HEADACHE
Novel Approaches to Diagnosis and Treatment

Primary vs Secondary Headaches

SNOOP4
S - systemic signs and symptoms (fever, weight loss) or secondary risk factors (HIV, cancer)
N - neurological signs and symptoms
O - onset, < one minute (thunder clap headache)
O - older (GCA, glaucoma)
P - previous headache history (new or changed)
P - postural or positional
P - precipitated by valsalva or exertion
P - papilledema

Classification of Primary Headaches
Migraine
Tension-type headache
Cluster headache and other trigeminal autonomic cephalalgias
Other primary headaches
Migraine
ICHDI-3 Diagnostic Criteria

At least 5 headaches lasting 4-72 hours (untreated or unsuccessfully treated)
with at least two of the following characteristics:
  unilateral location
  pulsating quality
  moderate or severe pain intensity
  aggravation by or causing avoidance of routine physical activity
  and one of:
  nausea and/or vomiting
  photophobia and phonophobia

Migraine and Tension-type Headache
Two ends of the continuum of benign recurrent headache or separate disorders?

Factors Supporting the Continuum of Benign Recurrent Headache
1. Most patients with frequent headaches exhibit the whole spectrum.
2. Triptans work for tension-type headaches (TTH).
3. Preventive medications (antidepressants, AEDs) work for TTH.
4. Neck pain is a common feature of migraine.
5. Patients with tension-type headache may experience migraine auras.
6. Plasma serotonin levels are decreased during migraine and TTH
7. The same increased number of T2 hyperintensities are seen on MRI.
Allodynia

(The Difference Between TTH and Migraine?)

Pain due to a stimulus which does not normally provoke pain.
Reflects peripheral and central sensitization.
Pulsatile pain (throbbing headache)
Photophobia
Phonophobia
Osmophobia
Cutaneous allodynia (scalp tenderness)

Does It Matter?
Yes
Ignoring anti-migraine treatment for chronic or frequent, episodic TTH gets you nowhere and leads to medication overuse.

For occasional, severe TTH, refractory to OTC analgesics, try a triptan.

No
Occasional, mild, TTH can usually be effectively treated with OTC analgesics.

Migraine — Demography

Thirty-six million Americans, about 12% of the population

One in four households affected

Women:men = 3:1

30% of women affected at sometime in their lives

All ages affected; most common late teens through 40s

3% of people have chronic migraine

Keep in mind a couple of developing consensuses:

Try to avoid the diagnosis of chronic TTH.
Think of chronic (formerly called “transformed”) migraine.
Look for medication overuse.

If some of a patients headaches are migraine, all of them are migraine.
Migraine — Comorbidity
Vascular Disease — Women with migraine with aura have a 91% increased risk of myocardial infarction and a 108% increased risk of stroke.

Fibromyalgia — 76% of patients with fibromyalgia have chronic headache; 35% of patients with chronic migraine have fibromyalgia.

Depression, insomnia and anxiety are common, especially with chronic migraine and MOH.

Migraine — Disability
Estimated 88 hours of lost productivity per year.

QOL < to patients with CHF, recent MI, diabetes, hypertension, depression, and osteoarthritis.
Neurovascular (Neuronal) Theory

Migraine is, largely, genetically determined.

Cortex (esp. occipital cortex) hyperexcitable at baseline. Cortical spreading depression.

Activation of the trigeminovascular system.

Impaired brainstem modulation of pain.

Migraine — Genetics

70% of migraineurs have an affected first degree relative. Risk of migraine is increased 4-fold in relatives of patients with migraine with aura.

The gene for 3 variants of hemiplegic migraine has been discovered.

Cortical Spreading Depression

Wave of neuronal excitation followed by inhibition. Self propagating at rate of 2-6 mm/min.

Responsible for migraine aura:
- visual
- sensory
- motor

Occurs in migraine without aura (cognitive dysfunction). Activates trigeminovascular system.
Trigeminovascular Activation

Activation of trigeminovascular system releases:
- substance P
- calcitonin gene related peptide (CGRP)
- neurokinin A
- nitric oxide

Causes sterile inflammation.
Leads to peripheral and, ultimately, central sensitization.
Probably not sufficient to cause pain of migraine.
Migraine Center

rCBF persistently increased in brainstem.

Locus ceruleus, dorsal raphe nuclei, PAG.

Modulates thalamic processing of pain.

