Colorado Pain Society Annual Meeting

Refractory chronic migraine (RCM)

A headache clinic perspective

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Disclosures

Advisory board for Abbvie, 2022

Objectives

Definitions: chronic migraine (CM) and refractory chronic migraine

Potential factors involved in CM refractoriness

Explore therapeutic approaches

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Potential factors involved in CM refractoriness

Explore therapeutic approaches

Migraine: 6th most common disease on the planet and 2nd most disabling

GBD 2016. Lancet 2017

What is migraine?

A chronic disease with episodic attacks

(CDEA)

Episodic migraine without aura (MOA)

A. At least 5 episodes of headache with features below

B. Lasts 4-72 hours; occur $<$ 15 days/month

C. Headache has $\geq$ 2:

   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity

D. During headache at least one:

   1. Nausea or vomiting
   2. Photophobia and phonophobia

E. Not attributed to another disorder

ICHD 3, Cephalalgia, 2018

Chronic migraine (CM)

Headache (TTH-like and/or migraine-like) on > 4 h/day, ≥15 d/mo for >3 mo and:

In a patient who has had ≥5 attacks fulfilling criteria for Migraine without aura and/or criteria for Migraine with aura

On ≥8 d/mo for >3 mo fulfilling any of the following:

1. criteria for Migraine
2. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

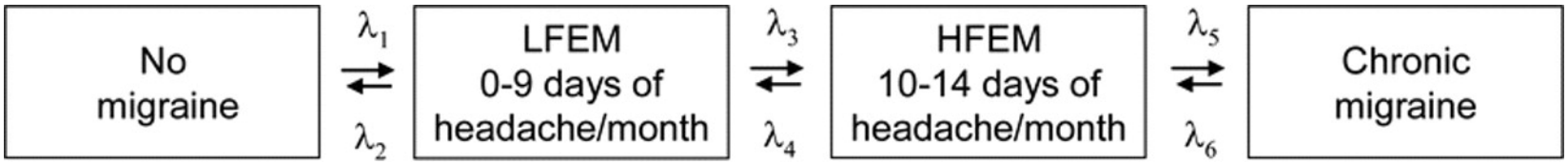
Not better accounted for by another ICHD-3 diagnosis

ICHD 3, Cephalalgia, 2018

Conceptual framework for transitions in migraine

Nonmodifiable- age, female gender, white race, low educational level/socioeconomic status, and genetic factors.

Modifiable: attack frequency, suboptimal treatment of attacks*, obesity, analgesics overuse, caffeine overuse, sleep apnea, psychiatric comorbidities*, stressful life events



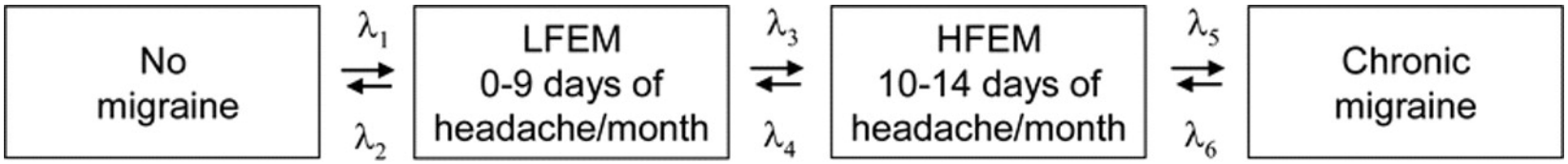
Effective abortive and preventive therapy
Weight loss
Detoxification
CPAP
Stress management/Behavioral treatments
Decrease caffeine intake
Treatment of other chronic pain

Bigal and Lipton, Neurology 2008

Conceptual framework for transitions in migraine

- Clinical transformation

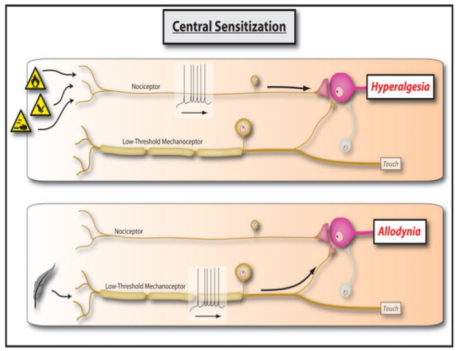
λ1: genetic or environmental



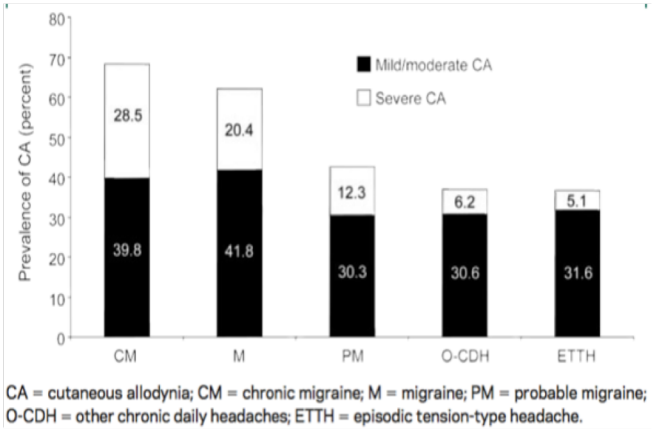
λ2: older, male, menopause

Bigal and Lipton, Neurology 2008

- Physiological transformation: **allodynia**



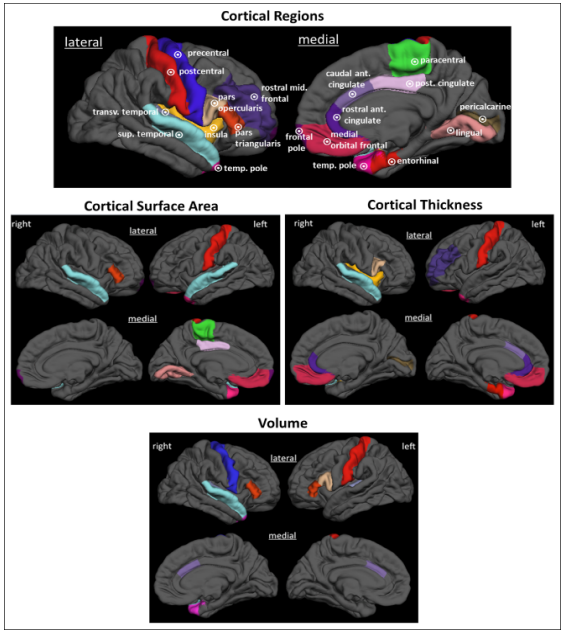
Woolf C, Pain 2011



CA = cutaneous allodynia; CM = chronic migraine; M = migraine; PM = probable migraine; O-CDH = other chronic daily headaches; ETTH = episodic tension-type headache.

Bigal et al, Neurology 2008

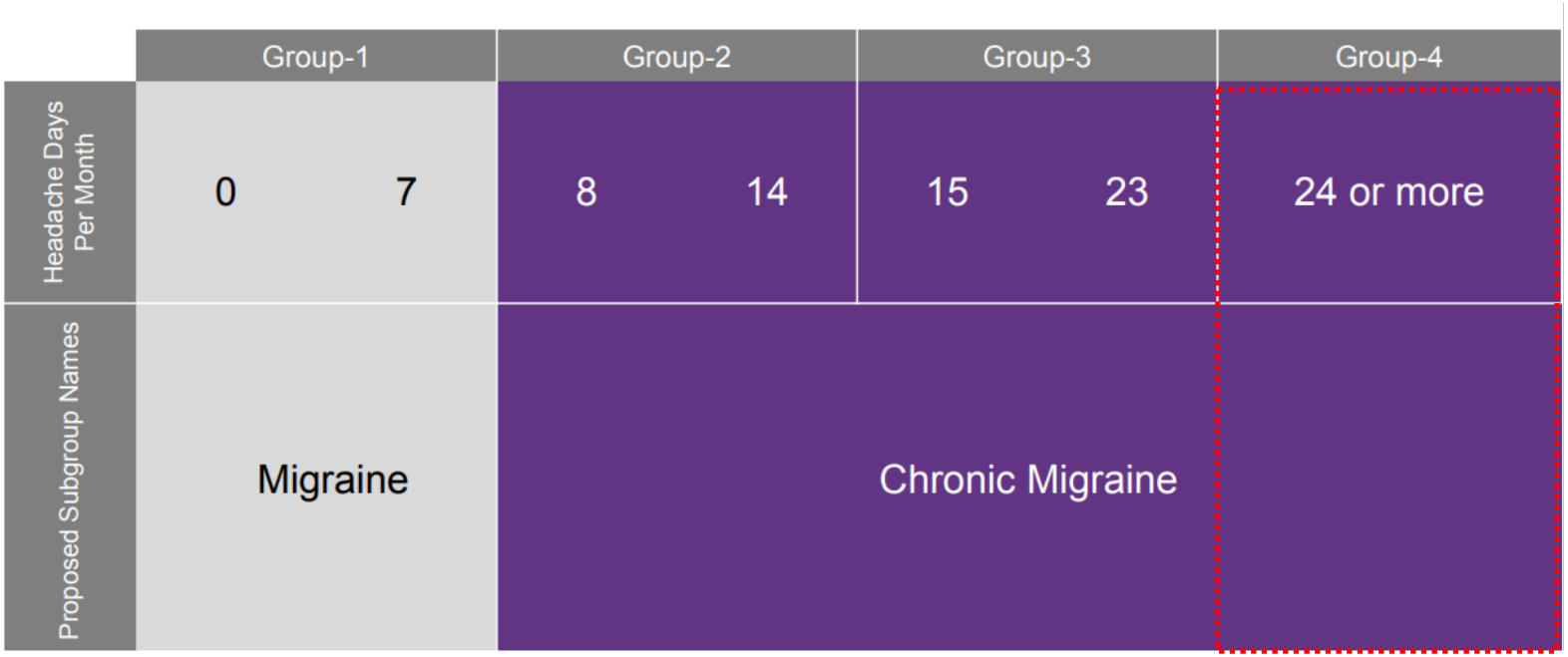
- Anatomical transformation



CM vs EM

Schwedt et al, Headache, 2015

Chronic versus episodic migraine: The 15-day threshold does not adequately reflect substantial differences in disability across the full spectrum of headache frequency

