Migraine: Migraine: 
Growing Understanding, Expanding Therapeutics 

Primary Care Medicine: Update 2011

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Pathophysiology

• The vascular theory of vasodilation HA and vasoconstriction aura is disproven
• New understanding more complex:
  – Trigeminovascular system innervates the cranial vasculature
  – Cortical spreading depression explains the aura
  – Role of serotonin
  – Role of calcitonin gene-related peptide

Trigeminovascular System

• Trigeminal fibers – from the trigeminal ganglion (TG) – innervate the large cerebral blood vessels
  – contain calcitonin gene related peptide (CGRP) and substance P and neurokinin A
• When the trigeminal ganglion is stimulated, the fibers release CGRP, substance P
  – Causes inflammation
  – Stimulates, dilates cranial vessels and is painful.
• TG fibers also innervating dura and dura fibers also innervate cerebral vessels

Cortical Spreading Depression

• A self-propagating wave of neuronal depolarization, spreading across the cerebral cortex
• This depolarization then activates the trigeminovascular systems and the trigeminal fibers, then causing the inflammatory response
• It is thought that Cortical Spreading Depression accounts for aura.
Serotonin

- Serotonin has a direct effect on cerebral vessels
- Low serotonin state causes a deficit in normal pain inhibition
- Allows the trigeminovascular system to be activated and the cortical spreading depression to occur

A Brain or A Pain Disorder?

- Migraine is also considered by some to be a PAIN DISORDER
  - Neurons become increasingly sensitized
  - Centrally and peripherally
- The pain threshold decreases, the magnitude of the pain response increases, and spontaneous neuronal activation occurs
- Cutaneous allodynia feature of migraine can involve entire body and not just head
  - Some consider the pain sensation to be the primary dysfunction of migraine

Patent Foramen Ovale?

- Link between PFO and migraine noted between 2000-2004
- Increased prevalence of PFO in migraineurs with aura
- Increased prevalence of migraine and migraine with aura in persons with PFO
- 1 controversial trial of PFO closure including sham closure (MIST) had negative results
- No definitive conclusions yet

Biological Explanation for PFO and Migraine Link

- Venous blood contains agents normally removed in the lungs
- With PFO / Right to Left shunts, these agents reach arterial system and brain
- Are migraines embolic events – with inflammation caused by emboli?
Conflicting Evidence for PFO

- Observational studies suggest an association but evidence is low-mod grade
- One large new observational study (NOMAS) among 1100 patients found no association
- Retrospective studies of PFO closure had benefits for 80% of migraine patients, but evidence is very low grade
- Total PFO prevalence is 27%

Migraine Intervention With STARFlex Technology (MIST) Trial

- Prospective, multicenter, United Kingdom
- Double-blind, Sham-Controlled
- TTE to evaluate for presence of PFO
  - 38% had large PFO, 60% had shunts of any type
- Sham procedure: Only cardiac catheterization lab staff knew whether pts received septal repair implant or sham
- No significant difference between 2 groups in cessation of migraines or change in frequency, severity or characteristics of migraines


Epidemiology

- Migraine is commonest form of disabling headache presenting to doctors
- 6% men, 17% women
- Runs in families
- Migraine without aura = most common

Migraine with aura and risk of hemorrhagic stroke in women

- Women’s Health Study
- 27,860 women age >45 yrs
- 13.6 yrs follow up, 85 hemorrhagic strokes
- Migraine with aura - increased risk of hemorrhagic stroke (2.25, 1.11 to 4.54, P=0.024).
- Migraine without aura - no increased risk
Practical Approach: 2 Main Questions for Primary Care Evaluating HA

1. Is the headache secondary / organic?

2. Is the headache migraine or tension?

Migraine without aura: simplified diagnostic criteria

Repeated attacks of headache lasting 4-72 hours that have these features
- A: Normal physical examination
- B: No other reasonable cause for the headache
- C: At least two of
  - Unilateral pain
  - Throbbing pain
  - Aggravation of pain by movement
  - Moderate or severe intensity of pain
- D: At least one of
  - Nausea or vomiting
  - Photophobia and phonophobia

International Classification of Headache Disorders - II

Features Suspicious for Secondary (Organic) Headache

- Pain of sudden onset
- Fever
- Marked change in pain character or timing
- Neck stiffness
- Pain associated with higher CNS complaints
- Pain associated with neurological disturbance, such as clumsiness or weakness
- Pain associated with local tenderness, such as of the temporal artery.

