Update in Headache Management

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- Headache Diagnosis
- Treatment options in migraine
- Treatment of other primary headaches
- Treatment of frequent / refractory headaches
- What’s in the Pipeline
The start of the day, Monday morning

- 42 y/o woman who demanded last week to be seen urgently, and your secretary obliged her. She is 15 min late for the appointment.
- She describes daily severe holocranial headaches for the last 2 years, having seen many physicians “who did not help me at all”.
- She takes 4-6 Fioricet® tabs daily, and an assortment of Excedrin®, acetaminophen, Advil®, and occasional Percocet®.

In early adolescence she began having menstrual headaches with nausea, photophobia, and phonophobia; these persisted into her 30’s but started to increase in frequency in mid 30’s. The headache severity and nausea become “horrible” if “I don’t take my pain pills”.
- She is “allergic” to most medication, and states that several doctors “almost killed me”. (Imitrex caused chest pain e.g.)
- She refuses to take any medication that “will make me fat”
PMH is + for Bipolar disorder ("but I don't think that psychiatrist knew what he was doing"), a history of depression ("I'm fine now if people don't get on my case"). Medical history is otherwise normal.

Her old PCP (whom she has just fired) has given her only enough Fioricet to last til today, and will not prescribe any more.

She is an attorney.

She has “cleared her morning” and “wants to get to the bottom of this”.

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**ICHD Classification - 2013 IHS**

**Primary HA**
1. Migraine
2. Tension-type HA
3. Cluster headaches relatives (TAC)
4. Exertional and other headaches

**Secondary HA**
5. Posttraumatic
6. Vascular disease
7. Abnormal ICP, Neoplasm, Hydrocephalus
8. Substances
9. CNS infection
10. Metabolic
11. Cervicogenic, Eyes, Sinuses, Jaw
12. Psychiatric HA
13. Neuralgias
The primary headaches

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

1.1 Migraine without aura

A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has ≥2 of the following characteristics:
   1. **unilateral location**
   2. **pulsating quality**
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (eg, walking, climbing stairs)
D. During headache ≥1 of the following:
   1. **nausea and/or vomiting**
   2. **photophobia and phonophobia**
E. Not better accounted for by another ICHD-3 diagnosis
1.2 Migraine with aura

A. At least 2 attacks fulfilling criteria B and C
B. ≥1 of the following fully reversible aura symptoms:
   1. visual; 2. sensory; 3. speech and/or language; 4. motor; 5. brainstem; 6. retinal
C. ≥2 of the following 4 characteristics:
   1. ≥1 aura symptom spreads gradually over ≥5 min, and/or ≥2 symptoms occur in succession
   2. each individual aura symptom lasts 5-60 min
   3. ≥1 aura symptom is unilateral
   4. aura accompanied or followed in <60 min by headache
D. Not better accounted for by another ICHD-3 diagnosis, and TIA excluded

1.3 Chronic migraine

A. Headache (TTH-like and/or migraine-like) on ≥15 d/mo for >3 mo and fulfilling criteria B and C
B. In a patient who has had ≥5 attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On ≥8 d/mo for >3 mo fulfilling any of the following:
   1. criteria C and D for 1.1 Migraine without aura
   2. criteria B and C for 1.2 Migraine with aura
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis
2.2 Frequent episodic TTH

A. At least 10 episodes occurring on 1-14 d/mo for >3 mo (\( \geq 12 \) and <180 d/y) and fulfilling criteria B-D
B. Lasting from 30 min to 7 d
C. \( \geq 2 \) of the following 4 characteristics:
   1. bilateral location
   2. pressing or tightening (non-pulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity
D. Both of the following:
   1. no nausea or vomiting
   2. no more than one of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

3. Trigeminal autonomic cephalalgias (TACs)

3.1 Cluster headache
3.2 Paroxysmal hemicrania
3.3 Short-lasting unilateral neuralgiform headache attacks
3.4 Hemicrania continua
TAC’s
- All involve unilateral pain
- Usually peri orbital & brief
- Duration decreases with name length

Cluster
15-180 min

Paroxysmal Hemicrania
2-30 min

Short lasting unilateral neuralgiform headaches
5-240 sec

3.4 Hemicrania continua
A. Unilateral headache fulfilling criteria B-D
B. Present >3 mo, with exacerbations of moderate or greater intensity
C. Either or both of the following:
   1. cranial autonomic activity e.g. ipsilateral symptoms or signs:
      a) conjunctival injection and/or lacrimation; b) nasal congestion and/or rhinorrhoea; c) eyelid oedema; d) forehead and facial sweating; e) forehead and facial flushing; f) sensation of fullness in the ear; g) miosis and/or ptosis
   2. a sense of restlessness or agitation, or aggravation of pain by movement
D. Responds absolutely to therapeutic doses of indomethacin
4. Other primary headache disorders