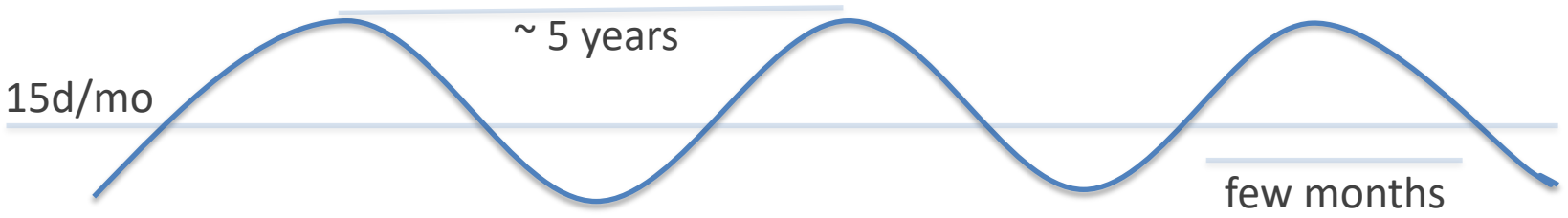


Proposed thresholds of headache frequencies for diagnosis of chronic migraine

Ishii et al, Headache 2021

Heather

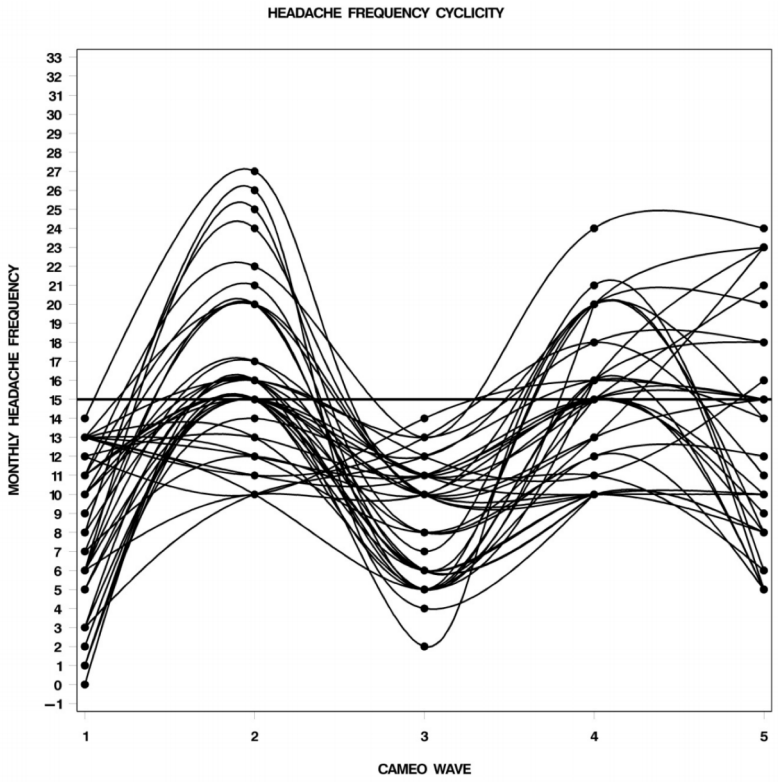
- 28 yo woman with hx. of migraine since age 13

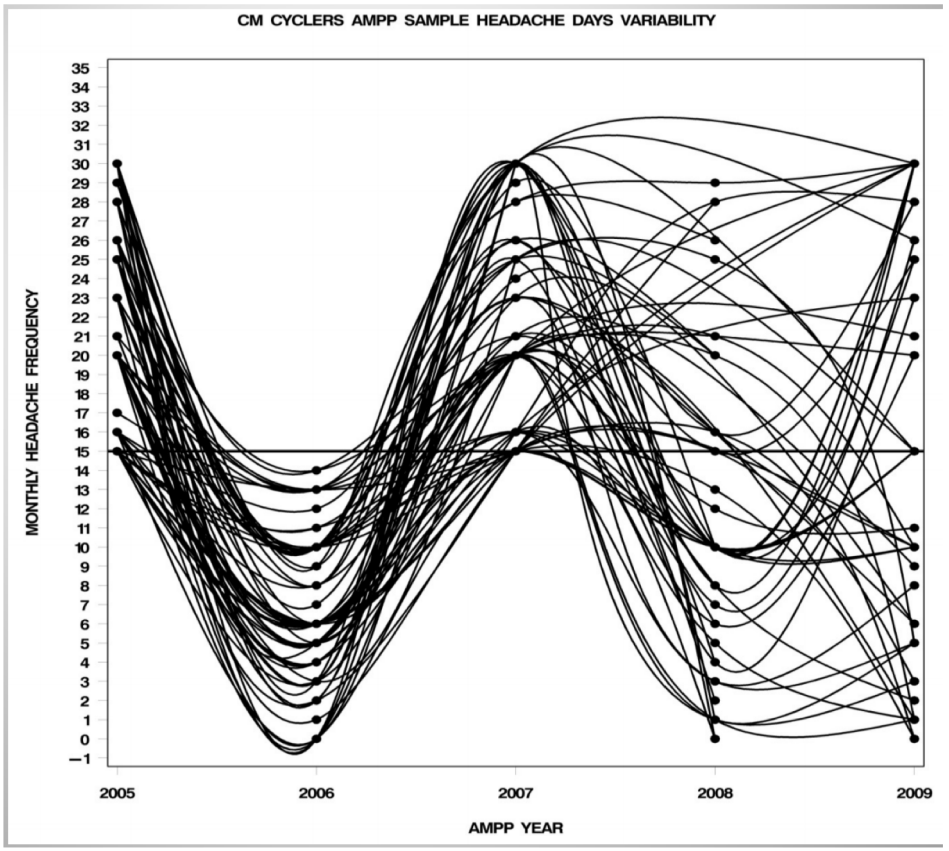


Pressure or throbbing, left side, fronto-temporal, with occipital radiation. Most of the days, her headaches are manageable, 4-5/10 in severity and respond to OTC analgesics. Approximately 2-3 times a month gets a severe attack with visual changes, 9-10/10 in severity, lasting from 4 hours to 3 days.

- Exam normal.
- *HIT 6 score **67**, MIDAS score **55**, PHQ 9 score **4***
- Meds: OCPs, prn simple analgesics, Frovatriptan, rarely Hydrocodone/Acetaminophen, rarely goes to ED
- **Dgn**: Chronic migraine vs Frequent episodic MOA + Episodic MA

Individual trajectories of EM and CM





Serrano et al, Journal of Headache and Pain, 2017

Diana

- 40 years old woman, with hx. of migraine since her early 20s as a PhD student. University professor of education - on disability due to her headaches. Lives with parents.
- Frequent severe headache predominantly right periorbital, radiating to forehead: pounding+/- stabbing HA, with P/P, nausea, diplopia (monocular).
- Multiple ED visits for her headaches (2-3 x/month). Saw multiple neurologists, tried "everything". "Tired of the repeated ED visits and having the headache simply come back a few hours after returning home."
- Exam normal except mild bilateral ptosis (constitutional)
- *HIT 6 -**68**, MIDAS - **92**, PHQ 9- **20***
- Preventives: Valproic acid, Topiramate, Nadolol, Nortriptyline, Desvenlafaxine, Abortives: Codeine/Acetaminophen 30/300, Sumatriptan inj, DHE inj, Ketorolac inj, Ondansetron, Methocarbamol, Lidocaine NS, Hydroxyzine, Clonazepam
- **Dgn**: Chronic migraine without aura. Depression and Anxiety. Hx of ischemic colitis

