headache Disorders
1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
3.1-3.4 (cluster headache, paroxysmal hemicrania, SUNCT/SUNA, hemicrania continua)
4. Other Primary Headaches
4.1-4.10 (cough headache, exercise headache, sexual activity headache, thunderclap headache, cold stimulus headache, external pressure headache, stabbing headache, new daily persistent headache)

Secondary Headache Disorders
5. Trauma or injury to the head
6. Cranial or cervical vascular
7. Intracranial non-vascular
8. Substance
9. Infection
10. Hormone
11. Disorder of head, neck, eyes, ...
12. Psychiatric

Cranial Neuralgias/Face Pain
- Trigeminal neuralgia
- Trigeminal neuropathy
- Glossopharyngeal neuralgia
- Nervus intermedius neuralgia
- Occipital neuralgia
- Tolosa-Hunt
- Burning mouth syndrome
ICHDI-IIIB

1. Primary Headaches

Migraine

Chronic Migraine Defined

Headache frequency ≥15 days/month, for ≥3 months.

Lifetime history of ≥5 attacks migraine (w/without aura).

On ≥8 days per month for 3 months (fulfills criteria for migraine, w/without aura):

• Typical migraine pain characteristics & nausea/sensitivity (light/sound/movement).
• Aura.
• Headache considered migraine by patient and relieved by triptans/ergots.
Practical Clinical Criteria

Headache $\geq 15$ days/month.
On $\geq 8$ days per month are migraine days.
Headaches last $\geq 4$ hr per day.
With or without medication overuse.

Pathophysiology

Migraine is an inherited central nervous system disorder.

Neurogenic inflammation eventually leads to the pain associated with a migraine.

Complex neuro-vascular contributing factors:
- Cortical spreading depression.
- Reduction in brain electrical activity and decrease in blood flow.
- Release of K+ and H+ activates sensory fibers.
- Activation of trigeminal and brain stem neurons.
- Precipitation of vasodilation.

Pathophysiology

Migraineurs have hyper excitable brains.

Migraine is progressive during an attack
- Central sensitization.
- It has been hypothesized that migraineurs have an altered peripheral glutamate homeostasis and persistent neuronal hyper-excitability that becomes heightened during migraine attacks.

(Ramadan, 2003)
Pathophysiology

• Unrestrained firing of the trigeminal nerve and upper cervical roots.
• Synapse on the nucleus caudalis.
• Causing wind-up.
• Leads to central sensitization (allodynia).

Cortical spreading depression (CSD) → trigemino-vascular system (TGVS) activation in migraine with aura and, perhaps, also migraine without aura.

Hypothesized Sequence of Events in Migraine

Adapted from Charles & Ben-Menachem, 2011
Pathophysiology

Neurogenic inflammation:

- Stimulation of the trigeminal nerve.
- Release of neuroinflammatory peptides (substance P, CGRP, and neurokinin A) from perivascular nerve fibers.
- Triggering neurogenic inflammation.
- Leads to the pain of migraine.

Prevalence

It is estimated that 12-15% (>300 million) of the global population.

The American Migraine Study II (AMS II) estimated that 28 million Americans suffer from migraine—approximately 18% of women and 7% of men (Lipton et al, 2001a).

Another study found a 1-year prevalence of 17% of women and 6% of men (Lipton et al, 2002).

Cost of Migraine

Migraine alone has been reported to cost the US economy billions of dollars, with $13 billion a year as a result of missed workdays and impaired work function.

The direct medical costs associated with migraine have been estimated at $9.5 billion.

Migraine sufferers use 2.5 times more prescription drugs than non migraine sufferers (Clouse & Osterhaus, 1994), at a cost of $2.7 billion annually in the US.

The reported cost of ED visits for migraine-related treatment in the US ranges from $>6 million - $2 billion annually.
Treatment

**MEDICATIONS**
- Abortive
- Preventive
- Infusions
- Steroids
- Oxygen therapy

**INTERVENTIONS**
- Nerve blocks
- Trigger point injections
- Implantable devices

**COMPLEMENTARY**
Cognitive/behavioral strategies, Manual therapies, Nutraceuticals

Predictors of Poor Treatment Outcomes

History of emotional, physical, sexual abuse.
Co-morbid Chronic disease history/chronic pain.
Multiple headache day a month.
High headache-related disability.
Poor treatment optimization.
Opioid/barbiturate use.
Persistent, frequent nausea w/headache.


Medications

**Preventative**
- Beta-blockers
- Anticonvulsants
- Calcium channel blockers
- Tricyclic antidepressants
- Onabotulinumtoxin A (Botox)™

**Abortive**
- Non-specific effects
  - NSAIDS
  - Anti-emetics
- Specific effects
  - Triptans
  - Dihydroergotamine/ergotamines
Abortive Medications

**Triptans**

Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan (oral, injectable, intranasal, transdermal), Zolmitriptan.