Clinical Features of Migraine

- Prodrome - hours or days ahead
- Commonly begins in morning
- Migraine aura -28%
- HA is gradual onset, dull or throbbing
- 70% unilateral, 30% bifrontal - global
- Cutaneous allodynia – up to 60%
- Autonomic or sinus symptoms – up to 84%
- Worsens with rapid head motion, coughing, sneezing, straining
- Associated with motion sickness as child
- Photophobia, phonophobia

Migraine Aura

- Progressive neurologic deficit, usually visual
- Can be deficit in sensory, motor, or speech
- Develops over 5-20 minutes
- Complete recovery in less than one hour
- Typical zig zag line in center of visual field, gradually progresses to periphery
- HA typically follows aura within 60 minutes
- Can occur without any headache developing

Precipitating Factors

- Emotional stress
- Hormones in women
- Not eating
- Weather
- Sleep disturbances
- Odors
- Neck pain
- Lights
- Alcohol
- Sleeping late
- Heat
- Food
- Exercise
- Sexual activity
- Medications
- Perfumes
- Smoke

Menstrual Migraine

- Due to decrease in estrogen levels
- Not usually associated with aura
- Usually longer, more severe and resistant
- Can be treated prophylactically because can be anticipated

Complications of Migraine

- Chronic migraine (15 d per month)
- Status migrainosus (more than 72 hrs)
- Prolonged aura (1 hr-1 wk)
- Persistent aura without infarction (> 1 wk)
- Infarction (aura > 1 hr + infarct imaging)
- Migraine triggered seizure
**Migraine Variants**

- Hemiplegic migraine
- Familial hemiplegic migraine
- Basilar type migraine
- Ophthalmoplegic migraine
- Retinal (ocular) migraine
- Migraine aura without headache
- Migrainous vertigo

**Use of Neuroimaging**

- Not necessary for most migraine patients
- If used, no data for CT vs. MRI
- Head CT with and without contrast usually
- MRI – if concern for posterior fossa lesion
- Consider imaging if:
  - Unexplained abnormal exam finding
  - Atypical HA features
  - Sudden and severe HA
  - Lack of coordination

**MRI – White Matter Lesions**

- MRI – deep white matter lesions
- Migraine is independent risk factor
- Occurs in migraine with and without aura
- Suspected cause is hypoperfusion and embolism, not atherosclerosis
- Relationship between migraine severity of lesion load
- Unknown whether lesions are functionally relevant long-term

**Approach to Acute Treatment**

- Patient Education
  - Prospective study of migraine education in primary care reduced HA frequency and improved quality of life
- Headache Diary
- Avoid precipitants
- Encourage participation in management
- Migraine specific agents

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1. Kruit MC. JAMA 2004; 291(4)
2. Swartz RH. Arch Neurol. 2004 Sep;61(9)

Mild Analgesics - Evidence for All

- NSAIDS – all may be beneficial, no comparative data
- Acetaminophen – 1000 mg
  - Can be used in combination with NSAIDS
  - Rebound HA, best to not use frequently
- Acetaminophen/ASA/Caffeine (Excedrin)
- Isometheptene/Dichloralphenzone/ Acetaminophen (Midrin)

Acetaminophen vs. Placebo

- Randomized placebo controlled trial,
- Primary care private practice settings
- Dose 1000 mg
- Statistically significant –
  - mild or no pain at 1 hr, 2 hr (p<0.001)
  - Associated sxs (nausea, photophobia, functional disability) at 2 hr, 6 hr (p<0.001)