4.1 Primary cough headache
4.2 Primary exercise headache
4.3 Primary headache associated with sexual activity
4.4 Primary thunderclap headache
4.5 Cold-stimulus headache
4.6 External pressure headache
4.7 Primary stabbing headache
4.8 Nummular headache
4.9 Hypnic headache
4.10 New daily persistent headache (NDPH)

4.3 Primary headache associated with sexual activity

B. Brought on by & occurring only during sexual activity
C. Either or both of the following:
   1. increasing in intensity with increasing sexual excitement
   2. abrupt explosive intensity around orgasm
D. Lasting from 1 min to 24 hr with severe intensity and/or up to 72 hr with mild intensity
4.9 Hypnic headache

A. Dull headache fulfilling criteria B-D
B. Develops only during sleep, and awakens patient
C. At least two of the following characteristics:
   1. occurs > 10 times/mo
   2. lasts ≥15 min after waking
   3. first occurs after age of 50
D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
E. Not attributed to another disorder

4.10 New daily persistent headache (NDPH)

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 h
C. Present for >3 mo
D. Not better accounted for by another ICHD-3 diagnosis
Diagnosing Primary Headaches – The essentials

**Migraine** - unilat, throbbing, female 3:1, nausea, +/- aura

**Tension-type HA** - milder, no nausea, no aura

**Cluster** - Unilateral, male predom, brief, recurring in cycles

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**Analgesic Rebound**
aka Medication overuse headache

- **Definition**: Production of headache by excessive use of analgesics (>2d/wk)

- **Mechanism**: withdrawal, receptor changes, antinociceptive system changes

- **Common causes**: acetaminophen, combination meds, butalbital, opioids, ergots

- Less likely: NSAIDs, triptans
The secondary headaches

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structure
12. Headache attributed to psychiatric disorder

Part 2:
The secondary headaches

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
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8. Headache attributed to a substance or its withdrawal
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11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structure
12. Headache attributed to psychiatric disorder
5.1 Persistent headache attributed to traumatic injury to the head

A. Any headache fulfilling criteria C and D
B. Traumatic injury to the head has occurred
C. Headache is reported to have developed within 7 d after one of the following:
   1. the injury to the head
   2. regaining of consciousness following the injury
   3. discontinuation of medication(s) that impair ability to sense or report headache following the injury
D. Headache persists for >3 mo after injury to the head
E. Not better accounted for by another ICHD-3 diagnosis

5.1 Persistent headache attributed to traumatic injury to the head

- A key component of the post-concussive syndrome
- Can resemble other headache types including migraine
- Resistant to treatment

7.1.1 Headache attributed to IIH

A. Any headache fulfilling criterion C
B. **Idiopathic intracranial hypertension (IIH)** diagnosed, with CSF pressure >250 mm CSF
C. Evidence of causation demonstrated by ≥2 of the following:
   1. headache has developed in temporal relation to IIH, or led to its discovery
   2. headache is relieved by reducing intracranial hypertension
   3. headache is aggravated in temporal relation to increase in intracranial pressure
D. Not better accounted for by another ICHD-3 diagnosis

7.2 Headache attributed to spontaneous low ICP

- A. Any headache fulfilling criterion C
- B. Low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging
- C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
- D. Not better accounted for by another ICHD-III diagnosis.
8.2 Medication-overuse headache (MOH)

A. Headache occurring on ≥15 d/mo in a patient with a pre-existing headache disorder
B. Regular overuse for >3 mo of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-3 diagnosis

Medication Overuse HA

• No particular HA features
• Frequency of HA >15/month
• Requirement for usage frequency:
  * ergotamine, triptan, opioid, comb meds: >10d/mo
  * acetaminophen, ASA, NSAIDs: >15 d/mo
• No requirement for resolution after discontinuation of the causal medication
11.2.1 Cervicogenic headache

A. Any headache fulfilling criterion C
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within cervical spine or soft tissues of neck, known to be able to cause headache
C. Evidence of causation demonstrated by ≥2 of:
   1. headache has developed in temporal relation to onset of cervical disorder or appearance of lesion
   2. headache has significantly improved or resolved in parallel with improvement in or resolution of cervical disorder or lesion
   3. cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
   4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply
D. Not better accounted for by another ICHD-3 diagnosis

