Treatment of refractory migraines – what to do when "nothing works"

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Lecture outline

- 1. Re-evaluate the diagnosis
- 2. Explore hidden triggers and contributing factors
- 3. Consider trying multiple drugs in each category
- 4. Try uncommon medications, daily triptans
- 5. Magnesium and other supplements
- 6. Address psychological factors
- 7. Neurostimulation
- 8. Never give up and always maintain hope

1. Re-evaluate the diagnosis

- Hemicrania continua (can occur without autonomic symptoms)
- High and low intracranial pressure
- Chiari malformation, hydrocephalus, cysts – can enlarge over time
- Benign tumors (meningioma, pituitary adenoma, osteoma, chondroma, schwannoma)
- Nerve entrapment (supraorbital, supratrochlear, occipital, etc.)
- Never diagnose *New Daily Persistent Headache*. It has no physiological basis and causes harm by making patients despondent. Instead, use *Chronic Migraine* or *Chronic Tension-Type Headache*
- Diagnose MOH mostly due to caffeine and opioids

Re-evaluate the diagnosis

27 y.o. woman; 8 years of chronic debilitating headaches.
Pain (7/10) is most frequent in the frontal area; pressure-like and sharp.
Has nausea, photophobia, and phonophobia. Triggers: weather changes, menses, and stress. No response to sumatriptan, eletriptan, rimegepant, ubrogepant, butalbital.
Sinus CT from 04/25/2022 - large osteoma obstructing both frontal sinuses and the left anterior ethmoid sinus. No surgery was offered. A year later, had a second opinion, surgery done, headaches improved.

Re-evaluate the diagnosis

A. B. is a 32-year-old man with headaches of 17 years in duration, daily for the past 5 years. Frontal in location, moderate in intensity, non-pulsatile, not associated with nausea, photo- or phonophobia. Pain-free upon awakening; headache starts in the afternoon. He has tried NSAIDs, nortriptyline, venlafaxine, beta blockers, verapamil, topiramate, gabapentin, Botox, erenumab, fremanezumab,.

No depression, but has chronic anxiety for which he had seen a psychiatrist.

Works full time and lives with his wife and 15-month-old daughter.

FH: Positive for headaches in a grandfather

Re-evaluate the diagnosis

A.B. reports that sumatriptan, 100 mg works very well for the entire day and without side effects.

He receives only 12 tablets a month as his physician does not want to cause medication overuse headache

One should not use the therapeutic response as a diagnostic tool (except for indomethacin-sensitive headaches), but do consider migraine drugs for any type of headache and facial pain

Re-evaluate the diagnosis (MOH)

- Opiates are associated with migraine progression;

  critical dose of exposure is around 8 days per month
- Barbiturates are associated with migraine progression. Critical dose of exposure is 5 days per month (what's the role of caffeine?)
- Triptans induced migraine progression in those with high frequency of migraine at baseline (10–14 days per month), but not overall
- NSAIDs were protective in those with <10 days of headache at baseline, and induced migraine progression in those with high frequency of headaches
- Specific classes of medications are associated with migraine progression, and *high frequency of headaches seems to be a risk factor for chronic migraine regardless of medication exposure*.

Bigal et al. *Headache* 2008;48(8):1157-1168

Re-evaluate the diagnosis (MOH)

- Most studies documenting MOH are observational, i.e. correlation does not mean causation
- Few withdrawal studies have control groups
- Withdrawal from an overused drug is only one aspect of the doctor-patient interaction; other aspects could be more crucial
- Patients are often left to suffer and are blamed for their headaches if they cannot stop the drug

Never diagnose NDPH

NDPH Is Not a Distinct Entity

- A headache that begins on a specific day and persists without interruption; may have migraine or tension-type features
- No parallel exists in medicine — there is no "new daily persistent" form of any other disease
- London study (n = 162): 90% had chronic migraine, 9% tension-type headache — authors argued it is "time to retire" the diagnosis
- Houston study (n = 328): 79% had a migraine phenotype
- A 2025 study of 30 inflammatory blood markers found no differences between NDPH and chronic migraine