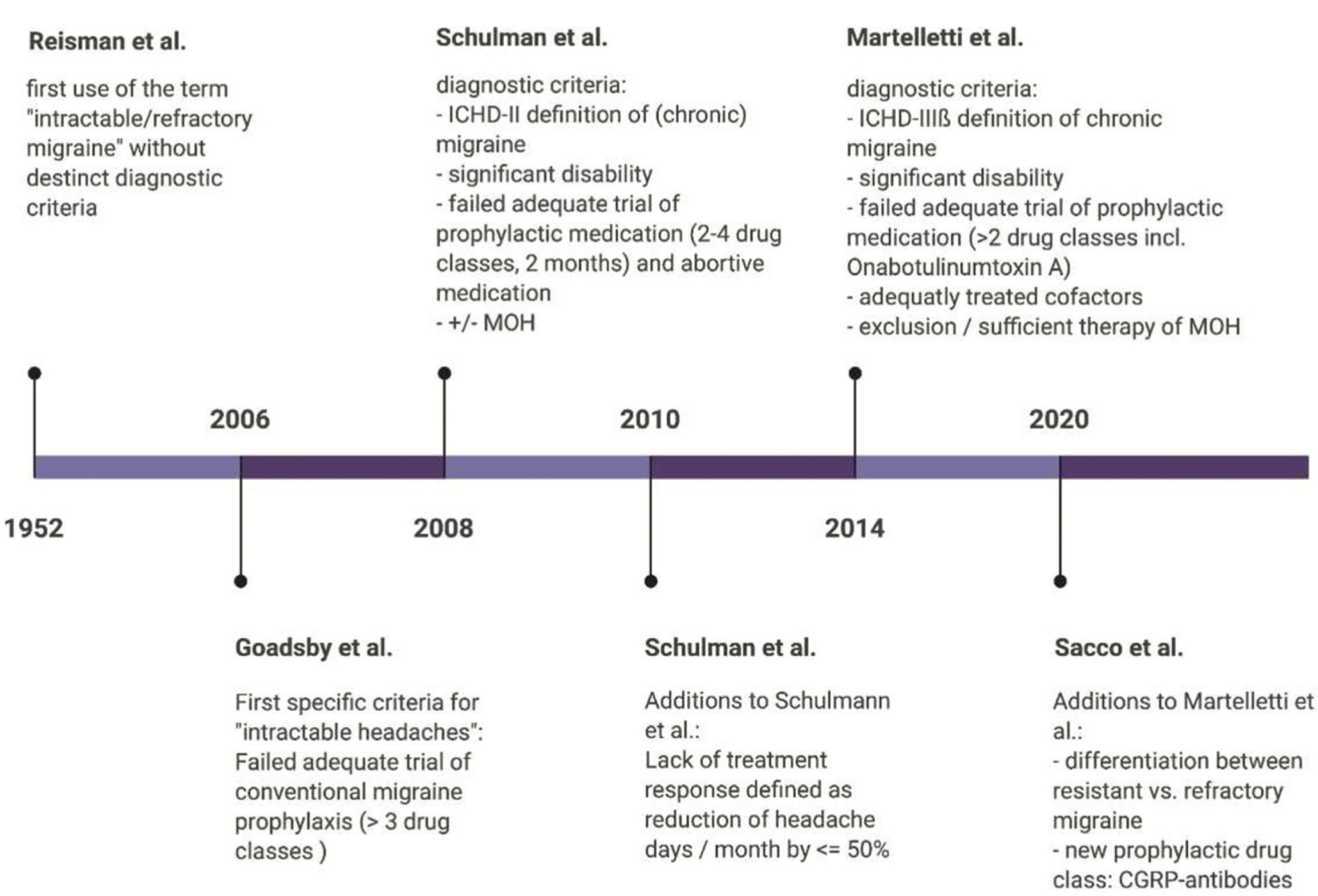


Figure 1. Chronological development of the concept of refractory migraine (created with BioRender.com®) Time line of the diagnostic criteria and its different components developed over the years of the concept of refractory migraine.

Fitzek et al, Expert Opinion on Pharmacotherapy, 2022

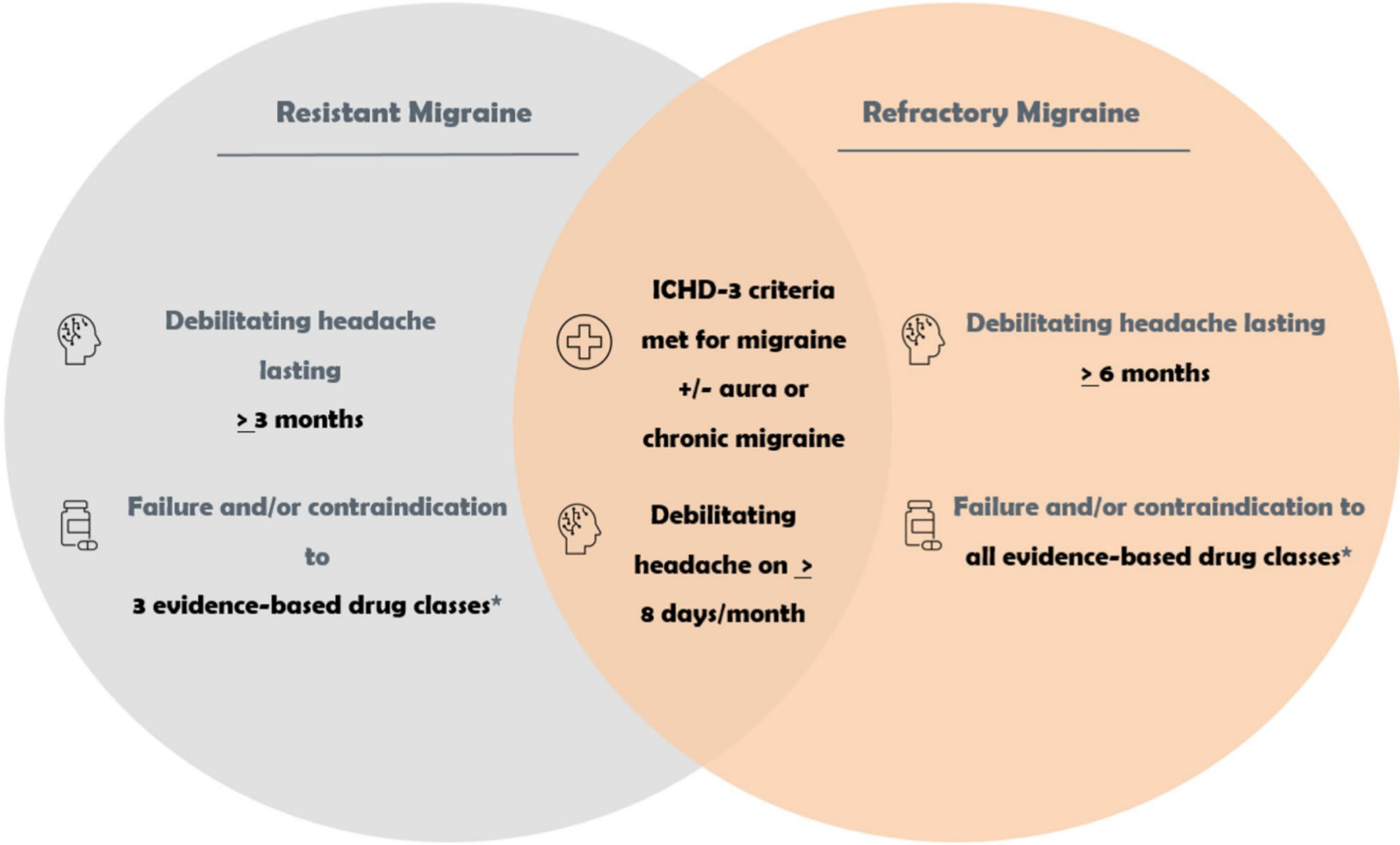


Fig. 1 European Headache Federation consensus criteria for resistant and refractory migraine

Marshall et all, Current Neurology and Neuroscience Reports, 2022

Definition of debilitating headache
Debilitating headache is defined as headache causing serious impairment to conduct activities of daily living, despite the use of pain-relief drugs with established efficacy at the recommended dose, and taken at the beginning of the attack; failure of at least two different triptans is required.
Drug classes considered for the diagnosis
1. Antidepressant (Amitriptyline, Venlafaxine); 2. Antiepileptic (Topiramate or Valproate); 3. Beta-blocker (Atenol, Metoprolol, Propanolol, Timolol); 4. Calcium channel blocker (Flunarizine or Cinnarizine); 5. Drugs acting on the CGRP pathway (Monoclonal antibodies and Gepants); 6. Angiotensin-converting enzyme inhibitor (Lisinopril) or angiotensin II receptor blocker (Candesartan); 7. OnabotulinumtoxinA (for chronic migraine only); 8. Other pharmacologic preventive treatments with established efficacy in migraine (e.g. any new developed drug).
Definition of drug failure
Failure, at any time, of migraine preventatives because of: 1. lack of efficacy due to persistence of headache with the required frequency for meeting criteria for resistant or refractory migraine, while the patient is on treatment with one of the recognized preventatives at an established dose and for an appropriate duration;[§] 2. lack of tolerability due to side effects which are unbearable for the patient, cannot be effectively managed and require stopping the drug.
Definition of contraindication
Contraindication is any specific situation in which the use of a given drug is inadvisable.[#]
Assessment of patients
To validate definitions, we suggest the following: 1. Resistant migraine, evaluation by a Headache specialist with review of medical charts; 2. Refractory migraine, evaluation in a tertiary level Headache Center with in-person follow-up for at least 6 months.
Medication overuse
1. For resistant migraine presence of medication overuse does not exclude the diagnosis; 2. For refractory migraine presence of medication overuse does not exclude the diagnosis but attempts of unsuccessful medication withdrawal needs to be documented.
Additional factors
Triggers and comorbidities need to be considered and managed; unsuccessful management of triggers and comorbidities is possible. Careful differential diagnosis with mimicking conditions must be done.

