Headache: Update and Review

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Disclosures
• Consulting for Allergan, Amgen, Lilly, Supernus
• Royalties from Anadem, Oxford Univ Press, Castle Connolly, Wiley-Blackwell
• Some name brands will be used in addition to generic names of medications

Update in Headache
- Headache diagnosis
- Treatment options in migraine
- Treatment of other primary headaches
- New advances in treating refractory headache disorders

Case 1 - Just so I can function
- 46 year old tech company CEO wanting to establish care with you
- She brings a list of concerns including insomnia, multifocal body aches, anxiety, and daily headaches for the last 2 years
- She takes 4-6 butalbital/acetamin/caffeine (Fioricet®) tabs daily, occasional Norco® (hydrocodone-acetamin) and an assortment of OTCs “...just so I can function”
- “I’ll need prescriptions for all of these”
Case 2 - Help!

- 16 year-old high school student with frequent HAs especially around menses
- Severe nausea along with prolonged throbbing hemicranial headaches are disabling, leading to missing school etc.
- She is on the debate team, lacrosse team, and is taking 3 AP classes, hoping to graduate early and go to Stanford.
- “Help me!”

Case 3 - Limited options

- 66 year-old retired executive describes headaches since his teens, some preceded by visual auras
- Now experiencing head pain to some extent every day and severe headaches 2-3x/wk. Hydrocodone helps “a little”.
- PMH of ulcer disease, coronary artery disease s/p successful stenting, HTN and mild type 2 DM
- “What can I do?”

Diagnosing Headaches

International Classification of Headache Disorders 2018

**Primary HA**
1. Migraine
2. Tension-type HA
3. Cluster headaches relatives (TAC)
4. Exertional and other headaches
International Classification of Headache Disorders 2018

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

1. Migraine without aura
Headache attacks lasting 4-72 h (untreated or unsuccessfully treated)
Headache has ≥2 of the following
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)
During headache ≥1 of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia

1.2 Migraine with aura
≥1 of the following fully reversible aura symptoms:
1. visual; 2. sensory; 3. speech and/or language; 4. motor; 5. brainstem; 6. retinal
≥2 of the following 4 characteristics:
1. ≥1 aura symptom spreads gradually over ≥5 min, and/or ≥2 symptoms occur in succession
2. each aura symptom 5-60 min
3. ≥1 aura symptom is unilateral
4. aura accompanied or followed in <60 min by headache

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. Tension type HA

≥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
Both of the following:
1. no nausea or vomiting
2. no more than one of photophobia or phonophobia

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

3.1 Cluster headache

Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 min
Either or both of the following:
1. ≥1 of the following ipsilateral symptoms or signs:
   a) conjunctival injection and/or lacrimation; b) nasal congestion and/or rhinorrhea; c) eyelid oedema; d) fore-head and facial sweating; e) forehead and facial flushing; f) sensation of ear fullness; g) miosis and/or ptosis
2. a sense of restlessness or agitation
Frequency from 1/2 d to 8/d for > half the time when active

TAC’s:

- Duration decreases with name length

HC
Years
Cluster 15-180 min
Paroxysmal Hemicrania 2-30 min
Short-lasting unilateral neuralgiform headaches 1-600 sec
4. Other primary headaches

Exertional headaches
- Cough headache
- Exercise headache
- Orgasmic headache
- Pre-orgasmic headache
- Thunderclap headache

HA related to stimulation
- HA attributed to cold stimulus
- External compression headache

Epicanias
- Nummular HA
- Epicrania fugax
- Stabbing headache (?)

Other HAs
- Hypnic HA
- New Daily Persistent HA

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

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
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
**Headache attributed to traumatic injury to the head**

- If persistent, a key component of the *post-concussive syndrome*
- Can resemble other headache types including migraine
- Resistant to treatment
- Divided by causative mild or severe head injury

**Headaches due to vascular disorders**

- Stroke
- Hemorrhage
- Arteritis
- Cerebral venous thrombosis
- Reversible cerebral vasoconstriction syndrome
- AVM
- Aneurysm
- Post endarterectomy
- CADASIL
- MELAS

**Reversible Cerebral Vasoconstriction Syndrome**

1. angiography with “strings and beads”
2. Focal subarachnoid hemorrhage
3. Thunderclap headache
4. Triggered by sexual activity, exertion, Valsalva manoeuvres, emotion, bathing and/or showering

**Headache attributed to IIH Pseudotumor Cerebri**

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
**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.

**Intracranial Hypotension**

HA MUCH worse upon arising
Antecedent LP, surgery, barotrauma
CSF pressure <60 mm CSF
Goal - Find the sight of leak and perform targeted blood patch

**IMAGING CLUES TO SIH**

- Brain sag
- Subdural collections
- Dural enhancement

**Cervicogenic headache**

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
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
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

Testing in HA

Secondary Headaches - When to look for them

Red Flags in HA

- Change
- Sick
- Focal

Headache Disorders - labs

- Blood tests - CBC, lites, 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
- Vestibular testing
Migraine Pathophysiology

- **Step 1** – Cortical spreading depression

https://www.youtube.com/watch?v=yZ9iof5yw

- **Step 2** – Trigeminal nerve activation with release of inflammatory substances in the vicinity of meningeal arteries – Substance P, CGRP