Triptans “Migraine Specific Treatments”

- Serotonin 1b/1d agonists
- Inhibits release of vasoactive peptides
- Promotes vasoconstriction
- Blocks pain pathways in brainstem
- Inhibits transmission in trigeminal nucleus

7 available Triptans

- Sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan – all oral
- Sumatriptan – also nasal and sq
- Zolmitriptan – also nasal
- Systematic reviews and RPCTs – all are effective
- Few head to head trials
Choice of Triptan

- 17 randomized controlled head to head
- No efficacy data to definitively support one versus another
- If failure with one triptan, reasonable to try other triptans
- Most patients have preference of individual triptan, when asked

Side Effects of Triptans

- Common minor adverse events
  - Chest and neck tightness, paresthesias, flushing, somnolence.
  - Most chest and neck tightness is not caused by coronary vasoconstriction
- Serious cardiovascular events are rare
  - 1 event per 4 million uses.
  - Zero events in cohort of 64,000 users
  - Almost all have CAD RFs

Loder E. NEJM. July 2010

Triptans - Additional Points

- Less effective once cutaneous allodynia has developed – these patients need to take triptans immediately
- Contraindications: uncontrolled HTN, pregnancy, basilar migraine, ischemic stroke/heart disease
- Emerging evidence: combination NSAID + Triptan – higher response, longer duration

Predictors of Response to Triptans

- Time to treatment (prompt)
- Degree of pretreatment pain
- Initial use of adequate dose
**Ergots**

- Dihydroergotamine (DHE 45)
  - Fewer side effects than ergotamine tartate
  - IV, IM, SQ, Intranasal
  - Intranasal:
    - 27% relief within 30 min, 70% within 4 hrs
    - Additional benefit if combine with antiemetic

- Ergotamine tartate
  - Oral or rectal, significant side effects, questionable efficacy. Not a drug of choice.

**Antiemetics**

- If migraine has nausea/vomiting
- Monotherapy
  - Antiemetic and pain relief
- Adjunctive therapy
  - With NSAIDS or any other treatment
- Chlorpromazine, metoclopramide, proclorperazine all effective in RPCTs
- Proclorperazine more effective than metoclopramide

**Preventive Treatment – Key Points**

- 2/3 of patients will have 50% reduction in frequency with most preventive drugs

- Drugs proven high efficacy in clinical trials:
  - Propranolol, metoprolol, timolol, amitriptyline, topiramate, valproate

- Verapamil easy to tolerate and least monitoring, though less data

- Efficacy usually seen starting at 4 weeks

**Beta Blockers**

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>60 mg/d</td>
<td>320 mg/d</td>
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<tr>
<td>Metoprolol</td>
<td>50 mg/d</td>
<td>300 mg/d</td>
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<tr>
<td>Atenolol</td>
<td>50 mg/d</td>
<td>150 mg/d</td>
</tr>
<tr>
<td>Nadolol</td>
<td>40 mg/d</td>
<td>240 mg/d</td>
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### Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Verapamil</td>
<td>120 mg/d</td>
<td>720 mg/d</td>
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<tr>
<td>Diltiazem</td>
<td>60 mg/d</td>
<td>360 mg/d</td>
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<tr>
<td>Nifedipine</td>
<td>30 mg/d</td>
<td>180 mg/d</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>20 mg/d</td>
<td>60 mg/d</td>
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### Tricyclic Antidepressants

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<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Nortriptyline</td>
<td>10 mg/d</td>
<td>125 mg/d</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 mg/d</td>
<td>250 mg/d</td>
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### SSRI and Bupropion