European headache federation (EHF) consensus:

on the definition of resistant and refractory migraine

Sacco et al. J Headache Pain 2020

European headache federation consensus on the definition of resistant and refractory migraine

Table 4 Suggested doses and duration for assessment of lack of efficacy

Drug	Usual dose	Minimum effective dose	Maximal effective dose	Minimum duration of treatment*
Monoclonal antibodies acting on the calcitonin-gene-related peptide pathway				
Erenumab	70-140 mg monthly	70 mg	140 mg	3 months
Fremanezumab	225 mg monthly 675 mg quarterly	225 mg/monthly 675 mg/quarterly	225 mg/monthly 675 mg/quarterly	3 months
Galcanezumab	120 mg monthly (240 mg loading dose)	120 mg/monthly	120 mg/monthly	3 months
Antidepressants				
Amitriptyline	25 mg once a day	10 mg once a day	75 mg once a day	2 months
Venlafaxine	75-150 mg once a day	37.5 mg once a day	300 mg once a day	2 months
Antiepileptics				
Topiramate	50 mg twice a day	25 mg twice a day	100 mg twice a day	2 months
Valproate	300 mg twice a day	200 mg twice a day	1000 twice a day	2 months
Antihypertensives				
Candesartan	16 mg once a day	8 mg once a day	32 mg once a day	2 months
Lisinopril	20 mg once a day	5 mg once a day	40 mg once a day	2 months
Calcium channel blockers				
Cinnarizine	75 mg once a day	75 mg once a day	150 mg once a day	2 months
Flunarizine	5 mg once a day	5 mg once a day	10 mg once a day	2 months
Beta-blockers				
Atenolol	100 mg once a day	50 mg once a day	200 mg once a day	2 months
Metoprolol	100 mg once a day (extended release)	25 mg once a day	200 once a day (extended release)	2 months
Propranolol	40 mg twice a day	40 mg once a day	80 mg three times a day	2 months
Timolol	10 mg twice a day	5 mg twice a day	30 mg twice per day	2 months
Onabotulinumtoxin A	195 UI quarterly	155 UI quarterly	195 UI quarterly	2-3 cycles (6-9 months)

*after reaching the therapeutic dose for drugs which require titration

Sacco et al. J Headache Pain 2020

Refractory chronic migraine: proposed scale

Adult Point System

Refractory to preventive approaches	2 points
Refractory to abortive medications	2 points
Duration (# of years) of migraine occurrence; if greater than 10 years	1 point
Number of headaches per month; if 25 or more days, on average	1 point
Medical comorbidities (irritable bowel syndrome [IBS], temporomandibular joint disorder [TMD], fibromyalgia, chronic fatigue, chronic pelvic pain, painful bladder syndrome); if two or more are present	1 point
Psychiatric comorbidities, whether a severe Axis I disorder (ie, an affective disorder) or any definite Axis II disorder (ie, a personality disorder), as defined by the Diagnostic and Statistical Manual of Mental Disorders	1 point
Disability (work and/or home)	1 point
Medication overuse headache (not simply medication overuse)	1 point

TOTAL OF 10 POSSIBLE POINTS
2 to 4 points = mild RCM
5 to 7 points = moderate RCM
8 to 10 points = severe RCM

Adolescent Point System

Refractory to preventive approaches (which may include Botox)	1 point
Refractory to abortive medications	1 point
Duration: headache occurrence greater than 1 year	1 point
Number of headaches per month; if 25 or more days, on average	1 point
Significant comorbidities; if at least one are present (IBS, TMD, fibromyalgia, or chronic fatigue)	1 point
Psychiatric comorbidities: severe Axis I, or a strong indication that Axis II may be present, as defined by the Diagnostic and Statistical Manual of Mental Disorders	1 point
Disability defined as an inability to go to school for at least 2 months due to headache (either homebound, or a greatly modified schedule), or a significant decrease in functioning	1 point
Severe family dysfunction, which may include a personality disorder pathology in the primary parent (usually the mother)	1 point

TOTAL OF 8 POSSIBLE POINTS
2 to 4 points = mild RCM
5 to 6 points = moderate RCM
7 to 8 points = severe RCM

Lawrence Robbins, Practical Pain Management 2019 and J Headache Pain, 2012

Objectives

Definitions: chronic migraine (CM) and refractory chronic migraine

Potential factors involved in CM refractoriness

Explore therapeutic approaches

What makes CM refractory?

- Wrong diagnosis
- Comorbidities: psychiatric and medical
- Provider related factors
- Patient related factors
- Disease related factors

What makes CM refractory?

Wrong diagnosis: primary headache disorders

- Chronic cluster headache
- Chronic tension-type headache
- New Daily Persistent Headache
- Hemicrania continua

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

ICHD-3. Cephalalgia 2018

NDPH

New daily persistent headache may have features suggestive of either

- 1. *Migraine* or
- 2. *Tension-type headache*.

ICHD-3. Cephalalgia 2018

Secondary Headache Disorders

Viral meningitis
- Meningismus underrecognized
- CSF analysis not performed during acute period
- Post-viral meningitis headache may be a discrete entity yet to be well defined

Giant cell arteritis
- Erroneous presumption that pain is temporal in location
- ESR is not a perfect screening test
- Temporal artery biopsy not pursued

RCVS
- Initial relapsing thunderclap headache pattern underrecognized
- Lack of focus of onset circumstances when presenting to a headache center several months or years after onset

SIH
- Headache patterns and associated symptoms aside from the typical orthostatic nature not recognized
- MRI performed without gadolinium

IIH
- Cases without overt papilledema easily missed
- Threshold for CSF analysis too high

Systemic illnesses
- Detailed review of systems or medical examination not performed
- HIV risk factors not routinely queried
- Follow up not long enough

