Diagnosis and Management of Migraine

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Disclosures

- None personally
- I will be discussing off-label treatments for migraine

Objectives

- Diagnostic criteria for migraine
- Overview of pharmacologic treatment for migraine rescue.
- Overview of pharmacologic treatments for migraine prevention.
- Overview of non-pharmacologic treatments.

Introduction

- Migraine is a complex neurological disorder
- Recurrent headaches with other associated symptoms
- More common in women
- 1-2% of global population has chronic migraine
- 2nd most disabling condition worldwide

Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. *Neurol Clin.* 2019 Nov;37(4):631-649. doi: 10.1016/j.ncl.2019.06.001. Epub 2019 Aug 27. PMID: 31563224.

Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache.* 2018 Apr;58(4):496-505. doi: 10.1111/head.13281. Epub 2018 Mar 12. PMID: 29527677.

Migraine without Aura

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  1. unilateral location
  2. pulsating quality
  3. moderate or severe pain intensity
  4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache at least one of the following:
  1. nausea and/or vomiting
  2. photophobia and phonophobia

Source: ichd-3.org

Migraine with Aura

- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
  - 1. visual
  - 2. sensory
  - 3. speech and/or language
  - 4. motor
  - 5. brainstem
  - 6. retinal
- C. At least two of the following four characteristics:
  1. at least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
  2. each individual aura symptom lasts 5-60 min
  3. at least one aura symptom is unilateral
  4. the aura is accompanied, or followed within 60 min, by headache

Source: ichd-3.org

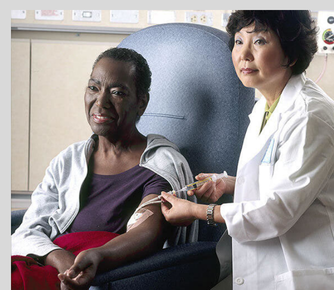
ICHD-3 Classification

- *Chronic Migraine*
- A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C
- B. Occurring in a patient who has had at least five 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 days per month for >3 months, 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

Source: ichd-3.org

Acute Migraine Treatment

- **Non-specific therapy:**
- Acetaminophen
- NSAIDs, including prescription indomethacin, diclofenac, etodolac, etc.
- Combination analgesics Excedrin (acetaminophen/caffeine/aspirin). AVOID butalbital-containing compounds due to risk of medication overuse headaches
- **Anti-emetics:**
- Prochlorperazine (rectal, oral, injectable), metoclopramide (oral or injectable), promethazine (rectal, oral, injectable)
- **Status:** steroid taper, IV cocktails-valproic acid, magnesium, ketorolac, methocarbamol, dexamethasone.



Source: National Cancer Institute

Source: Becker, W. J. (2015) "Acute Migraine Treatment." *Continuum*; 21 (4): 953-972.

Acute Migraine Treatment

- Triptans $(5\text{-HT})_{1B/D}$ agonists.
- **Longer-acting**: frovatriptan, zolmitriptan (pill and nasal spray), naratriptan
- **Shorter-acting**: sumatriptan (pill, nasal powder, injectable, nasal spray), almotriptan, rizatriptan (dissolvable tablet), eletriptan
- **Least side effects**: naratriptan, almotriptan, frovatriptan
- naratriptan/frovatriptan- mini-prophylaxis for menstrual migraine.
- Ergots
- DHE (subcutaneous or nasal spray)

Acute Migraine Treatment

- Lasmiditan (Reyvow)
- Ditans: selective 5-HT_{1F} receptor agonists-**No vasoconstriction**
- 2-hour pain freedom rates were between 28% and 39% at doses of 50 mg, 100 mg, and 200 mg versus 15% for placebo (*P*<.001).

Dosed 50 mg, 100 mg, and 200 mg-once every 24 hours
Schedule V controlled substance.
No driving for 8 hours after the use of Lasmiditan.