<table>
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<tr>
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<th>Starting Dose</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>10 mg/d</td>
<td>80 mg/d</td>
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<tr>
<td>Paroxetine</td>
<td>10 mg/d</td>
<td>40 mg/d</td>
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<tr>
<td>Sertraline</td>
<td>25 mg/d</td>
<td>200 mg/d</td>
</tr>
<tr>
<td>Bupropion</td>
<td>75 mg/d</td>
<td>300 mg/d</td>
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</table>

### Anticonvulsants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Special Notes</th>
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<tbody>
<tr>
<td>Carbamazapine</td>
<td>100 mg/d - 600 mg TID</td>
<td>Need to monitor CBC, LFTs</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>250 mg BID – 500 mg QID</td>
<td>Need to monitor LFT, teratogenicity</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100 mg TID – 800 mg TID</td>
<td>No blood monitoring needed</td>
</tr>
<tr>
<td>Topirimate</td>
<td>25 mg/d – 100 mg BID</td>
<td>Slow uptitration, wt loss, metab acidosis</td>
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Other Agents for Prevention
- Botulinum toxin
- Magnesium
- Riboflavin
- Coenzyme Q10
- NSAIDS
- Butterbur
- Feverfew

2010 FDA Approves Botulinum Toxin A for Severe Chronic Migraine
- FDA approved October 2010
- Has been being used by headache specialists “off-label”
- PREEMPT trials - two double-blind, placebo-controlled clinical trials involving 1,384 adults from 122 sites

Botox
- Indicated for chronic migraine of 4 hrs/day for 15 days/month
- Effect lasts 3 months
- Primary endpoint of the trials were total number of days with headache at week 24
- Decreased total headache days and hours
- Worsened migraines in 1% - typically in 1st week after injection

Mini-Prophylaxis for Menstrual Migraine
- Start 1-2 days before expected onset
- NSAIDS are first line
Non-Pharmacologic Therapies

- Acupuncture
  - 3 sham controlled trials
- Relaxation training, biofeedback
- Behavioral therapy

Chronic Migraine

- Headache on >15 days/month x at least 3 months
  - For at least 8 days/month x 3 months these meet criteria for migraine without aura
- Some patients with episodic migraine transform to chronic migraine pattern
- High frequency of comorbidities – psychiatric or sleep disorders, fatigue, GI complaints
- First line treatment is same medications used for prophylaxis of episodic migraines

Medication Overuse Headache (Analgesic Rebound HA)

1. Headache present on >15 day/month
2. Regular use for >3 months of 1 or more acute treatment drugs
3. HA developed or worsened during medication overuse

* International Headache Society criteria

Causative Drugs for Medication Overuse HA

- All medications used for acute HA can cause
- Butalbital containing analgesics
- Opioids
- Acetaminophen
- Excedrin – Acetaminophen / ASA / Caffeine
- Risk with triptans is intermediate-high
- Aspirin
- Lowest risk with NSAIDS
Basilar-Type Migraine
- Rare form of migraine with aura
- Primary signs refer to brainstem or both cerebral hemispheres
- Adolescent women - Age of onset 7-20 yo
- Alarming nature of the symptoms
- Strong family history of migraine
- Attacks of aura 5-120 minutes
- Headache within 60 min of aura
- Migraine with typical aura must have already occurred

Basilar Type Aura Symptoms
- Vertigo
- Dysarthria
- Tinnitus
- Diplopia or bilateral visual symptoms
- Bilateral paresthesias
- Decreased level of consciousness, syncope
- Hyperacusis

Differential Diagnosis
- TIA
- Familial or sporadic hemiplegic migraine
- Temporal lobe epilepsy, complex partial
- Basilar aneurysm, subarachnoid hemorrhage
- Meniere’s disease
- Benign positional vertigo
- Psychogenic, behavioral spells

Therapy – Basilar Type Migraine
- No randomized controlled trials
- Triptans are contraindicated
- Antiemetics and non-vasoconstrictors are recommended for acute treatment
- Also recommended to avoid beta blockers and ergot derivatives
- Verapamil recommended for prevention