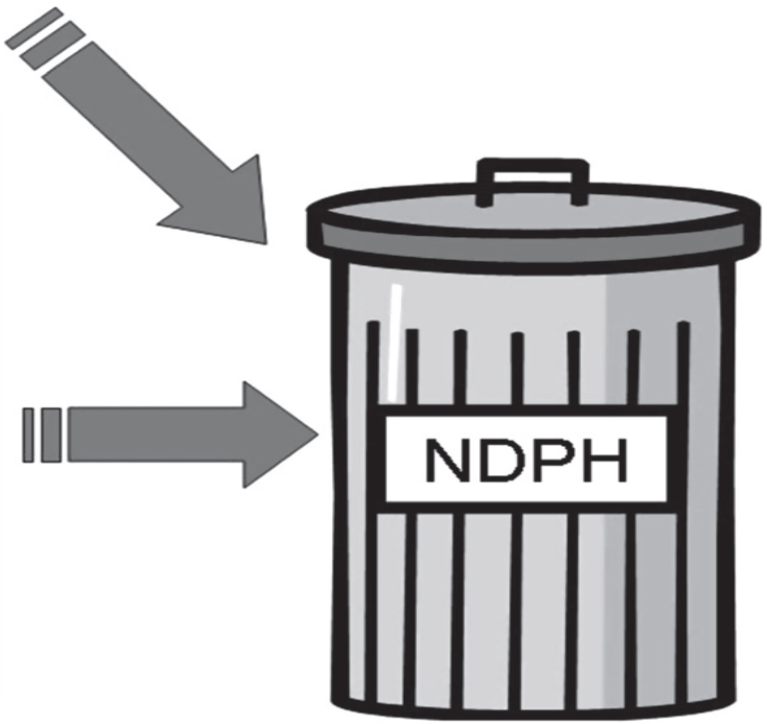
Primary Headache Disorders

CM
- Antecedent escalating headache frequency underestimated

CTTH
- Antecedent escalating headache frequency underestimated

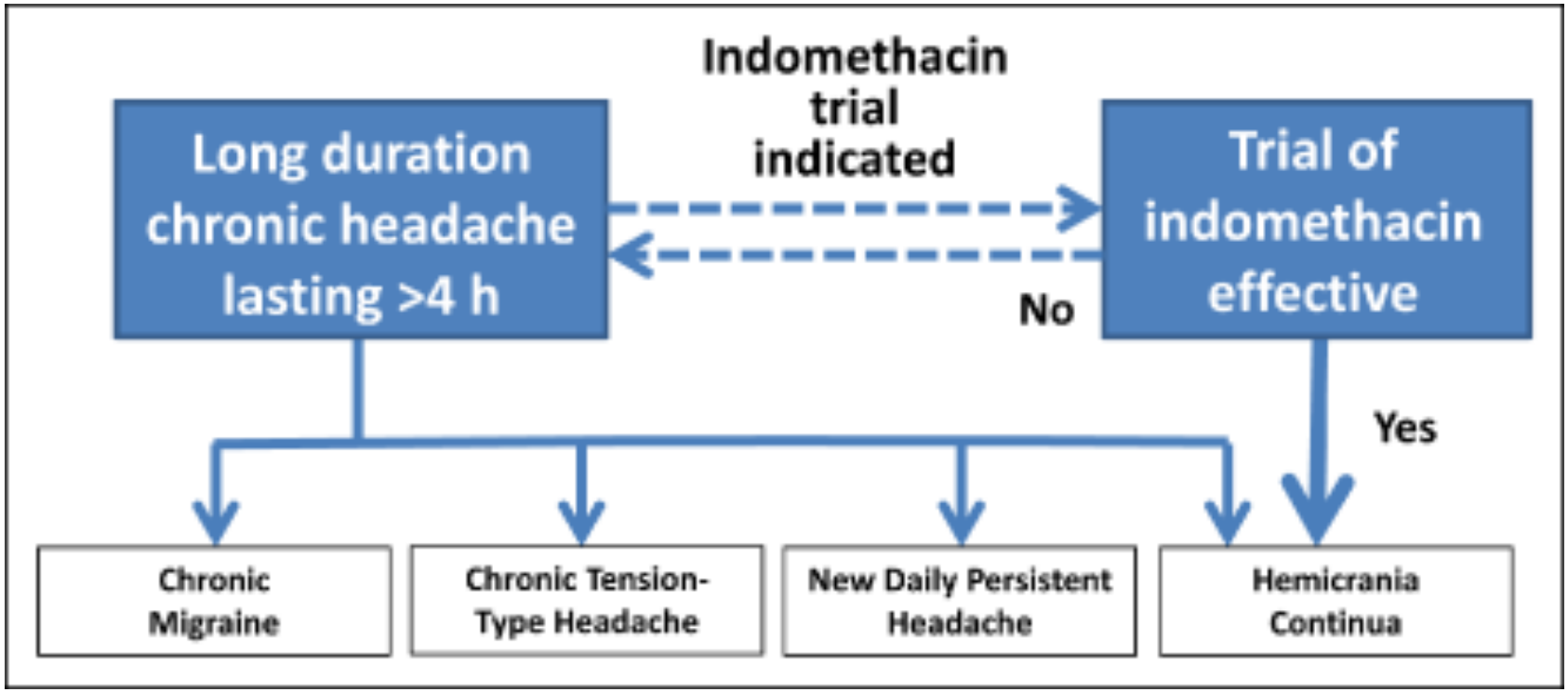
NH
- Cranial palpation not routinely performed on clinical examination
- Circumscribed nature underrecognized
- Bifocal cases underrecognized

HC
- Diagnosis or indomethacin trial not considered in cases of bilateral head pain



Robbins MS, Evans RW, Headache. 2012

Chronic daily headache of long duration



Silberstein and Lipton, Headache, 2015

What makes CM refractory?

Wrong diagnosis: secondary headache disorders

- Medication overuse headache (MOH)
- Spontaneous intracranial hypotension (SIH)
- Idiopathic intracranial hypertension (IIH, w/wo papilledema)
- Cervicogenic headache
- Head trauma
- COVID-19
- Alpherpesviral reactivation
- Other secondary headaches

Medication Overuse Headache

Diagnostic criteria:

A. Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months 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.

ICHD-3. Cephalalgia. 2018

Medication Overuse

Ergot, triptan, opioid, or simple combo analgesics

Taken on a regular basis ≥ 10 d/mo

Butalbital containing analgesics (e.g. Fioricet)

Taken on a regular basis ≥ 5 d/mo

Other analgesics

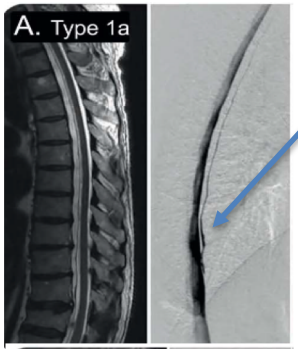
Taken on a regular basis ≥ 15 d/mo

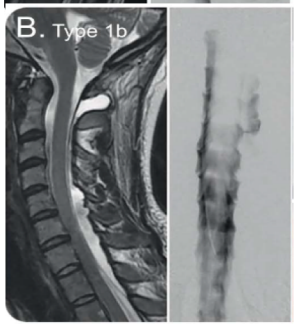
Total exposure

All acute drugs combined ≥ 15 d/mo

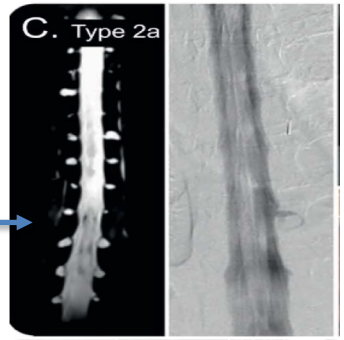
ICHD-3. Cephalalgia. 2018

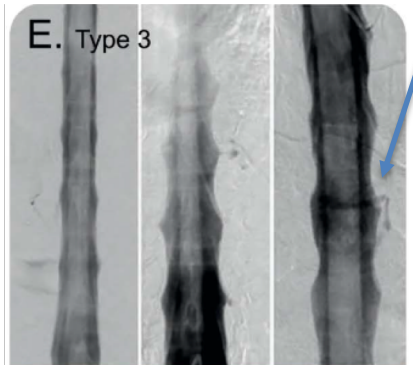
Headache attributed to low cerebrospinal fluid (CSF) pressure: SIH





Type 1	Dural tear a. Ventral b. Dorsolateral
Type 2	Meningeal diverticulum a. Simple b. Complex
Type 3	CSF-venous fistula
Type 4	Indeterminate/unknown
Extradural CSF	Yes: positive No: negative

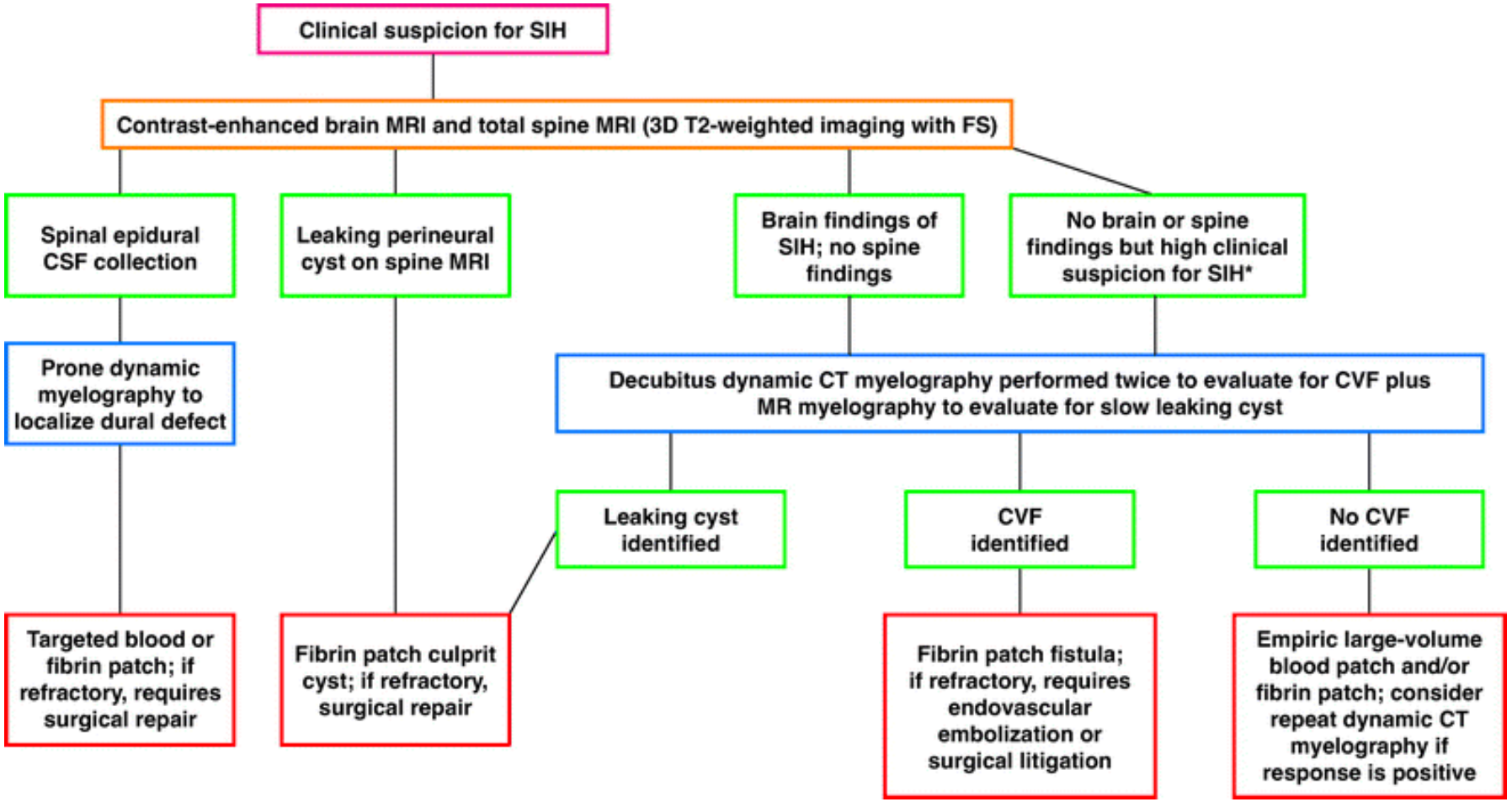




Classification of spontaneous CSF leaks

Schievink et al, Neurology 2016

Algorithmic Multimodality Approach to Diagnosis and Treatment of Spinal CSF Leak and Venous Fistula in Patients With Spontaneous Intracranial Hypotension



University of Colorado Hospital protocol

Callen et al, A J Roent., 2022

IIH without papilledema*

Table 2. Studies detailing characteristics of IIHWOP in different headache populations.