Never diagnose NDPH

Why the Label Causes Harm

- Has not led to any specific research or treatment
- Internet searches yield no effective treatment, amplifying hopelessness and depression
- May discourage clinicians from pursuing migraine treatments, which often help

Don't Miss CSF Leak

- Spontaneous CSF leak can mimic NDPH (not always positional)
- May require digital subtraction myelography or CT myelography
- Epidural blood patch or surgical repair can be curative

2. Explore hidden triggers and contributing factors

- Magnesium, CoQ_{10}, Vitamin D, B1, B2, B6, and B_{12} deficiency (measure levels; for magnesium – RBC magnesium level)
- Anemia and iron deficiency
- Underactive thyroid
- Caffeine
- Medications
- Mercury (if high tuna/swordfish consumption)
- Weight gain
- Restless leg syndrome, sleep apnea
- Nerve entrapments, nasal septum contact point

3. Consider trying multiple drugs within each category

- Triptans: try all seven if there is a partial response or AEs
- Beta-blockers: nebivolol, atenolol, timolol, metoprolol
- ACE inhibitors/ARBs: candesartan, lisinopril, losartan, olmesartan,
- Epilepsy drugs: lamotrigine, levetiracetam, pregabalin, lacosamide
- Antidepressants: mirtazapine, desvenlafaxine, phenelzine
- CGRP mAbs: try all four
- Gepants: try all four (rimegepant, ubrogepant, zavegepant, atogepant)
- NSAIDs: meloxicam, celecoxib, mefenamic acid, indomethacin

3. Consider trying multiple drugs within each category

"For over fifty years, I have had migraines. I tried every kind of medicine, and I mean EVERY. Nothing worked, and I just figured this was the way it would be until I died.

This summer, my hand was hurting and the doctor prescribed Celebrex). It did not help my hand, but my migraines WENT AWAY!!! Yes, after 50 some-odd years, no migraines. I thought it was a fluke, but no… my migraines are gone.
I take a Celebrex every morning after breakfast. If I even start to feel a headache, I take 2 Advil, and the headache is gone for the day. Every once in a while, I do get a migraine and I will take sumatriptan, but it is rare."

4. Uncommon medications

- Daily triptan, for acute or prophylactic therapy
- Metformin; GLP-1s semaglutide, dulaglutide,
- Aripiprazole (if anxiety, depression, or insomnia)
- Memantine (with magnesium)
- Ketamine (IV, nasal, oral)
- Lidocaine (IV, IA)
- Clonidine
- Acetazolamide, especially when the weather is a trigger
- Opioids (if no: psych hx, prior addictions, fam hx; sign a contract)
- Suzetrigine (Journavx)

Triptan safety

Consensus Statement: Cardiovascular Safety Profile of Triptans ($5\text{-}HT_{1B/1D}$ Agonists) in the Acute Treatment of Migraine.

Dodick D, Lipton RB, et al. *Headache* 2004;44(5)414-425.

"The incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low "

Long-term daily intake (acute or prophylactic) of a triptan is probably safer than taking topiramate, divalproex sodium, amitriptyline, and other prophylactic migraine drugs.

Triptan safety

Risk of Acute Myocardial Infarction, Heart Failure, and Death in Migraine Patients Treated with Triptans

- Ghanshani S, et al. *Headache* 2020;60:2166-2175

189,684 patients age ≥18 years had a diagnosis of migraine.

130,656 were exposed to triptans.