**Triptan/NSAID**

Sumatriptan/naproxen: 85 mg/500 mg at onset and repeat in 2 hs prn.

**Anti-inflammatory Drugs**

Ibuprofen 600-800 mg q 4 hr pm, Ketorolac oral 10 mg, repeat once in 2 hr pm, Ketorolac IV/IM 30 mg, repeat once in 1 to 2 hr pm, Ketorolac, nasal 1 spray q6-8hr (maximum 4 sprays – 63mg/d). Naproxen sodium 550 mg, repeat once in 2 hr pm. Corticosteroids: dexamethasone i.v.

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Abortive Medications

**Combination Drug**

Isometheptene/dichloralphenazone/acetaminophen (Midrin) Two capsules at onset, then one or two in 1 hr.

Butalbital/acetaminophen(aspirin)/caffeine (Fioicet/Fiorinal)

**Ergot Alkaloids** (dihydroergotamine, D.H.E.-45)

DHE mesylate, nasal 1 puff in each nostril, repeat in 15 min. This is the dose for 1 day.

DHE mesylate, IV, IM, and SC 0.5-1 mg, repeat in 1 hr. (Maximum dose is 3 mg in 24 hr).

Ergotamine tartrate/caffeine, oral 2 tabs at onset, repeat once every 0.5 hr up to a maximum of 5 tabs. Ergotamine tartrate/caffeine, suppository 1/2 to 1 at onset, repeat once in 1 hr. Ergotamine tartrate, sublingual 1 at onset, repeat once in 0.5 hr pm

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<table>
<thead>
<tr>
<th>Triptan</th>
<th>Formulation</th>
<th>Doses</th>
<th>Max daily</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Tablets, Nasal spray, SC injections, Suppositories</td>
<td>25, 50, 100 mg</td>
<td>200 mg</td>
<td>Maximum recommended monthly dose: 18 (50mg) tabs/ equivalent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5, 10 mg</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2, 5 mg</td>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 mg</td>
<td>3 mg</td>
<td>Using only if not contraindicated with MAOI, slower onset.</td>
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<tr>
<td>Rizatriptan</td>
<td>Tablets, Oral dissolving (MLT), Nasal spray</td>
<td>2.5, 5 mg, 10 mg</td>
<td>20 mg</td>
<td>Propranolol increases serum concentration of rizatriptan.</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Tablets, Oral dissolving</td>
<td>1.25 mg, 2.5 mg, 5 mg</td>
<td>3 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg</td>
<td>3 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.25 mg</td>
<td>25 mg</td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Tablet</td>
<td>0.5 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Tablet</td>
<td>0.5 mg</td>
<td>25 mg</td>
<td>Longest half life, slower onset.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg</td>
<td>3 mg</td>
<td></td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Tablet</td>
<td>20, 40 mg</td>
<td>60 mg</td>
<td></td>
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</tbody>
</table>
Preventatives

**Beta Blockers**
Atenolol 50-100 mg, Metoprolol succinate/tartrate 50-150 mg, Nadolol 20-160 mg, Propranolol 60-240 mg, Timolol maleate 10-20 mg

**Antiepileptic Drugs**
Divalproex Sodium 250-1500 mg, Gabapentin 300-1800 mg, Pregabalin 50-200 mg, Topiramate 25-150 mg, Zonisamide 100-200 mg, Valproic Acid 250-500 mg

**Calcium Channel Blockers**
Amlodipine besylate 10-20 mg, Diltiazem 80-240 mg, Nimodipine 60-120 mg, Verapamil 180-480 mg

Preventatives

**Antidepressants**
Amitriptyline 25-150 mg, Citalopram 20-60 mg, Desipramine 25-100 mg, Doxepin 25-150 mg, Duloxetine 30-90 mg, Fluoxetine 20-60 mg, Nortriptyline 25-100 mg, Phenelzine 15-45 mg, Protriptyline 5-10 mg, Sertraline 50-150 mg, Venlafaxine 37.5-150 mg

**Nonsteroidal Anti-inflammatory Drugs**
Celecoxib 200-400 mg, Naproxen sodium 500-1000 mg, Indomethacin 75-150 mg
### Level A: Medications with established efficacy (≥2 Class I trials)

<table>
<thead>
<tr>
<th>Antiepileptic drugs</th>
<th>Divalprox sodium</th>
<th>Sodium valproate</th>
<th>Topiramate</th>
<th>Metropil</th>
<th>Propranolol</th>
<th>Timodil®</th>
<th>Triptans (MRM®)</th>
<th>Frovaniptan®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ace inhibitors</td>
<td>Lamotrigine</td>
<td>Carbamazepine</td>
<td>Verapamil</td>
<td>Nitrofurantoin</td>
<td>Tolterodine</td>
<td>Pregabalin</td>
<td>Nortriptyline</td>
<td>Zolmitriptan</td>
</tr>
</tbody>
</table>