Study	Headache Phenotype as Reported by Authors	Study Population Number	IIHWOP							
			Number with IIHWOP	% Lumbar Puncture Opening Pressure > 20 cm CSF	% Lumbar Puncture Opening Pressure > 25 cm CSF	Female:Male	Age in Years (Range or Standard Deviation [±] Where Reported)	Obesity Description or Body Mass index (kg/m^2) (Range or Standard Deviation [±] Where Reported)	Mean Lumbar Puncture Pressure (Range or Standard Deviation [±] Where Reported)	% Improved Post-LP
1996 Mathew et al. [13]	refractory transformed migraine type of chronic daily headache	85	12	14.1%	12.9%	10:2	34 (13–54)	100% males obese, 50% females obese	31.2 (23.0–45.0) cm CSF	33%
2001 Quattrone et al. [40]	chronic daily headache	114	5	4.4%	1.8%	5:0	31.6 (18–46)	33.1 (28.7–43.4) 80% obese	26.4 (22.4–31.5) cm CSF	..
2006 Bono et al. [31]	chronic migraine	724 (98 had LP)	19	* 4.5%	* 4.1%	18:1	35.0 ± 7.2	31.7 ± 3.9	282.5 ± 40.6 mm CSF	68.4%
2008 Vieira et al. [14]	chronic migraine	60	6	10%	5%	6:0	41.2 (26–52)	29.5 (21.8–33.3) 50% obese	26.2 (24.4–30) cm CSF	100% immediate
2008 Bono et al. [32]	chronic tension-type headache	198 (58 had LP)	9	* 6.3%	* 4.2%	9:0	40.8 ± 6.6	33.7 ± 7.6	270. 4 ± 34.1 mm CSF	89%
2010 Bono et al. [38]	Headache sufferers	98	18	18.3%	..	17:1	39.6 ± 13.6	29.9 (21.4–40.8)	24.7(20.5–32.9) cm CSF	"majority" of patients had benefit reported at 2–4 weeks
2014 De Simone et al. [30]	Unresponsive chronic migraine	44	38	86%	43%	Study population mainly female	Study population 37.5 (33–40)	Study population 56.8% overweight/obese		38.7% at 4 months
2018 Bono et al. [33]	chronic daily headache	148	93	63%	25%	80:13	$40.1 ± 15.1 $	$32.5 ± 5.7	$25.6 ± 20.1 cm CSF	100%
2018 Favoni et al. [34]	chronic daily headache	40	9	22%	5%	8:1	50 ± 8	32 (25–38)	24.5 (21.1–25.8)	78% at 1 month

* estimate based on multiple calculations; $ pooled mean ± SD.

* Controversial entity

Mollan et al, Life 2021

Cervicogenic headache

ICHD-3.org and Cephalalgia, 2018

A. Any headache fulfilling criterion C

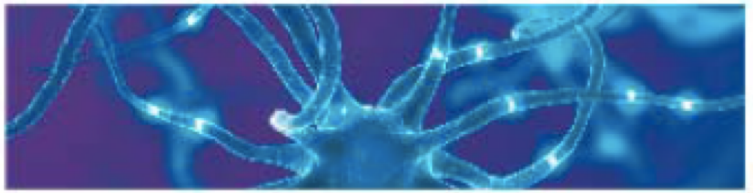
B. Clinical and/or imaging evidence of a **disorder or lesion** within the cervical spine or soft tissues of the neck, known to be able to cause headache

C. **Evidence of causation** demonstrated by at least two of the following:
- headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
- headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
- cervical range of motion is reduced and headache is made significantly worse by provocative manœuvres
- headache is abolished following diagnostic blockade of a cervical structure or its nerve supply

D. Not better accounted for by another ICHD-3 diagnosis.

Antonaci, Inan. Cephalalgia 2021

A. Any headache fulfilling criterion C
B. Clinical and or imaging evidence[1] of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache.[2]
In the absence of disorder or lesion. Presence of unilateral head pain without side shift which is starting posteriorly and ending anteriorly. Presence of same side shoulder and arm pain.
C. Evidence of causation demonstrated by at least two of the following:
1. Headache has improved 50% or more or resolved in parallel with improvement in or resolution of the cervical disorder or lesion. In the absence of disorder or lesion, same proportion decrease with specific treatment for cervicogenic headache and not responding to specific treatment for migraine (like triptans).
2. Cervical range of motions is reduced in rotation equal to or more than 10° on the symptomatic side.
3. Headache is made significantly worse by provocative manoeuvres or pressing (3–4 kg) with the finger against the upper trapezius and splenis area and against facet joints. The provoked headache should start posteriorly and spread to the anterior.
4. Headache is abolished following diagnostic blockade of a cervical structure or its nerve supply. A sensitivity of 95% can be reached by blocking a cervical structure or its supply nerve using randomly short/long acting anaesthetic and placebo.
D. Not better accounted for by another ICHD-3 diagnosis.[3–5]



Worrisome Headache Red Flags—"SNOOP"

- **S**YSTEMIC SYMPTOMS (fever, weight loss) or SECONDARY RISK FACTORS (HIV, systemic cancer)
- **N**EUROLOGIC SYMPTOMS or abnormal signs (confusion, impaired alertness or consciousness)
- **O**NSET: sudden, abrupt, or split-second
- **O**LDER: new onset and progressive headache, especially in middle age >50 yr (giant cell arteritis)
- **P**REVIOUS HEADACHE HISTORY: first headache or different (change in attack frequency, severity, or clinical features)

Dodick DW. *Adv Stud Med*. 2003;3(6C):S550-S555.

Table 1 SNNOOP10 list of red and orange flags

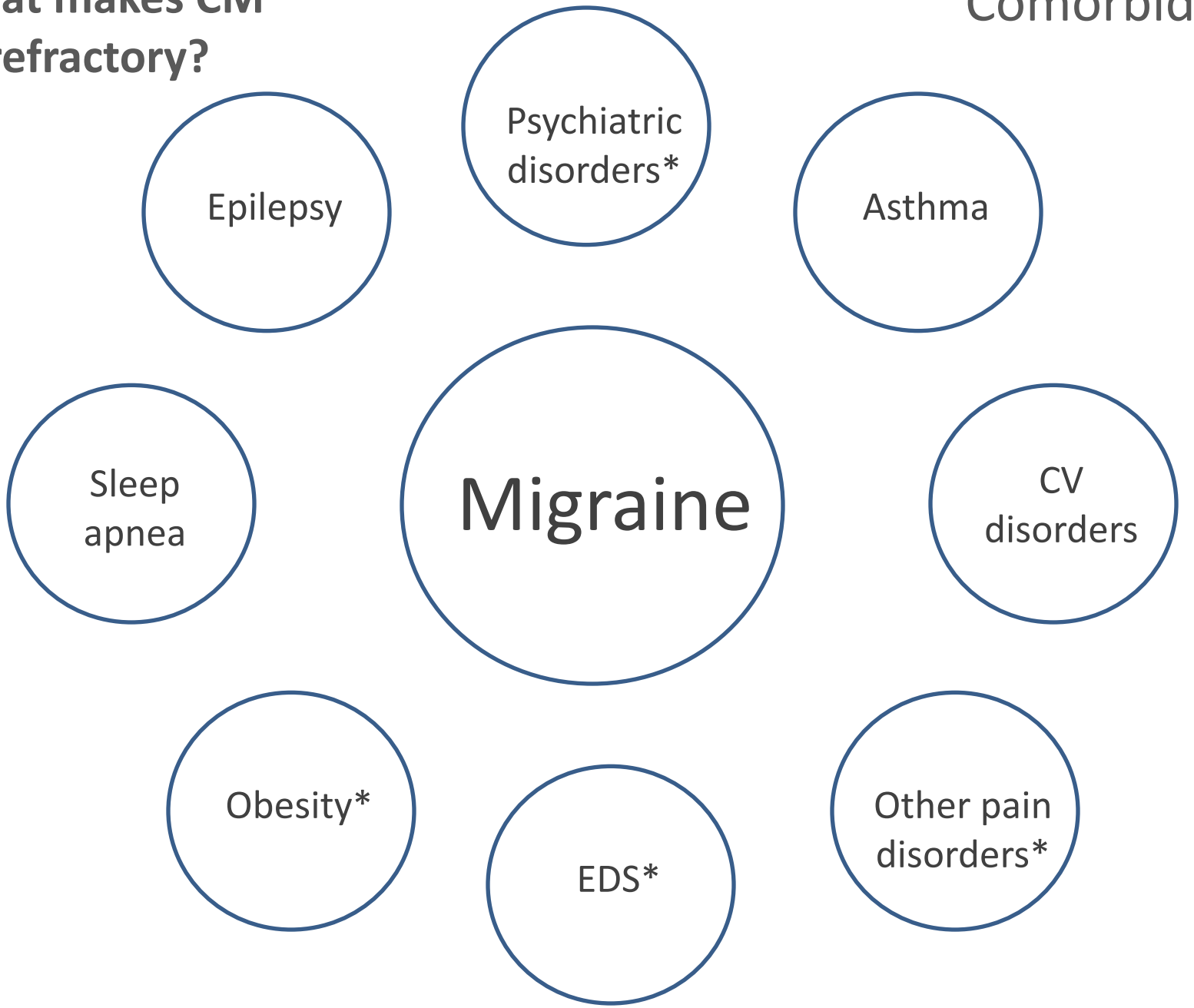
	Sign or symptom	Related secondary headaches (most relevant ICHD-3b categories)	Flag color
1	Systemic symptoms including fever	Headache attributed to infection or nonvascular intracranial disorders, carcinoid or pheochromocytoma	Red (orange for isolated fever)
2	Neoplasm in history	Neoplasms of the brain; metastasis	Red
3	Neurologic deficit or dysfunction (including decreased consciousness)	Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections	Red
4	Onset of headache is sudden or abrupt	Subarachnoid hemorrhage and other headaches attributed to cranial or cervical vascular disorders	Red
5	Older age (after 50 years)	Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders	Red
6	Pattern change or recent onset of headache	Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders	Red
7	Positional headache	Intracranial hypertension or hypotension	Red
8	Precipitated by sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation	Red
9	Papilledema	Neoplasms and other nonvascular intracranial disorders; intracranial hypertension	Red
10	Progressive headache and atypical presentations	Neoplasms and other nonvascular intracranial disorders	Red
11	Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (e.g., preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes	Red
12	Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome; ophthalmic causes	Red
13	Posttraumatic onset of headache	Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders	Red
14	Pathology of the immune system such as HIV	Opportunistic infections	Red
15	Painkiller overuse or new drug at onset of headache	Medication overuse headache; drug incompatibility	Red