Serotonin
Onset of migraine characterized by increased serotonergic activity f/b serotonin depletion.

Serotonin depletion during migraine headaches facilitates cortical hyperexcitability, CSD and trigeminovascular activation.

5-HT1D receptors present on trigeminal neurons and trigeminal nucleus caudalis.
5-HT1B receptors present on meningeal blood vessels.
Triptans are 5-HT1B/D receptor agonists.

Dopamine
Prodrome symptoms reflect dopamine pathway stimulation:
yawning
cognitive impairment
mood changes: euphoria, depression, irritability
physical symptoms: diarrhea, thirst
Dopamine blocking antiemetics (droperidol, prochlorperazine, metochlopramide):
abort headache, if given during prodrome
relieve nausea and vomiting
relieve headache in up to 75%
What Is Migraine?
A hereditary susceptibility of the brain to decrease modulation of afferent impulses, thus permitting and augmenting the perception of head pain, sensitivity to light, sounds, and smells, vascular pulsation and scalp tenderness.

Peter Goadsby 2009

Migraine (Acute Treatment)
Dark, quiet room, ice
OTC analgesics: NSAIDS, APAP, ASA (caveat - MOH)
Dopamine blocking antiemetics (metoclopramide, prochlorperazine)
Triptans
Avoid opioids and butalbital (MOH)
Ergotamine tartrate
Dihydroergotamine

Triptans
Effective and well tolerated.
Should be taken early.
Consider nasal spray.
May provoke typical “triptan” side effects.
Avoid in patients with risk for CAD.
Should not give within 24 hours of ergotamine or dihydroergotamine.
## Serotonin Syndrome and Triptans

**FDA warning (2006):** There is the potential for life-threatening serotonin syndrome in patients taking 5-hydroxytryptamine receptor agonists (triptans) and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly. Based on 29 anecdotal cases. Most did not meet established criteria for serotonin syndrome. Frequency not clearly increased with concomitant treatment. Triptans are selective 5 HT1B/D/F agonists. Serotonin syndrome mediated by 5 HT2A receptors.  

**AHS Position Paper (2010):** The currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome. However, given the seriousness of serotonin syndrome, caution is certainly warranted and clinicians should be vigilant to serotonin toxicity symptoms and signs to insure prompt treatment.

## Peripheral Nerve Blocks

May provide prompt, definitive relief of headache for days, weeks or months.  

Safe and well tolerated.  

Greater occipital, supraorbital, supratrochlear, auriculotemporal nerves are treated, depending on headache pattern.  

Lidocaine or bupivacaine; corticosteroids can be used for GON.  

Useful for status migrainosus, chronic migraine, and cluster headache. Prolonged analgesia likely due to effects on central pain modulation.

## Migraine Prevention — Lifestyle

Regular Sleep - too much or too little can trigger migraine  
Regular meals - fasting a common trigger  
Regular exercise  
Manage stress - caveat: holiday or weekend headache  
Stop smoking  
Attain or maintain ideal weight  
Avoid bright light, loud noises and strong or unpleasant smells  
Caffeine - too much or withdrawal can cause headaches  
Avoid dietary triggers: red wine, beer, aged cheese,nuts, processed meats (hot dogs, sausage), MSG  
Elimination diet (?) - data are mixed  
Avoid medication overuse

## Medication Overuse Headache  
(Transferred Migraine)

Most common cause of migraine progression  
Can result from overuse of any symptomatic treatment  
Rule of thumb: > 2-3/week for 3 months  
Butalbital 5/month  
Opiates 8/month  
Triptans 10/month  
ASA/APAP/caffeine 10/month  
ASA, APAP, NSAID 15/month  
Headaches increase in frequency and don’t respond to preventive treatment
Migraine Prevention — Prescription Meds

FDA approved:
- Propranolol
- Timolol
- Divalproex Sodium
- Topiramate
- Methysergide
- Botulinum Toxin Type A (chronic migraine only)

Consensus:
- Other Beta Blockers (nadolol, atenolol, metoprolol)
- Amitriptyline, Nortriptyline
- Calcium Channel Blockers (amlodipine, verapamil)
- Possibly Effective:
  - Gabapentin, ACE inhibitors, ARBs, SNRIs, methylergonovine, cyproheptadine

Beta Blockers

FDA approved: propranolol, timolol
Likely effective: nadolol, metoprolol, atenolol

Mechanism of action:
- reduction of firing rates in PAG and locus coeruleus neurons
- possible effects on brain 5 HT receptors and 5 HT synthesis

Side Effects: reduced exercise tolerance, lethargy, depression, hypotension, bradycardia

Contraindications: asthma, congestive heart failure, diabetes

Dose:
- propranolol LA 60 - 240 mg daily
- timolol 10 mg BID initially, then 20 - 30 mg daily

Topiramate

Mechanism of Action:
- Blocking voltage dependent sodium channels?