No association was found between exposure to triptans and an increased risk of cardiovascular events

Triptan safety

Presentation at the AHS meeting in 2022

- Mass General Brigham Research Patient Data Registry database
- The risk of major adverse cardiovascular events (MACE) in patients with preexisting cardiovascular (CV) conditions.
- 12,121 prescriptions: 33% for triptans, 17% for NSAIDs, 50% for opioid/barbiturates
- MACE occurred in 1% of those taking triptans, 3.8% taking NSAIDs and 4.5% taking opioid/barbiturates

Triptans

Practical issues

- Maximum single dose
  - Why rizatriptan can be taken 3 times a day, while others, 2?
  - Eletriptan, 20 or 40 mg; in some countries, 80 mg, up to twice a day
  - Naratriptan, 10 mg SC – 88% pain-free at 2 hrs, suma 6 mg – 55%
- Maximum daily, weekly, monthly dose – don't set arbitrary limits
- Mixing triptans is OK (Rothrock, 2011)
- Cost

  Sumatriptan, rizatriptan, eletriptan, naratriptan – about $.60 a pill

Medication overuse headache is a myth

Medication overuse headache: An entrenched idea in need of scrutiny

Scher AI, Rizzoli PB, Loder EW *Neurology* 2017; 89 (12):1296-1304

"These findings raise serious questions about the value of withholding or withdrawing symptom-relieving medications from people with frequent headaches solely to prevent or treat MOH. The benefits of doing so are smaller, and the harms larger, than currently recognized. The concept of MOH should be viewed with more skepticism. Until the evidence is better, we should avoid dogmatism about the use of symptomatic medication. Frequent use of symptom-relieving headache medications should be viewed more neutrally, as an indicator of poorly controlled headaches, and not invariably a cause."

5. Magnesium and other supplements

- Magnesium
- CoQ10
- B12, B2 and other B vitamins
- Boswellia
- Vitamin D
- Feverfew
- Butterbur (Petadolex brand, not cheap substitutes)
- Exogenous ketones (BrainRitual)
- Palmitoylethanolamide (PEA) 600 mg BID

Magnesium and migraine

Known effects of IMg^{2+}

- glutamate
- angiotensin II
- potassium
- serotonin
- G proteins
- CGRP
- acetylcholine
- nitric oxide
- norepinephrine
- calcium
- enzyme complexes (325)

Magnesium and migraine

Potential causes of magnesium deficiency

- Stress
- Alcohol & caffeine
- Genetics of absorption and renal excretion
- Low dietary intake
- Gastro-intestinal disorders (IBS, colitis, celiac)
- Chronic illness

Magnesium and migraine
Practical considerations

Clinical symptoms of hypomagnesemia

- Headaches
- Leg and other muscle cramps
- Coldness of extremities or body
- PMS
- Palpitations
- Mental fog
- Irritability, depression

Magnesium and migraine
Practical considerations

Oral supplementation

- Start with 400 mg of magnesium glycinate or another chelate
- If not tolerated, try other magnesium salts
- If tolerated but ineffective, consider increasing the dose to 400 mg BID – TID; always with food

Intravenous magnesium

- One gram of magnesium sulfate in 10 cc's of saline, over 5 minutes
- IV push may be more effective than IV drip

Coenzyme Q_{10}

Efficacy of coenzyme Q_{10} in migraine prophylaxis: A randomized controlled trial

P. S. Sándor, L. Di Clemente, G. Coppola *Neurology* 2005;64:713-715

Double-blind, randomized, placebo-controlled trial

42 patients; CoQ_{10} 100 mg TID vs placebo

50% responder rate for attack frequency

14.4% for placebo and 47.6% for CoQ_{10}

Coenzyme Q_{10}

Coenzyme Q_{10} deficiency and response to supplementation in pediatric and adolescent migraine

Hershey AD, et al. *Headache* 2007;47:73-80

- 1550 patients – 32.9% deficient
- Supplementation with 1-3 mg/kg/day
- CoQ_{10} levels improved, $p<.0001$
- HA frequency improved from 19.2 to 12.5, $p<.001$
- HA disability improved from 47.4 to 22.8, $p<.001$

Neurostimulation

- Peripheral nerve stimulation (PNS)
  - Cefaly
  - Nerivio
  - Electroacupuncture
  - Implanted peripheral nerve stimulators
- Vagus nerve stimulation (VNS)
  - gammaCore, Truvaga, Pulsetto, Implanted - SetPoint
- Transcranial magnetic stimulation (TMS)
  - Single pulse (eNeura)
  - Repetitive (rTMS)

