Update in Headache Management

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Mo Levin Disclosures
Consulting
Transept
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Oxford Univ Press
Anadem Press
Castle Connolly
Wiley Blackwell

International Classification of Headache Disorders 2013

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

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

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

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 autonomc cephalalgias (TACs)

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) forehead 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

3.2 Paroxysmal hemicrania
Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 min
≥1 of the following ipsilateral symptoms or signs:
1. conjunctival injection and/or lacrimation
2. nasal congestion and/or rhinorrhea
3. eyelid oedema
4. forehead and facial sweating
5. forehead and facial flushing
6. sensation of fullness in the ear
7. miosis and/or ptosis
Frequency >5/d for > half the time
Prevented absolutely by therapeutic doses of indomethacin
3.3 Short-lasting unilateral neuralgiform (SUN) attacks
A. At least 20 attacks fulfilling criteria B-D
B. Moderate or severe unilateral pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting 1-600 s and occurring as single stabs, series of stabs or in a saw-tooth pattern
C. ≥1 of the following ipsilateral cranial autonomic symptoms or signs: 1. conjunctival injection and/or lacrimation; 2. nasal congestion and/or rhinorrhea; 3. eyelid oedema; 4. forehead and facial sweating; 5. forehead and facial flushing; 6. sensation of fullness in the ear; 7. miosis and/or ptosis
D. Frequency ≥1/d for > half the time when active

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 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
Epicranias
Nummular HA
Epicrania fugax
Stabbing headache (?)
Other HAs
Hypnic HA
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

4.10 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, nausea, +/- aura
Tension-type HA - milder, no nausea, no aura
Cluster - Unilaterial, male predom, brief, cyclic

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.

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

Headaches due to medications, toxins and other substances

3 mechanisms:
- Direct effects of substance
- Withdrawal
- Medication overuse

Medication and substances which induce HA:

- Hydralazine
- Isosorbide, Nitroglycerin
- Nifedipine, Enalopril (Vasotec)
- Amantadine, L-Dopa
- Phenothiazines
- Ranitidine, famotidine, cimetidine
- Sildenafil (Viagra; also Levitra, Cialis)
- Trimethoprim-Sulfa, Tetracyclines
- Estrogen, Progesterone, Tamoxifen
- Theophylline
- Pseudoephedrine, sympathomimetics
- Tetracyclines, Trimethoprim
- Indomethacin, NSAIDs
- Cyclophosphamide
- Amphetamines, Cocaine
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.

Clinical Approach to the HA patient

Goals:
1. Exclude secondary causes of HA.
2. Identify co-morbid conditions.
3. Think about prevention.

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

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
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

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

Migraine pathophysiology

- Step 1 - Cortical spreading depression

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

https://www.youtube.com/watch?v=yZ9Jnu85mg
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

<table>
<thead>
<tr>
<th>Non-specific analgesics</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>
<td></td>
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<tr>
<td>Promethazine</td>
<td>Phenergan</td>
<td>5 mg IM, IV</td>
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<tr>
<td>Prochlorperazine</td>
<td>Compazine</td>
<td>5-10 mg IV, IM</td>
<td></td>
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<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>10-25 mg IV, IM</td>
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<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>Valpoate</td>
<td>5-10mg IM, 2-5 IV</td>
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<tr>
<td>Valproate</td>
<td>Depacon</td>
<td>500 mg</td>
<td></td>
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<tr>
<td>Mg Sulfate</td>
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<td>1 g</td>
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Acute Migraine - Tx options

<table>
<thead>
<tr>
<th>Specific migraine agents</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>
<td></td>
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<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>10 mg po</td>
<td></td>
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<tr>
<td>Zolmitriptan</td>
<td>Zomig</td>
<td>2.5-5 mg po</td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Azert</td>
<td>12.5 mg po</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova</td>
<td>2.5 mg po</td>
<td></td>
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<tr>
<td>Eletriptan</td>
<td>Relpax</td>
<td>40-80 mg po</td>
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<tr>
<td>Dihydroergotamine</td>
<td>DHE-50</td>
<td>1 mg IV, IM</td>
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<tr>
<td></td>
<td>Migranol</td>
<td>2 mgNS</td>
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</table>
Common Triptan AE’s and Contraindications

AEs:
- Tingling
- Warmth
- Rushing
- 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.

Acute Migraine Tx - barriers

NSAIDS
- GI, renal adverse effects

DA antag
- Dystonia, akathisia

Opioids
- Tolerance and addiction

Ergot
- Vasoconstriction

Triptans
- Contraindications

Choices in Migraine Prophylaxis

- Anticonvulsants – topiramate, valproate
- Beta blockers – propranolol, atenolol
- Cyclic antidepressants – amitriptyline, nortrip
- Calcium channel blockers – verapamil, flunarizine
- Angiotensin receptor blockers - candesartan
- Antispasmodics – baclofen, tizanidine
**Choices in Migraine Prophylaxis - Good options**

- Anticonvulsants – topiramate 100-200 mg hs
- Beta blockers – propranolol 80 mg bid
- Cyclic antidep – nortriptyline 25-75 mg hs
- Calcium channel bl – verapamil 80 mg tid
- Angiotensin receptor bl – candesartan 4-16 mg

**Other choices in Migraine Prophylaxis**

- B2
- Magnesium,
- Feverfew
- 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 - Verapmil, 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

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, presc rip, dietary)
- Designing a “bridge therapy”
- Starting prophylactic meds
- Choosing effective abortive meds
**Chronic HA due to MOH**

Bridge therapies in MOH tx
- Steroids
- Benzodiazepines
- Clonidine
- Longer acting barbiturates
  - Ratio Phenobarb:butalbital = 30:100
- Caffeine (NoDoz)
- DHE
- NSAIDs

**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 nasal delivery - Onzeta

**New forms of triptans**

- Sumatriptan iontophoresic 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
- 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 - Arteus 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

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
Inpatient Tx of Intractable Primary Headache

**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

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