Side Effects:
- Cognitive impairment, paresthesias, acute glaucoma(1/50,000), metabolic acidosis, nephrolithiasis.

Dose:
- 25 - 100 mg nightly, maybe more

Sodium Divalproex
# Migraine Prevention — Nutraceuticals

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<th>Nutraceutical</th>
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| **Butterbur**  | Petasites Hybridus  
Safety and effectiveness establish in three RCTs.  
Efficacy equal to the FDA approved migraine preventives.  
Mechanism: anti-inflammatory v blockade of presynaptic VG Ca channels.  
Must be free of pyrrolizidine alkaloids (PA Free).  
Minor GI side effects (increased burping). |
| **Melatonin** | Slightly more effective than amitriptyline in one RCT.  
Minimal side effects (excessive daytime sleepiness?)  
Dose: 3 mg hs. |
| **Feverfew (MIG-99)** | Likely effective for migraine.  
Anti-inflammatory.  
Efficacy less robust than Butterbur and Melatonin.  
Potency varies widely among different preparations (> 400%).  
Best data for MIG-99: 6.25 mg tid |
| **Magnesium** | |
| **Riboflavin (Vit B2)** | |
| **CoQ10** | |
Magnesium

Magnesium levels reduced in menstrual migraine and migraine with aura.
RCT results have been mixed.
May decrease post synaptic excitation.
May cause diarrhea.
Dose: 600 mg of Magnesium Citrate daily.

Riboflavin

(Vitamin B2)

RCTs have demonstrated mixed results.
May improve mitochondrial function.
Rare reports of diarrhea and polyuria.
May turn urine bright yellow.

Coenzyme Q 10

(CoQ10)

In a small RCT was moderately effective.
May improve mitochondrial function.
Rare side effects: nausea, anorexia, dyspepsia, diarrhea, and rash.
Dose: 100 mg tid

Alternative/Complimentary Therapy

Chiropractic Treatment
Acupuncture
Stress management / CBT
Biofeedback
**Chronic Migraine**
Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month. Formerly called transformed migraine.
80% of patients with chronic migraine overuse symptomatic medication (MOH).
Anxiety and depression are frequent; 80% have depression.
Treatment:
- stop medication overuse
- lifestyle changes: regular sleep, diet/weight loss, stress reduction
- preventive medication
- peripheral nerve blocks
- Botox

**Menstrual Associated Migraine**
Caused by drop in estrogen levels prior to menses.
Pure menstrual migraine => migraines confined to -2 to +3 days of the period. Menstrual related migraine => HAs on other days.
Acute treatment — the same as that given for any migraine patient.
Short term prophylaxis — start 2 days before headaches typically begin and continue for a week:
- naproxen
- triptans — frovatriptan, naratriptan, zolmitriptan
- estrogen
Continuous prophylactic treatment:
- hormonal — long duration oral contraceptive treatment
- non-hormonal — the same as for all migraine patients

**Migraine-Associated Vertigo**
Varied symptoms:
- vertigo - episodic true vertigo or positional imbalance
- movement associated disequilibrium
- lightheadedness
Occurs in up to 38% of patients with migraine
Before, during or in the absence of headache
Variable duration:
Cause:
- some patients have a rocking sensation lasting weeks
- neuropeptide induced increased firing rate of vestibular endothelium
Cluster Headache
Occur daily to several times daily for wks to mos f/b wks to mos without headache.
Last 30 to 180 min.
Occur about the same time every day, often 02:00 to 03:00.
Unilateral, side locked, retro-orbital.
Associated with ptosis, miosis, conjunctival injection, rhinorrhea, tearing.
Unlike migraine, patients with cluster headache are restless.
Other headaches can occur in clusters, but they aren’t cluster headaches.
Dx of “cluster migraine” is erroneous and leads to confusion.