Acute Migraine Treatment

- Gepants- CGRP receptor antagonists

Rimegepant (Nurtec)
-Approved for rescue and prevention (every other day)
-Dosing: 75 mg ODT, once a day

Ubrogepant (Ubrelvy)
- Dosing: 50 mg and 100 mg tablets (max dose 200 mg per day)

Zavegepant (Zavzpret)
-Newest gepant –only nasal spray
-Dosing: 10 mg – one spray in one nostril (max dose 10 mg per day)

Acute therapy contraindications

NSAIDs	Cardiovascular, GI, renal disease
Triptans and ergotamines	Stroke, CAD, hemiplegic migraine, migraine with brainstem aura, uncontrolled hypertension
Ditans	Driving restriction for 8 hours after use
Gepants	Medications that use CYP3A4 system: coreg, verapamil, pregnancy

• Ailani, Jessica ,CONTINUUM: Lifelong Learning in Neurology27(3):597-612, June 2021.
doi: 10.1212/CON.0000000000000956

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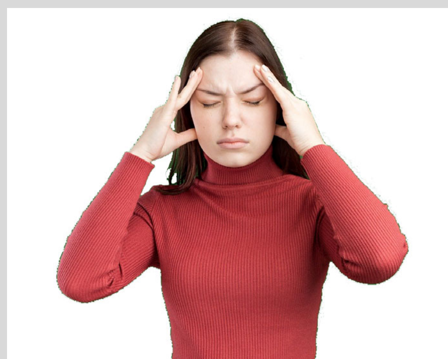
Prophylactic Treatment

- -Should be considered on any patient reporting 4 migraine days per month or less if debilitating
- -Some patients choose to start with lifestyle modifications, supplements.



Prophylactic Treatment

Antiepileptic drugs	Divalproex sodium, topiramate, gabapentin
Antidepressant drugs	TCAs, SNRIs
Beta-blockers	Propranolol, metoprolol, timolol, nadolol
Other antihypertensive drugs	Verapamil, candesartan
Neurotoxins	OnabotulinumtoxinA
Calcitonin gene –related peptide therapies	CGRP mabs, gepants
Other	Memantine, cyproheptadine
Herbal and nutritional supplements	Magnesium, vitamin B12, riboflavin feverfew, coenzyme Q10, melatonin

Prophylactic Treatment

- Level A Evidence: valproic acid, metoprolol, propranolol, topiramate, Botox
- Level B Evidence: amitriptyline, venlafaxine
- Level C Evidence: candesartan, lisinopril, cyproheptadine

Level U Evidence: gabapentin, verapamil

Other: memantine, duloxetine, nortriptyline, pregabalin, keppra

Burch, Rebecca CONTINUUM:Lifelong Learning in Neurology27(3):613-632, June 2021.
doi: 10.1212/CON.0000000000000957

Prophylactic Treatment

- -Consider contraindications and comorbidities when choosing prophylaxis:

Contraindications	Avoid
Hypotension	Antihypertensive drugs
Kidney stones	Topiramate, zonisamide
Possibility of pregnancy	Valproate, topiramate, candesartan, CGRP therapies
Glaucoma	Topiramate, amitriptyline

Prophylactic Treatment

- -Consider contraindications and comorbidities when choosing prophylaxis

Comorbidities	Consider
Insomnia	Amitriptyline, nortriptyline
Anxiety	Beta-blockers, SNRI
Depression	SNRIs
Hypertension	Beta blockers, candesartan
Obesity	topiramate
Frequent aura	Verapamil, memantine, magnesium, lamotrigine, topiramate, valproate

Prophylactic Treatment

- OnabotulinumtoxinA- Botox
- -FDA approved for chronic migraine in 2010
- -155 units every 3 months- PREEMPT protocol.

Source: Marco Verch Professional Photographer

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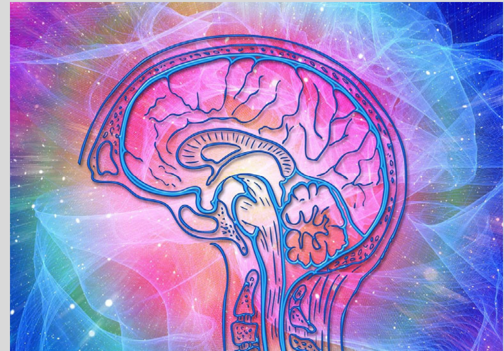
CGRP monoclonal antibodies

- **Erenumab** (*Aimovig*)-targets the receptor, most side effects- hypertension, constipation, two doses 70 mg and 140 mg.
- **Galcanezumab** (*Emgality*) –loading dose (two shots the first month) also approved for cluster headache.
- **Fremanezumab** (*Ajovy*)- can be given every 3 months
- **Eptinezumab** (*Vyepti)*-only infusion, every 3 months, usually after other treatments have failed, two doses 100 mg and 300 mg.