(Silberstein, 2012)

### Level B: Medications are probably effective (≥1 Class I study)

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Sertraline</th>
<th>Fluoxetine</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Propranolol</th>
<th>TCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Escitalopram</td>
<td>Sertraline</td>
<td>Fluoxetine</td>
<td>Citalopram</td>
<td>Propranolol</td>
<td>TCA</td>
</tr>
</tbody>
</table>

(Silberstein, 2012)

### Level C: Medications are possibly effective (≤1 Class II study)

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>Loratadine</th>
<th>Cetirizine</th>
<th>Fexofenadine</th>
<th>Montelukast</th>
<th>Zafirlukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
<td>Prednisolone</td>
<td>Methylprednisolone</td>
<td>Beclomethasone dipropionate</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>Cough suppressants</td>
<td>Codeine</td>
<td>Guaifenesin</td>
<td>Dextromethorphan</td>
<td>Diphenhydramine</td>
<td>Dimenhydrinate</td>
</tr>
</tbody>
</table>

(Silberstein, 2012)
Medication Overuse Headache

Interventions

**Nerve Blocks**
- Occipital
- Cervical spine
- Cervical medial branch
- Peripheral nerve block

**Trigger point Injections**
- Onabotulimumtoxin A via PREEMPT
- Other myofascial TP injections

**Infusions**
- Dihydroergotamine, lidocaine, divalproex, magnesium, ketamine, propofol.

**Implantable Devices**
- Occipital nerve stimulator, deep brain stimulator, IT infusion pump, ganglion sphenopalatine stimulation, dorsal column stimulator – cervical.
Complementary

- Acupuncture/acupressure
- Aromatherapy
- Biofeedback
- Meditation
- Massage
- Herbs, vitamins & minerals
- Nutrition
- Exercise/stress reduction/trigger identification (avoidance)

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Acupuncture for recurrent headaches: a systematic review of randomized controlled trials

Melchart, D., Linde, K., Fischer, P. et al. – Dept. of Internal Medicine II, Klinikum rechts der Isar, Technische Universität, Germany


Design:
Systematic Review using electronic databases (Medline, Embase, Cochrane Field for Complementary Medicine, Cochrane Controlled Trials Register), personal communications & bibliographies.

Question:
To assess whether there is evidence that acupuncture is effective in the treatment of recurrent headaches.

Findings:
- Twenty-two trials, including a total of 1042 patients, met criteria.
- Fifteen trials were in migraine patients, six in tension-ha patients, & in one trial patients with various headaches were included.
- The majority of the 14 trials comparing true and sham acupuncture showed at least a trend in favor of true acupuncture.
- The eight trials comparing acupuncture and other treatment forms had contradictory results.
- Overall, the existing evidence suggests that acupuncture has a role in the treatment of recurrent headaches.
Alternative headache treatments: nutraceuticals, behavioral & physical treatments

Sun-Edelstein, C., Mauskop, A. - Department of Clinical Neurosciences, St Vincent's Hospital, Melbourne, Vic., Australia.

Headache. 2011 Mar;51(3):469-83

**Design:**
Systematic Review of the available scientific literature.

**Question:**
Review body of literature that explored the evidence supporting the efficacy of various complementary & alternative medicine approaches in the management of headache disorders.

**Findings:**
- Vitamins & Supplements (magnesium, riboflavin, coenzyme Q(10), and alpha lipoic acid).
- Herbal Preparations (feverfew, and butterbur).
- Cognitive behavioral therapy & Bio-behavioral training (biofeedback, relaxation training).
- Physical Treatments, were not well defined in the literature (acupuncture, oxygen therapy, transcutaneous electrical nerve stimulation, occipital adjustment, cervical manipulation, physical therapy, massage, chiropractic therapy, and osteopathic manipulation).

Behavioral & non-pharmacological treatments of headache

Lake, A.E. – Michigan Head-Pain & Neurological Institute, Ann Arbor, Michigan, USA.


**Design:**

**Question:**
Apply a cognitive-behavioral analysis & assessment to the following behavioral domains:
1) Headache frequency & severity
2) Analgesic & abortive medication use/overuse,
3) Behavioral & stress risk factors
4) Co-morbid psychiatric disorders
5) Degree of overall disability.
Behavioral & non-pharmacological treatments of headache

Findings:
• CBTs for migraine have a prophylactic efficacy of about 50%, roughly equivalent to propranolol.
• The combination of behavioral therapies with prophylactic medication creates a synergistic effect, increasing efficacy beyond either type of treatment alone.
• Overuse of abortive medications impedes the effectiveness of behavioral & prophylactic medication therapies.
• Behavioral therapies can help sustain improvement after analgesic withdrawal.
• Cognitive factors (an enhanced sense of self-efficacy & internal locus of control), appear to be important mediators of successful behavioral treatment.