Treatment of Cluster Headache
Acute Treatment:
Sumatriptan injection or nasal spray
Oxygen
DHE 45
Octreotide injection
Intranasal lidocaine
Preventive Treatment:
Calcium channel blockers
Lithium
Corticosteroids
Occipital nerve block and stimulation
Ergots
Melatonin
Topamax
Sodium valproex

Hypnic Headache
Benign recurring headache beginning age 50-70
Dull, aching, moderate severity
Like cluster headache, related to circadian rhythm
Occur nightly between 1 and 3 AM
Triggered by decreased brainstem antinociceptive activity during REM sleep
Treatment:
melatonin
lithium
calcium channel blockers
indomethacin
ergots
gabapentin
acetazolamide
caffeine at bedtime

Reversible Cerebral Vasoconstriction Syndrome
Thunderclap headache presentation
Results in segmental spasm of cerebral arteries
Fluctuating focal neurological symptoms and signs
Often occurs peripartum, associated with eclampsia/preeclampsia
Some cases of coital headache can be associated with RCVS
Vasoactive drugs may trigger RCVS:
cannabis
SSRIs
OTC decongestants
Spontaneously resolves over days to weeks
Calcium channel blockers may attenuate spasms
Paroxysmal Hemicrania - Hemicrania Continua
Persistent "side locked" headache disorders.
Both associated with autonomic features: ipsilateral ptosis, miosis, excessive lacrimation, nasal congestion, conjunctival injection.
PH - headaches last 2-30 minutes occur 5-40 times a day.
If you are considering CH in a woman think PH.
HC - headaches are continuous.
Unlike migraine, patients with HC are restless.
Both respond to indomethacin.

Migraine in Children
Common
Presentation similar to adult migraine
unilateral headache less common
children may have trouble describing aura
Headache tends to resolve with sleep
Acute treatment:
cool, dark, quiet, room - encourage sleep
OTC analgesics - NSAIDs, APAP, not ASA (Reye’s syndrome)
Triptans - consider nasal sprays
Avoid opioids and butalbital
Avoid MOH
Preventive treatment:
encourage regular sleep, meals, and exercise
exercise, recreation, rest
avoid environmental and dietary triggers
nutraceuticals - butterbur, melatonin, feverfew, B2, magnesium, CoQ10
beta blockers - watch for lethargy, depression, decreased exercise tolerance
cyproheptadine - really is associated with sedation and weight gain in children
topiramate and divalproex sodium are last resorts

Periodic Syndromes (migraine equivalents)
Cyclic vomiting
recurrent episodes of vomiting lasting 6-48 hours
begins in toddlers - headache may not show up until adolescence
often there is a family history of migraine
Recurrent vertigo
vertigo, trouble with balance, nausea lasting minutes
starts in childhood - headache usually shows up later
Episodic confusion
confusion, agitation, delirium, aphasia, memory loss
older children
sometimes provoked by minor head trauma
resolves with sleep
Paroxysmal torticollis of infancy
episodes of head tilt lasting hours to days a/w headache, nausea, and vomiting
Abdominal migraine
episodes of abdominal pain lasting hours and relieved with sleep
headaches may occur between attacks or may occur later

Migraine Pathophysiology
Vascular Theory
Vasoconstriction induced ischemia causes aura
Vasodilation causes throbbing headache
Problems
Ischemia not sufficient to cause aura
Headache begins during initial cerebral hypoperfusion
Doesn’t explain prodrome
Some preventive medications have no effect on CBF
Cough, Exertion, Coital Headache

Triggered by sudden increase in ICP

Abrupt onset, severe, brief

- 10% associated with structural abnormalities
  - Chiari malformation
  - Other cranio-cervical junction abnormalities
  - Tumors
  - Aneurysms

Cranial MRI/MRA required

Indomethacin, ? other NSAIDS, beta blockers often help

Surgery may be required for structural causes

Thunderclap Headache

Headache that builds to its maximum intensity in less than one minute. Often associated with cough, exertion, and coital headache.

May occur spontaneously.

Usually benign.

Can be associated with:

- Subarachnoid hemorrhage - sentinel bleed
- Pituitary apoplexy
- Arterial dissection
- Colloid cyst of the 3rd ventricle
- Stroke
- Cerebral venous sinus thrombosis
- Severe hypertension - PRES
- Reversible cerebral vasoconstriction syndrome

Cranial MRI, head and neck MRA, MRV, LP may be needed.