Gepant for prevention

- **Atogepant** (*Qulipta*)
- -Daily oral preventative treatment: 10 mg, 30 mg, 60 mg
- -Most common side effects: nausea, constipation, fatigue.
- -strong CYP3A4 inhibitors :10 mg daily
- -avoid use in patients with severe hepatic impairment
- -Approved now for chronic and episodic migraine

Neuromodulation



- **Remote Electrical Stimulation:**
- Nerivio
- -approved for rescue, age 12 and above, covered by some insurances

  Non-invasive Vagus Nerve Stimulation:
- Gammacore
- -rescue and prevention

- **Supraorbital nerve stimulation :**
- Cefaly, prevention and rescue

- **Combined supraorbital and occipital stimulation** (Relivion MG)
- -acute therapy

Other treatments

Level A Evidence for: Biofeedback (EMG and thermal combined with relaxation training)

-Cognitive behavioral therapy

-Cervical physical therapy

-Acupuncture

General Pearls

- Headache lifestyle is very important: keep caffeine intake steady, hydration, exercise, sleep, regular meals, mood.
- Many patients, especially with chronic migraine for many years, may require a multidisciplinary approach including physicians, physical therapy, and psychologists.

Other Primary Headache Disorders

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Disclosures

- Dr. Weber receives research funding through Lundbeck and Lilly
- The Headache Division receives fellowship funding through Abbvie.
- Lots of off label uses for medications. Few FDA approved medications for these disorders.

Tension type headache

- Last 30 minutes-7 days
- Typically bilateral, band-like, mild-moderate, and devoid of migraine features like photo/phonophobia or nausea/vomiting.
- Most common type of headache, ranging from 30-78% of the population depending on the study
- Treated with NSAIDs, muscle relaxers, amitriptyline, topiramate.

Source: ICHD-3.org

Trigeminal Autonomic Cephalgias

- Cluster headache
  - Chronic and episodic
- Paroxysmal hemicrania and Hemicrania continua
- Short unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT) or short unilateral neuralgiform headaches with autonomic features (SUNA)
  - All SUNCTs are SUNAs, but not all SUNAs are SUNCTs!

Case

- 53 yo M, presents to you after seeing two neurologists before
- Every few months, he will get 4-10 weeks of severe daily headaches, multiple times per day.
- Then they disappear!
- Attacks have ipsilateral (to pain) conjunctival injection, tearing, rhinorrhea, ptosis. They last about 20 minutes each. Usually at least one wakes him up at 3 AM
- SEVERE pain. He wants to pace, has thought about slamming his hand into a drawer during attacks to distract from it
- Alcohol worsens symptoms

Case

- Other history: no family history of these headaches. Mom had migraines “nothing like this.”
- Smoker
- He is a contractor.
- Exam is normal.
- Doesn’t think he’s had MRI. Other docs “gave me amitriptyline and Imitrex (sumatriptan), I think. They didn’t help.”
- Differential? Diagnostic workup?

Episodic Cluster HA (ICHD-3)

1. At least five attacks fulfilling criteria B-D
2. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)
3. Either or both of the following:
    1. at least one of the following symptoms or signs, ipsilateral to the headache:
        1. – conjunctival injection and/or lacrimation
        2. – nasal congestion and/or rhinorrhoea
        3. – eyelid oedema
        4. – forehead and facial sweating
        5. – miosis and/or ptosis
    2. a sense of restlessness or agitation
4. Occurring with a frequency between one every other day and 8 per day

Chronic Cluster (ICHD-3)

- Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year.
- Episodic (ICHD-3): At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months.

Paroxysmal Hemicrania (ICHD-3)

1. At least 20 attacks fulfilling criteria B-E
2. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes
3. Either or both of the following:
    1. at least one of the following symptoms or signs, ipsilateral to the headache:
        1. – conjunctival injection and/or lacrimation
        2. – nasal congestion and/or rhinorrhoea
        3. – eyelid oedema
        4. – forehead and facial sweating
        5. – miosis and/or ptosis
    2. a sense of restlessness or agitation
4. Occurring with a frequency of >5 per day
5. Prevented absolutely by therapeutic doses of indomethacin