A. Mauskop, NY Headache Center

6. Psychological factors

- Severe anxiety and catastrophizing

    Explore family conflicts

- Personality disorder

    “Nobody could help me, but I know that you will”

    Dialectical-behavioral therapy

- PTSD

Psychological factors: PTSD

- Childhood abuse or neglect was reported by 58% of 1,348 migraine sufferers (G.E. Titjen et al.)
- Soldiers with PTSD had twice as many headaches as soldiers without PTSD (J.F. Rosenthal et al.)
- 8.8 percent of head-injured patients met the criteria for PTSD compared with only 2.2 percent of control patients three months after the injury. (E. Lagarde et al.)

Ideally, refer to a psychologist specializing in trauma therapy

Psychological factors: PTSD

Screening questions for PTSD:

If you suffered a traumatic event (car accident, major injury or illness, physical, emotional, or sexual abuse), do you:

- Have nightmares or unwanted thoughts about the event
- Try to avoid reminders of it
- Are you constantly on guard or easily startled
- Do you feel numb or detached from people or activities
- Do you feel guilty or blame yourself for the event

Psychological factors: PTSD

Explain to patients that PTSD is more of a physiological rather than a psychological problem.

"You are stuck in a fight-or-flight response. This leads to what psychologists call hypervigilance. Your brain cells are "wound up" and are always ready to fire. This is why patients with one type of pain often develop another type of pain. Those with chronic migraines are more likely to develop back pain, stomach pains (IBS), or diffuse muscle pains (fibromyalgia). Your brain is hypersensitive.

This is why epilepsy drugs can be helpful – they reduce the excitability of your neurons. Antidepressants can also calm you and your brain. Trauma therapy with a psychologist is often the most important component."

Psychological factors: Interventions

- Meditation and biofeedback
- Cognitive-behavioral therapy (CBT)
- Dialectical-behavioral therapy (DBT)
- Acceptance and commitment therapy (ACT)
- Pain reprocessing therapy (PRT)
- Drugs

ThisWayUp.org.au – Validated self-administered CBT courses on Chronic Pain, Depression, Generalized Anxiety, Health Anxiety, PTSD, Insomnia, Panic, etc.

8. Never give up and always maintain hope!

Just as man cannot live without dreams, he cannot live without hope
--*Elie Wiesel*

To live without hope is to cease to live
--*Fyodor Dostoyevsky*

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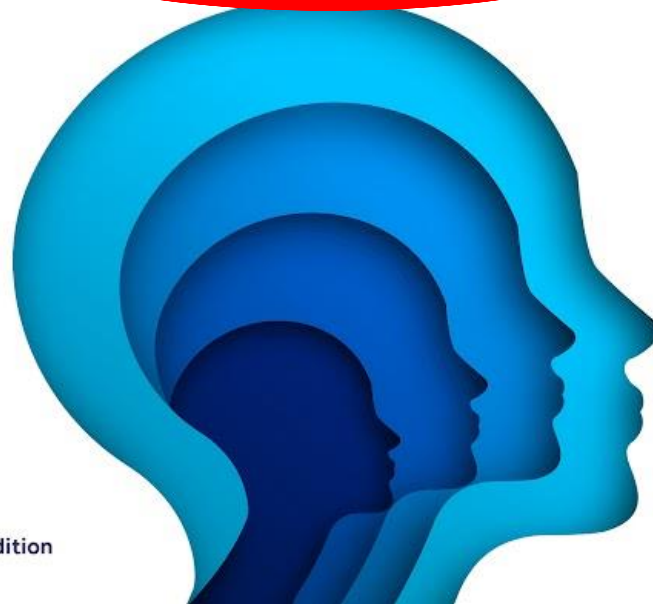
"This comprehensive, accessible and dynamic manual for understanding and managing migraine is a *tour de force*."
John F. Rothrock, MD
Professor of Neurology, The George Washington University School of Medicine

THE END OF MIGRAINES

150 WAYS TO STOP YOUR PAIN



2nd Edition

Summary

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