Abbreviation: ICHD-3b = International Classification of Headache Disorders 3b.
An overview of signs and symptoms, their related secondary headache, and distribution in red and orange flags.

DO TP et al, Neurology 2019.

What makes CM refractory?

Comorbidities



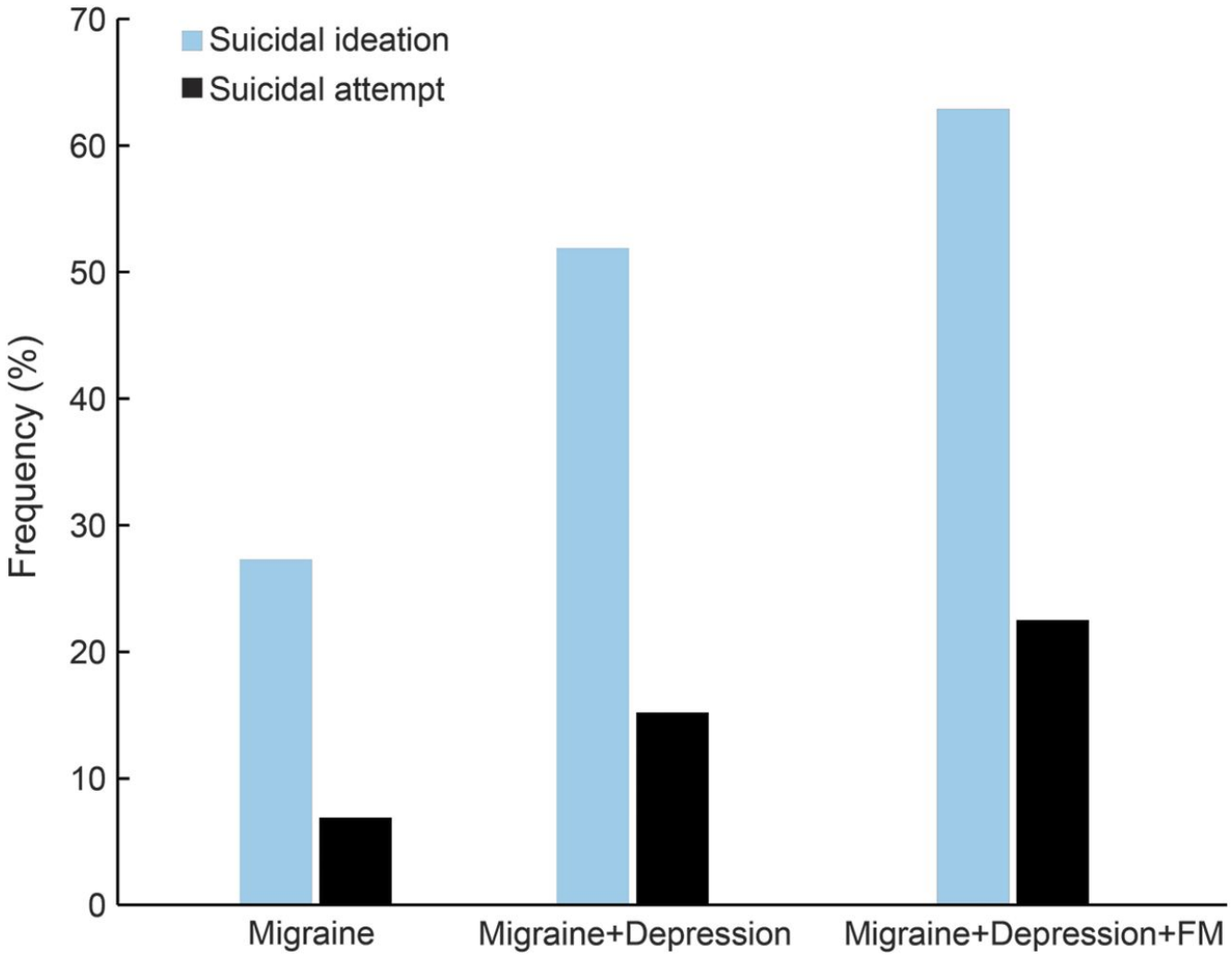
CM subgroups based on comorbidities:

LCA (latent class analysis)

	Class 1 Most comorbidities (n = 676; 5.7%)	Class 2 Resp/psych (n = 1,332; 11.3%)	Class 3 Resp/pain (n = 913; 7.7%)	Class 4 Respiratory (n = 2,355; 19.9%)	Class 5 Psychiatric (n = 898; 7.6%)	Class 6 Cardiovascular (n = 917; 7.7%)	Class 7 Pain (n = 720; 6.1%)	Class 8 Fewest comorbidities (n = 4,026; 34.0%)	Average probability across classes
Respiratory									
Allergies (SR-PD)	70%	69%	73%	60%	23%	34%	22%	21%	32%
Bronchitis (SR-PD)	70%	67%	75%	64%	16%	36%	19%	15%	30%
Chronic bronchitis (SR-PD)	27%	13%	16%	7%	0%	4%	4%	1%	3%
Sinusitis (SR-PD)	79%	89%	89%	88%	24%	48%	24%	20%	41%
Cardiovascular									
Hypertension (SR-PD)	54%	22%	45%	8%	8%	74%	21%	7%	24%
Diabetes (SR-PD)	27%	7%	14%	2%	3%	31%	8%	2%	9%
High cholesterol (SR-PD)	58%	21%	46%	11%	11%	75%	31%	11%	28%
Digestive									
Gastrogeophageal reflux (SR-PD)	55%	26%	46%	11%	8%	22%	14%	3%	12%
Irritable bowel syndrome (SR-PD)	36%	19%	23%	9%	10%	4%	8%	2%	7%
Psychiatric									
Anxiety (SR-PD)	93%	95%	14%	8%	92%	15%	21%	4%	28%
Depression (SR-PD)	88%	76%	33%	17%	74%	22%	33%	9%	31%
Panic (SR-PD)	51%	42%	1%	1%	31%	2%	2%	0%	7%
PTSD (SR-PD)	30%	13%	4%	2%	11%	3%	5%	1%	4%
Joint/pain									
Arthritis (SR-PD)	41%	17%	33%	10%	6%	25%	24%	4%	14%
Chronic back pain (SR)	77%	28%	60%	14%	14%	21%	68%	9%	25%
Chronic pain (SR)	55%	8%	25%	2%	3%	4%	30%	1%	8%
Fibromyalgia (SR-PD)	31%	5%	14%	1%	1%	4%	7%	1%	3%
Neck pain (SR)	82%	53%	79%	36%	32%	33%	76%	26%	40%
Osteoarthritis (SR-PD)	35%	9%	33%	6%	2%	19%	14%	2%	8%
Central nervous system									
Insomnia (SR)	79%	63%	58%	33%	44%	35%	49%	23%	37%
Restless leg syndrome (SR-PD)	26%	7%	11%	3%	3%	5%	6%	1%	4%
Vertigo (SR)	60%	32%	38%	16%	16%	18%	27%	8%	17%

Lipton et al, Neurology, 2019 - CAMEO

Suicide risk in patients with migraine, migraine with comorbid depression, and migraine with comorbid depression and fibromyalgia.



Liu et al, Neurology 2015

Provider:
should we ever give up to a patient?

I don't, but of course there is no "right" answer

Reasons to stop trying approaches: with the severe refractory patient, where nothing has helped for many years, maybe we are "wasting" their time and money, and creating false hopes.