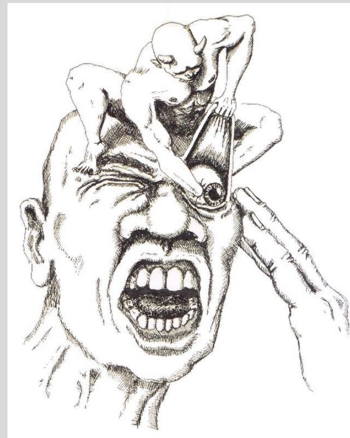
Hemicrania Continua (ICHD-3)

1. Unilateral headache fulfilling criteria B-D
2. Present for >3 months, with exacerbations of moderate or greater intensity
3. Either or both of the following:
    1. at least one of the following symptoms or signs, ipsilateral to the headache:
        1. – conjunctival injection and/or lacrimation
        2. – nasal congestion and/or rhinorrhoea
        3. – eyelid oedema
        4. – forehead and facial sweating
        5. – >miosis and/or ptosis
    2. a sense of restlessness or agitation, or aggravation of the pain by movement
4. Responds absolutely to therapeutic doses of indomethacin

SUNCT/SUNA (ICHD-3)

1. At least 20 attacks fulfilling criteria B–D
2. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern
3. At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:
    1. conjunctival injection and/or lacrimation
    2. nasal congestion and/or rhinorrhoea
    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
4. Occurring with a frequency of at least one a day

Case



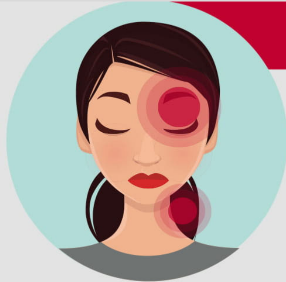
Source: Wikimedia

Case

- Attacks could be cluster OR paroxysmal hemicrania
- Why likely cluster?
- Ask the patient about circadian rhythmicity
- US Cluster Headache Survey:
  - 21% got correct diagnosis at initial presentation
  - 42% took greater than 5 years
  - Migraine was most common incorrect diagnosis

Source: Rozen T and Fishman RS. "Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden." *Headache.* 2012 Jan;52(1):99-113.

Case



CLUSTER HEADACHES

- Excruciating pain behind or around one eye, possibly radiating to other areas of face, head, neck
- Pain on one side of the head/face
- Watering eyes, swelling and/or drooping lid on affected eye
- Eye redness, stuffy or runny nose, sweating on affected side
- Pale or flushed face

Source: OSUWMC

Case

- How to treat the patient?
- Induce remission:
  - Prednisone
  - Ipsilateral occipital nerve block – with steroids
  - Verapamil +/- topiramate
  - Depakote
  - Lithium
  - Melatonin
  - Kudzu
  - Galcanezumab

CGRP Episodic Data - galcanezumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Galcanezumab in Prevention of Episodic Cluster Headache

Peter J. Goadsby, M.D., Ph.D., David W. Dodick, M.D., Massimo Leone, M.D., Jennifer N. Bardos, Pharm.D., Tina M. Oakes, Ph.D., Brian A. Millen, Ph.D., Chunmei Zhou, M.S., Sherie A. Dowsett, Ph.D., Sheena K. Aurora, M.D., Andrew H. Ahn, M.D., Ph.D., Jyun-Yan Yang, M.D., Robert R. Conley, M.D., and James M. Martinez, M.D.

CGRP Episodic Data - galcanezumab

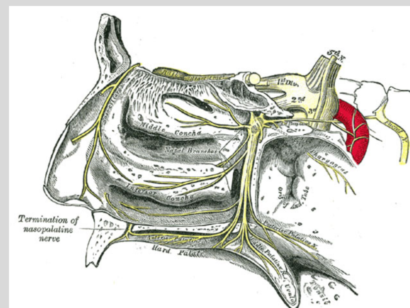
- Mean frequency of cluster attack reduction was -8.7 in treatment group vs. 5.2 in placebo group, $p = 0.04$ in weeks 1-3

Acute Cluster Treatment

- Sumatriptan nasal spray/powder or injection
- DHE injection or nasal spray
- Zolmitriptan nasal spray
- O2
  - Not covered by CMS – ongoing controversy and battle
- Octreotide
- Non-invasive Vagal Nerve Stimulation (FDA approved!)
  - Works for episodic cluster for rescue treatment
  - Works for chronic cluster for prevention treatment

SPG (Sphenopalatine Ganglion) Stimulation

- Promising data
  - Chronic and episodic
  - Prophylaxis and abortive
  - Company went under
- Role for SPG blocks?
- Intranasal lidocaine?