Nutraceuticals

Disclaimer: suggestions from existing research, any prescribing should be done understanding the unique patient medical history/intolerances/medications/allergies.

• Some evidence exists that the herbs feverfew and butterbur may prevent migraines or reduce their severity.
• A high dose of riboflavin also may prevent migraines by correcting tiny deficiencies in brain cells.
• Coenzyme Q10 supplements may be helpful in some individuals.
• Oral magnesium sulfate supplements may reduce the frequency of headaches in some people.

The Keeler Migraine Method
The Keeler Migraine Method

Three Part Individualized Treatment Plan

Lifestyle Modification
- Sleep hygiene
- Exercise
- Dietary habits
- Trigger management
- Stress management
- Hormonal influences (menstruation/pregnancy)

Prevention
- Medication options, mind-body therapies, hormone adjustment, nutraceuticals.

Rescue "plan your plan"
- Rescue environment, organize resources, abortive medications.

The Keeler Migraine Method

Eating
- Omega-3 fatty acids, instead of omega-6
- Anti-inflammatory foods
- Consistency/timing/"healthy diet"
- Avoid triggers (red wine, cheese, chocolate)

Exercise
- Pacing, variety, start with physical therapist
- Higher endorphin levels
- Higher pain thresholds
- Improved sleep

Sleep
- Good sleep hygiene (behavioral modification)
- Avoid habitual use of sleep medications
- Natural remedies (melatonin, chamomile tea, valerian root)
- Limit caffeine

Work
- Minimize workplace triggers (stress, computers, physical strain, shift work, lighting).
- Rescue in the workplace (medications, space, ride home).
Highlights from American Headache Society Annual Conference

Acute Migraine Treatment:

Allodynia & Timing of Triptan Therapy:
Patients who never develop cutaneous allodynia can be successfully treated with triptans at any time during their migraine attack, whereas those who develop cutaneous allodynia must be treated early, before central sensitization can be established.

COX-2 Inhibitor for Migraine:
A long-acting selective cyclooxygenase-2 (COX-2) inhibitor, may be as effective as nonselective NSAIDs and opioid analgesics in the treatment of acute pain.

acetaminophen/aspirin/caffeine (Excedrin Migraine) versus Sumatriptan:
acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg (Excedrin Migraine) has been shown to be effective in the acute treatment of migraine.


Highlights from American Headache Society Annual Conference

Preventive Treatment:

• Menstrual Migraine:
For intermittent prophylaxis of menstrual migraine, naratriptan 1 mg twice daily was well tolerated and more effective than placebo but appears to be less effective than frovatriptan 2.5 mg twice daily (38.4% vs 50%).

• Migraine Prophylaxis with Anticonvulsant Drugs:
Anticonvulsant medication is increasingly recommended for migraine prevention because of placebo-controlled, double-blind trials that prove them effective. Topiramate has demonstrated efficacy in migraine prevention in several open-label studies and pilot trials. MOA could either directly inhibit the trigemino-cervical complex or influence the neural network that controls sensory input.


Hot off the presses …

Monoclonal antibodies for Migraine prevention

Dr. David Dodick of the Mayo Clinic in AZ, an author of two studies looking at drugs that target the calcitonin gene-related peptide, which is thought to be important in migraine pathogenesis.

The study participants had migraine 4-14 days a month. On one medication participants had 5.6 fewer migraines per month (a decrease of 66%); on the other, 4.2 fewer migraines per month (63% decrease).

"While we’ve moved from the blood vessel to the space between the blood vessel and the nerve to the brain, we are now focused on molecular targets within the brain."
Hot off the presses …

Use of Social Media by patients

A study recently published in The Journal of Medical Internet Research proved to be a powerful source of knowledge in migraine research. This study reveals the modern characteristics and broad impact of migraine headache suffering on patients’ lives as it is spontaneously shared via social media.

The researchers also noted that the growth of social media has facilitated a trend toward the cathartic sharing of physical, as well as emotional pain.

The study also showed that people are willing to use social media to communicate about their migraines during an attack, provided that they can do it quickly.

May help Practitioners to develop new tools to interact with migraine patients and identify headache patterns.

Resources

American Academy of Neurology: http://www.aan.com/
American Headache Society: http://www.americanheadachesociety.org/
Cleveland Clinic Headache Center
Johns Hopkins Medical Center:
http://www.hopkinsmedicine.org/neurology_neurosurgery/specialty_areas/headache/
Mayo Clinic Headache Center
National Headache Foundation: http://www.headaches.org/
Stanford Headache Center
World Health Organization: http://www.who.int/topics/headache_disorders/en
Selected References


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