- **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

Migraine Treatment
Acute & Prophylactic

Acute Migraine - Tx options

Non-specific

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Naproxen sodium</td>
<td>550 mg po</td>
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<tr>
<td>Indomethacin</td>
<td>50 mg po, pry</td>
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<tr>
<td>Ketorolac</td>
<td>30-60 mg IM</td>
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<tr>
<td>Promethazine</td>
<td>5 mg IM, IV</td>
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<td>Prochlorperazine</td>
<td>5-10 mg IV, IM</td>
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<tr>
<td>Chlorpromazine</td>
<td>10-25 mg IV, IM</td>
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<tr>
<td>Butorphanol</td>
<td>1 mg nasal</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50-150 mg IM</td>
</tr>
<tr>
<td>Morphine</td>
<td>1 mg IM, 2-5 IV</td>
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<tr>
<td>Valproate</td>
<td>500 mg</td>
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<tr>
<td>Mg Sulfate</td>
<td>1 g</td>
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Specific:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Sumatriptan</td>
<td>6 mg IM/20 NS, 50-100 po</td>
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<td>Naratriptan</td>
<td>2.5 po</td>
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<td>Rizatriptan</td>
<td>10 mg po</td>
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<tr>
<td>Zolmitriptan</td>
<td>2.5-5 mg po, 2.5/5 NS</td>
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<tr>
<td>Almotriptan</td>
<td>12.5 mg po</td>
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<tr>
<td>Frovatriptan</td>
<td>2.5 mg po</td>
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<tr>
<td>Eletriptan</td>
<td>40-80 mg po</td>
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</table>

Ergot derivatives - Broad serotonin receptor agonists

<table>
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<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Dihydroergotamine</td>
<td>1 mg IV, IM</td>
</tr>
<tr>
<td>Migranal</td>
<td>2 mg NS</td>
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### Common Triptan AE’s and Contraindications

<table>
<thead>
<tr>
<th>AE</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tingling</td>
<td>Hemiplegic or “basilar Mig”</td>
</tr>
<tr>
<td>Warmth</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Flushing</td>
<td>Concomitant use of MAO</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>Use within 24 hrs of an ergot</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
</tr>
<tr>
<td>HA recurrence</td>
<td></td>
</tr>
</tbody>
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### Triptan concerns

- Contrainindicated 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 SS is felt to be due to 5HT1,2A

### Choices in Migraine Prophylaxis

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

### Choices in Migraine Prophylaxis

- Anticonvulsants – topiramate 100-200 mg
- Beta blockers – propranolol 80-160
- Cyclic antidepressants – nortriptyline 25-75
- Calcium ch blockers – verapamil 120-240
- ARBs– candesartan 4-16
- Memantine -10-20
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
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

New treatment options in Migraine

New forms of triptans
- Sumatriptan breath actuated nasal
A new class of triptans – Serotonin 1F receptor blockers - lasmiditan

**THE LANCET Neurology**
Volume 11, Issue 5, May 2012, Pages 405-413

**Article**
Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study

Prof. Wouter Fakiniks, MD, Prof. Hans-Christian Deen, MD, Prof. Gilles Cansier, MD, Prof. Miguel Llanes, MD, Prof. Juan Schrander, MD, Rafael Hennet, MD, Iñigo Ubaldo, MD, and Luz Sanchez, MD

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Lasmiditan</th>
<th>Triptans</th>
</tr>
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<tbody>
<tr>
<td>Primary Site of Action</td>
<td>Trigeminal Pathway</td>
<td>Blood Vessels</td>
</tr>
<tr>
<td>Receptor</td>
<td>5-HT_{1F}</td>
<td>5-HT_{1B/D}</td>
</tr>
<tr>
<td>CNS Penetrant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Vasodilator</td>
<td>No</td>
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**DHE via inhalation**

Levadex → Semprana inhaled powder

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**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
- Olcegapant – 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, Lilly
- 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 - Teva
- 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

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

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
Case 1 - Just so I can function

- 46 year old tech company CEO wanting to establish care with you
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- PMH of ulcer disease, coronary artery disease s/p successful stenting, HTN and mild type 2 DM
- “What can I do?”

Headache Update in Headache Management

- Headache diagnosis
- Treatment options in migraine
- Treatment of other primary headaches
- New advances in treating refractory headache disorders
Case 1 – *Med Overuse HA*

- Solution = “Bridge Therapy” options
  - Steroid “burst” – prednisone 60 mg x 4 days reducing over the next 6 days
  - IV Dihydroergotamine (DHE) x 5 d
  - IV Chlorpromazine
- Coupled with discontinuation of previous analgesics
- Replacement with rescue meds which are less likely to cause MOH
- Preemptive treatment of withdrawal
Case 1 – *Med Overuse HA*

**Analgesic hierarchy** –
- Opioids (hydrocodone, oxycodone)
- Ergotamine
- Barbiturates (Fioricet®)
- Caffeine containing combination meds (Excedrin®)
- Triptans
- NSAIDS, acetaminophen
- Antihistimincs
Case 1 – *Med Overuse HA*

**Preemptive treatment of withdrawal**
- Opioids – clonidine .1 mg – titrate dose to symptoms
- Barbiturates – lorazepam .5-1 mg on a schedule titrated to withdrawal symptoms
- Triptans – DHE, NSAIDs