Source: Wikimedia

Treatment for Other TACs

- Paroxysmal hemicrania/Hemicrania continua
  - Indomethacin
  - onabotulinumtoxinA, occipital nerve blocks, gabapentin, melatonin, topiramate
  - Non-invasive Vagal nerve stimulation (FDA Approved!)
- SUNCT/SUNA
  - Lamotrigine
  - Lacosamide? Gabapentin, topiramate, oxcarbazepine, carbamazepine, occipital nerve block
  - For status SUNCT, use lidocaine drip.

Primary Cough Headache (ICHD-3)

1. At least two headache episodes fulfilling criteria B
2. Brought on by and occurring only in association with coughing, straining and/or other Valsalva manœuvre
3. Sudden onset
4. Lasting between 1 second and 2 hours

Primary Cough Headache

- Occur in older patients
- Treat with indomethacin, acetazolamide
- Must image with MRI

Source: Pixabay

Exercise/Sex Headaches (ICHD-3)

1. At least two episodes of pain in the head and/or neck fulfilling criteria B-D
2. Brought on by and occurring only during sexual activity
3. Either or both of the following:
    1. increasing in intensity with increasing sexual excitement
    2. abrupt explosive intensity just before or with orgasm
4. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity

Exercise/Sex Headaches

- MRI/MRA
- Try indomethacin/NSAIDS prior to activity, scheduled if bothersome
  - Can taper after a few months to see if resolved
- Propranolol also an option for prophylaxis

Nummular Headache (ICHD-3)

1. Continuous or intermittent head pain fulfilling criterion B
2. Felt exclusively in an area of the scalp, with all of the following four characteristics:
   1. sharply-contoured
   2. fixed in size and shape
   3. round or elliptical
   4. 1-6 cm in diameter

Nummular Headache

- Tough to treat
- We try indomethacin, melatonin, all the migraine meds, neuropathic pain meds, botox, trigger points

Source: Pixabay

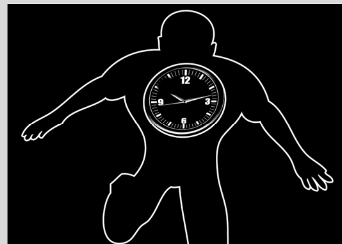
Primary stabbing headache

- "stabs and jabs"
- Treat with indomethacin, gabapentin, melatonin
- Definition (ICHD-3):

1. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B and C
2. Each stab lasts for up to a few seconds
3. Stabs recur with irregular frequency, from one to many per day
4. No cranial autonomic symptoms

Hypnic Headache (ICHD-3)

1. Recurrent headache attacks fulfilling criteria B-E
2. Developing only during sleep, and causing wakening
3. Occurring on ≥10 days/month for >3 months
4. Lasting from 15 minutes up to 4 hours after waking
5. No cranial autonomic symptoms or restlessness



Source: Pixabay

Hypnic Headache

- Older folks
- Caffeine before bedtime first line treatment!
- Can try lithium, gabapentin, melatonin
- Notorious difficult to treat, like nummular headache and…

New Daily Persistent Headache (NDPH)

Source: Pixabay

NDPH (ICHD-3)

1. Persistent headache fulfilling criteria B and C
2. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours
3. Present for >3 months

NDPH

- Sometimes there is a precipitant, like trauma (but then wouldn't it's be post-traumatic headache too?), or infection. Other times no cause is known
- Sometimes lasts for months-years. Typically "peters out" as I tell patients
- Treatment is typically treating like the headache type it resembles (usually migraine)
- One study (presented as poster at a conference): doxycycline 100 mg and montelukast 10 mg, dosed BID for 3 months
  - Doxy and montelukast = TNF-α inhibition?

Source: Rozen T and Swidan SZ. "Elevation of CSF tumor necrosis factor alpha levels in new daily persistent headache and treatment refractory chronic migraine." *Headache*. 2007 Jul-Aug;47(7):1050-5.

Other Disorders

- Cold-stimulus headache
- External Compression Headache
- Primary Thunderclap Headache
  - Really have to exclude aneurysm/SAH, RCVS, to lesser extent vasculitis with this
  - Usually get MRI/MRA, and even tap, sometimes angio
  - Controversy over whether this is even really a primary disorder