Clinical Approach to the HA patient

Goals:

1. Exclude secondary causes of HA
2. Identify co-morbid conditions
3. Think about prevention
4. Find an effective acute treatment
Headache Disorders – History

- Location, frequency, duration, accompaniments
- Age of onset
- Triggers, relieving factors
- Past and current meds
- Drugs, ethanol, nicotine, caffeine intake
- Family hx
- Toxic exposure, sleep pattern
- Neurological and psych symptoms and history

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Headache Dx: Mode of Onset

1. **Chronic Intermittent**
   - migraine, tension-type, cluster
2. **Subacute**
   - neoplasm, hydrocephalus, metabolic
3. **Sudden**
   - subarachnoid hem, dissection

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Sensation
April 1 - April 7

Distress
April 1 - April 7
Average of All Days

[Bar Graph]

[Diagram with Time Periods and Average Values]
Headache Disorders - Exam

- **General** - Vital signs, cardiac, pulmonary

- **Head and Neck** - trauma, carotids, paranasal sinuses, C-spine, occipital and supraorbital n., TMJ, submandibular, funduscopic, otoscopic

- **Neurological** - MS, cranial n, motor, reflexes, sensation, coordination, gait

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Dx Testing in HA

“Well, Bob, it looks like a paper cut, but just to be sure let’s do lots of tests.”
Headache Disorders - Labs

- Blood tests - CBC, lytes, Ca, Mg, BUN, creat, liver enzymes, thyroid, ESR, HIV
- C-spine X-ray, sinus X-rays
- MRI, CT - if red flags
- Lumbar puncture - if suspect
  - 1) Subarachnoid hemorrhage
  - 2) Hi or low intracranial pressure
  - 3) meningitis/encephalitis
- MRA, MRV, CTA, Cerebral arteriography

Secondary Headaches - When to look for them

Red Flags in HA

- New or Change in pattern
- Onset in middle age or later
- Effort induced or Positional
- Febrile or Systemic illness - AIDS, Cancer
- Change in personality or cognition
- Neurological findings
Severe Recurring Headache

Usually Migraine

Migraine pathophysiology

- Step 1 – Cortical spreading depression

https://www.youtube.com/watch?v=yZr9Joe85wg
Migraine pathophysiology

- Step 2 – Trigeminal nerve activation with antidromic release of inflammatory substances in the vicinity of meningeal arteries

Migraine pathophysiology

- Step 3 activation of central trigeminal system and autonomic centers with central sensitization and reactive vasodilation
Migraine pathophysiology: a unified hypothesis

- Targeting any of these steps might help to prevent or relieve HA in migraine, e.g.:
  - Antiepileptics – CSD
  - Triptans – Trigeminovascular activation

Acute Migraine - Tx options

**Non-specific**

NSAIDs

Dopamine antagonists

Opioids
## Acute Migraine - Tx options

### Non-specific

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<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Dosage</th>
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<tr>
<td>Naproxen sodium</td>
<td>Alleve</td>
<td>550 mg po</td>
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<tr>
<td>Indomethacin</td>
<td>Indocin</td>
<td>50 po, pry</td>
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<tr>
<td>Ketorolac</td>
<td>Toradol</td>
<td>30-60 mg IM</td>
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<td>Promethazine</td>
<td>Phenergan</td>
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<td>Prochlorperazine</td>
<td>Compazine</td>
<td>5-10 mg IV, IM</td>
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<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>10-25 mg IV, IM</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Stadol</td>
<td>1 mg nasal</td>
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<tr>
<td>Meperidine</td>
<td>Demerol</td>
<td>50-150 mg IM</td>
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<tr>
<td>Morphine</td>
<td></td>
<td>5-10mg IM, 2-5 IV</td>
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<tr>
<td>Valproate</td>
<td>Depacon</td>
<td>500 mg</td>
</tr>
<tr>
<td>Mg Sulfate</td>
<td></td>
<td>1 g</td>
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### Specific:

- Triptans
- Ergots
## Acute Migraine - Tx options

### Specific:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Trade Name</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Sumatriptan</td>
<td>Imitrex</td>
<td>6mg IM, 20 NS, 50-100 po</td>
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<tr>
<td>Naratriptan</td>
<td>Amerge</td>
<td>2.5 po</td>
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<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>10 mg po</td>
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<td>Zolmitriptan</td>
<td>Zomig</td>
<td>2.5-5 mg po</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Axert</td>
<td>12.5 mg po</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova</td>
<td>2.5 mg po</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax</td>
<td>40-80 mg po</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>DHE-50</td>
<td>1 mg IV, IM</td>
</tr>
<tr>
<td></td>
<td>Migranol</td>
<td>2 mgNS</td>
</tr>
</tbody>
</table>

### Triptans

![Triptan Meds](Image)
Acute Migraine Tx - barriers

- NSAIDS: GI, renal adverse effects
- Dystonia, akathisia
- Tolerance and addiction
- Vasoconstriction
- Contraindications

Common Triptan AE’s and Contraindications

**AEs:**
- Tingling
- Warmth
- Flushing
- Chest discomfort
- Dizziness
- Somnolence
- HA recurrence

**Contraindications**
- Hemiplegic or “basilar Mig”
- Uncontrolled hypertension
- Concomitant use of MAO
- Use within 24 hrs of an ergot
- Pregnancy category C
Triptan concerns

Contraindicated because of their vasoconstrictive effects: Coronary disease, stroke - But they are minimally vasoconstrictive

Contraindicated in hemiplegic migraine and migraine with basilar auras – but these are not due to vasoconstriction

Worrisome for some clinicians due to possible serotonin syndrome in patients on SSRI/SSNI - but evidence is weak; & they are 5HT1B and D agonists and SSS is felt to be due to 5HT1,2A

$28.24 for 9 sumatriptan 100 mg
Choices in Migraine Prophylaxis

- Anticonvulsants – topiramate, valproate
- Beta blockers – propranolol, atenolol
- Cyclic antidepressants – amitriptyline, nortriptiline
- Calcium channel blockers – verapamil, flunarizine
- Angiotensin receptor blockers - candesartan
- ACE inhibitors - lisinopril
- Antispasmodics – baclofen, tizanidine

Choices in Migraine Prophylaxis

- Anticonvulsants – valproate 500-1000 mg
- Beta blockers – propranolol 80-160
- Cyclic antidepressants – nortriptyline 25-75
- Calcium channel blockers – verapamil 120-240
- Angiotensin receptor blockers – candesartan 4-16
- ACE inhibitors – lisinopril 10
- Antispasmodics – baclofen 10-30
Other choices in Migraine Prophylaxis

- B2, Magnesium,
- Feverfew, Butterbur
- Co Q 10
- Melatonin
- Ginger

Non medicinal Tx

Lifestyle adjustment
  - Avoidance of triggers
  - Exercise
  - Sleep regulation
Relaxation techniques
  - Biofeedback, yoga
  - meditation, hypnotherapy
Manual therapies
  - Acupuncture, TENS
Cluster Headache treatment

- **Break cycle**: Prednisone
- **Prophylaxis**:  
  - Calcium channel blockers – Verapimil, Amlodipine
  - Lithium
  - Antiepileptics – Valproate, Lamotrigine
- **Acute treatment**:  
  - Oxygen 8-10 L/min
  - Sumatriptan subcutaneous
  - Occipital nerve blocks

Tension type Headache treatment

- **Prophylaxis**:  
  - Lifestyle
  - Relaxation/manual therapies
  - Cyclic antidepressants
- **Acute treatment**:  
  - Acetaminophen
  - NSAIDs
  - Triptans
  - Manual therapy
Why bother to diagnose if we use the same treatments for all headaches?

Frequent and Refractory Headaches

1. Primary CDH
- Chronic Migraine
- Chronic Tension type headache
- New Daily Persistent Headache
- Hemicrania continua

2. Secondary CDH
- Post-trauma, post infection
- Medication Overuse Headache
- Cervicogenic Headache
**Chronic Migraine (>15/mo)**

- Topiramate
- Other typical prophylactic migraine medications
- Botox
- Nerve blocks
- Inpatient infusion therapies

**Botulinum toxin for Chronic Migraine**

31 injections 5U each in forehead, temples, occiput, neck, trapezius
Repeated every 3 mo
AE’s – facial asymmetry, neck pain
**Chronic HA due to MOH**

- Education of patient and family
- Stopping the offending medications (OTC, prescrip, dietary)
- Designing a “bridge therapy”
- Starting prophylactic meds
- Choosing effective abortive meds

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**Chronic HA due to MOH**

**Bridge therapies in MOH treatment**

- Steroids
- Benzodiazepines
- Clonidine
- Longer acting barbiturates
  - Ratio Phenobarb:butalbital = 30:100
- Caffeine (NoDoz)
- DHE
- NSAIDs
Chronic Daily Headache due to trauma, NDPH etc

- Management strategy is similar to migraine
- Evidence best for
  - Topiramate
  - Amitriptyline
  - Tizanidine
  - Fluoxetine
  - Valproate
  - Gabapentin

New treatment options in Headache

- New forms of triptans & other older meds
- CGRP as a target
- Monoclonal antibodies
- Neurostimulation
- Non-pharmacological and Non-device treatments
New forms of triptans

- Sumatriptan Optinose
- Sumatriptan iontophoretic patch

A new class of triptans – Serotonin 1F receptor blockers

- lasmiditan, the first “ditan”, has clear proof of principle in 2 studies
- It is nonvascular so safer
DHE via inhalation

New forms of NSAIDs

- Diclofenac K in sachet
- Diclofenac suppositories
CGRP and the aim of blocking it in migraine – antagonists and antibodies

Calcitonin gene related protein – a key neurotransmitter in pain
- Elevated CGRP is seen during migraine
- CGRP higher in general in migraine patients
- Injection of CGRP induces migraine

CGRP receptor antagonists
- Telcagepant – abandoned because of liver toxicity
- Olcegaptant – and others, being studied
CGRP antibodies

4 monoclonal antibodies being developed for monthly injection to prevent migraine

- LY2951742 - mAb anti-CGRP - aimed at preventing episodic migraines - Arteaus Therapeutics
- ALD403 – mAb anti CGRP – aimed at preventing episodic migraines - Alder Biopharmaceuticals.
- LBR-101 - fully humanized monoclonal antibody aimed at preventive treatment of chronic migraine. Labrys Biologics
- AMG 334 – an anti GCRP receptor Ab - Amgen

Neural Stimulation for HA

- Transcutaneous supraorbital nerve stim
- Implanted Occipital and Supraorbital stim
- Sphenopalatine ganglion implanted stim
- Surface vagal nerve stim
- Transcutaneous magnetic stimulation
- Deep brain stimulation
Neural Stimulation

“I think I have the placebo.”
The UCSF Headache Center

- Intractable migraine, cluster headaches, post-traumatic headaches and other unusual or difficult headache disorders
- Outpatient treatment
- Inpatient treatment
- Telemedicine
- Research

Interventional treatment of migraine and other headaches

- Face and head nerve blockade
Interventional treatment of headaches

Botulinum toxin

Interventional treatment of Migraine and other headaches

- Non-invasive neural stimulation
Inpatient treatment of refractory headaches

- Intravenous Dihydroergotamine (DHE)
- Intravenous Chlorpromazine
- Intravenous Lidocaine
- Safe discontinuation of pain medications

**Indications**

- Intractable head pain despite appropriate tx
- Significant analgesic rebound
- Serious psychiatric co-morbidity
- Medical illnesses requiring monitoring
- Significant lifestyle stress
Update in Headache Management

- Headache diagnosis
- Treatment options in migraine
- Treatment of other primary headaches
- Treatment of frequent / refractory headaches
- What’s in the Pipeline

Our Headache Case

- 42 y/o woman who demanded last week to be seen urgently, and your secretary obliged her. She is 15 min late for the appointment.
- She describes **daily severe holocranial headaches for the last 2 years**, having seen many physicians “who did not help me at all”.
- She takes 4-6 Fioricet® tabs daily, and an assortment of Excedrin®, acetaminophen, Advil®, and occasional Percocet®.
Our Headache Case

- In early adolescence she began having menstrual headaches with nausea, photophobia, and phonophobia; these persisted into her 30's but started to increase in frequency in mid 30's. The headache severity and nausea become “horrible” if “I don't take my pain pills”.
- She is “allergic” to most medication, and states that several doctors “almost killed me”. (Imitrex caused chest pain e.g.)
- She refuses to take any medication that “will make me fat”

Our Headache Case

- PMH is + for Bipolar disorder (“but I don’t think that psychiatrist knew what he was doing”), a history of depression (“I’m fine now if people don’t get on my case”). Medical history is otherwise normal.
- Her old PCP (whom she has just fired) has given her only enough Fioricet to last til today and will not prescribe any more.
- She is an attorney
- She has “cleared her morning” and “wants to get to the bottom of this”.

Migraine
Headache diagnosis and treatment
An interesting game

UCSF Headache Medicine