Dr. Lawrence Robbins

Neuropalliative clinic: discuss care goals

Provider:
reasons to not give up

"Probably the best we can do for a patient is to provide hope"

Dr. Lawrence Newman

We often are the "last-line" treaters, there may be little beyond what we can offer

The relationship is very important to the patient.

We often can at least find SOMETHING that has helped in the past

The patient often is devastated when told "nothing else to do"….

AND, of course your intuitive "gestalt": putting everything together, what is your best instinct as to what are the top ten therapies, 1.outside of meds and 2. meds

Dr. Lawrence Robbins

Provider burnout

Headache doctors (and neurologists): High rate of burnout (50% or more)

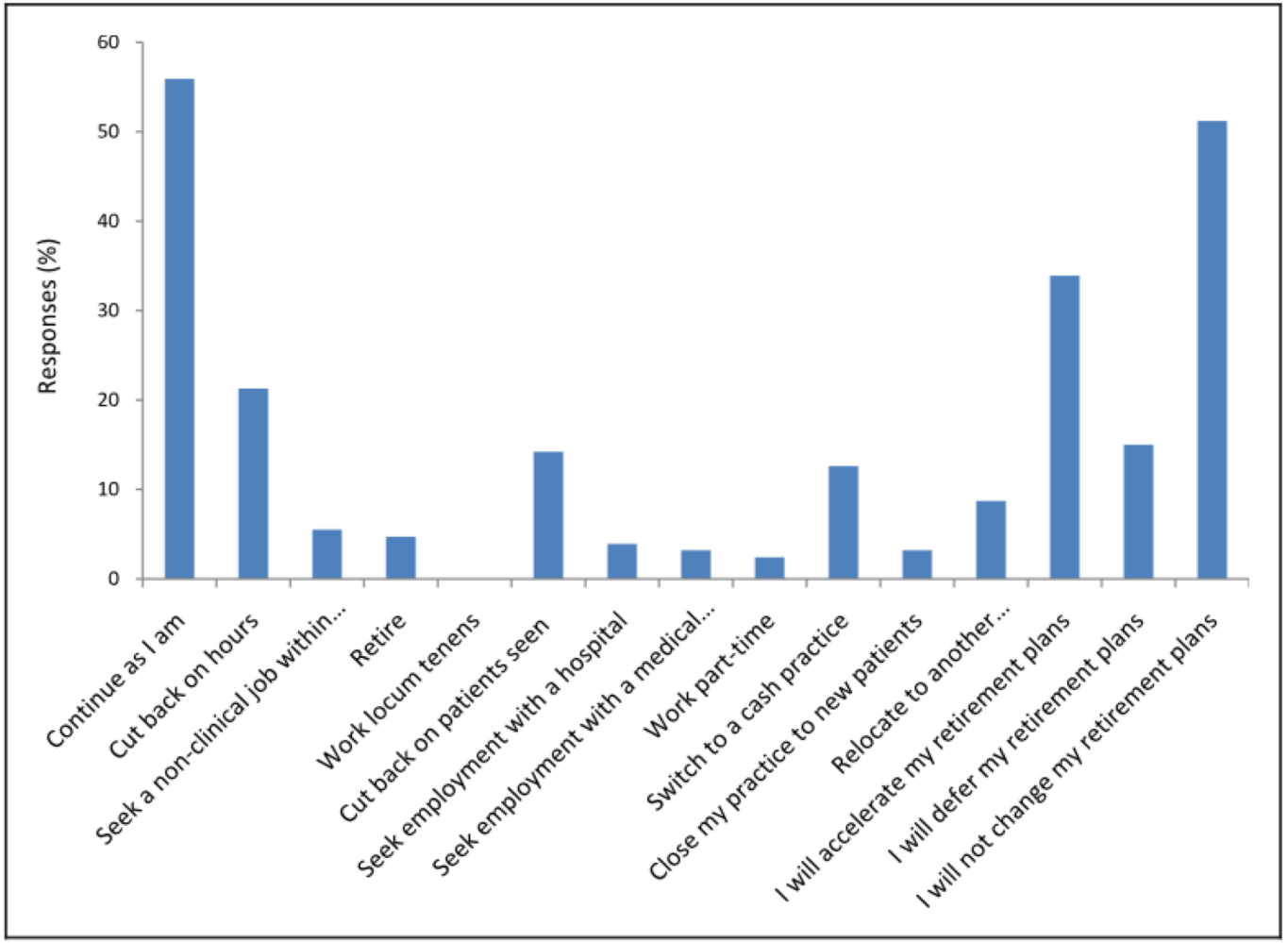
Many strategies to minimize burnout

Staff burnout should also be addressed/minimized

Providers and staff have only so many “emotional marbles” for their day or week; we have to choose where we spend our “marbles”(we also have only so many “energy marbles”)…

To “save our emotional marbles” we have to somewhat limit the RCM patients who have moderate or severe personality disorders…

A Survey of Headache Medicine Specialists on Career Satisfaction and Burnout



Evans&Ghosh. Headache 2015

Patient related factors

- **Acceptance**: we can improve acceptance…"Lack of acceptance by proxy" in spouses/parents. It can take years, the road to acceptance may be littered with many stop-offs at alternative clinics looking for the "aha moment cure"
- **Coping: p**romote active coping

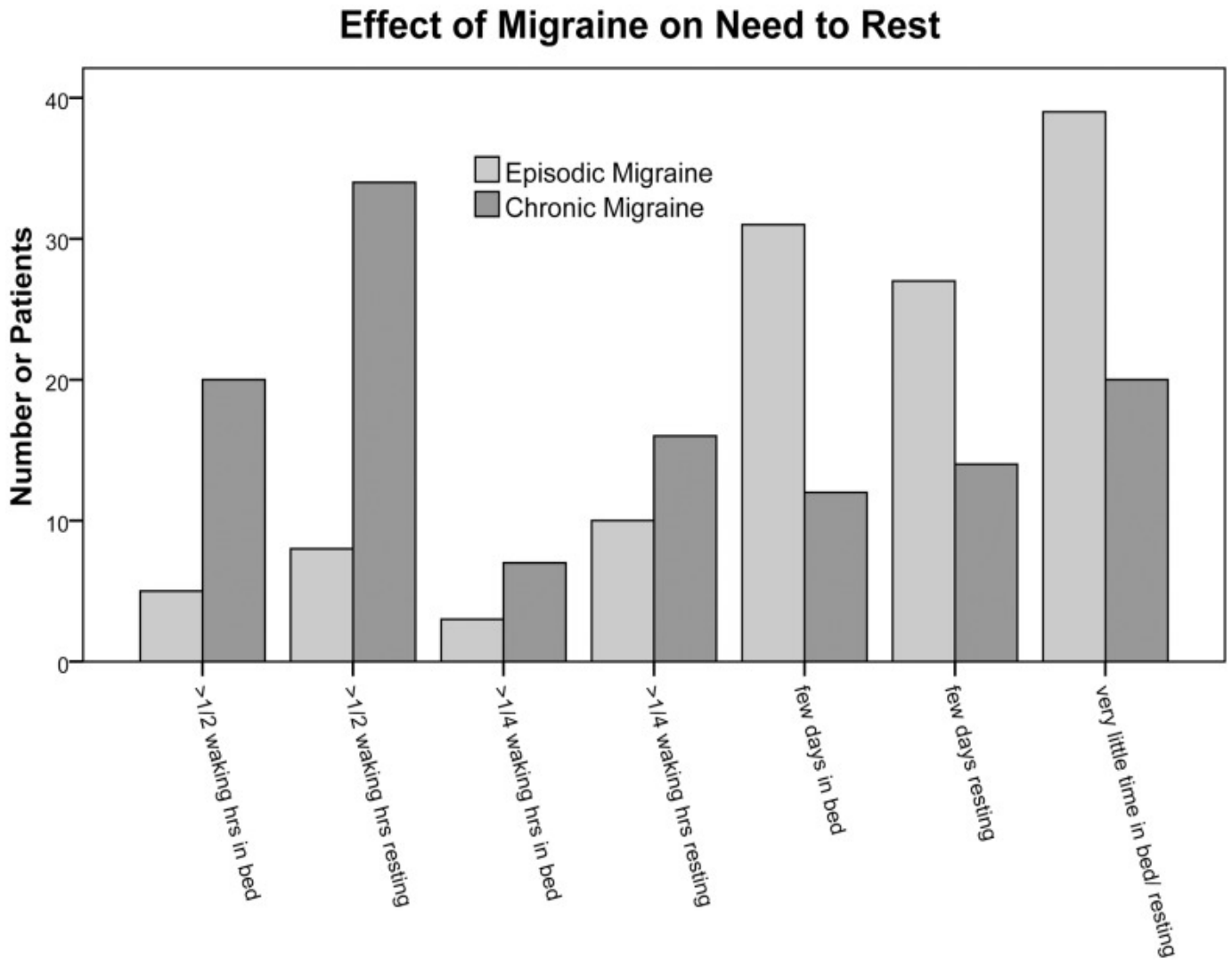
Passive coping is a factor in disability

- **Functioning**: Improving functioning is a goal, but not easy to achieve…we may be able to help with pain, but functioning may remain poor…
- **Caretakers:** Difficult position, they need support

Psychotherapy and support groups may help

Dr. Lawrence Robbins

The stigma of migraine

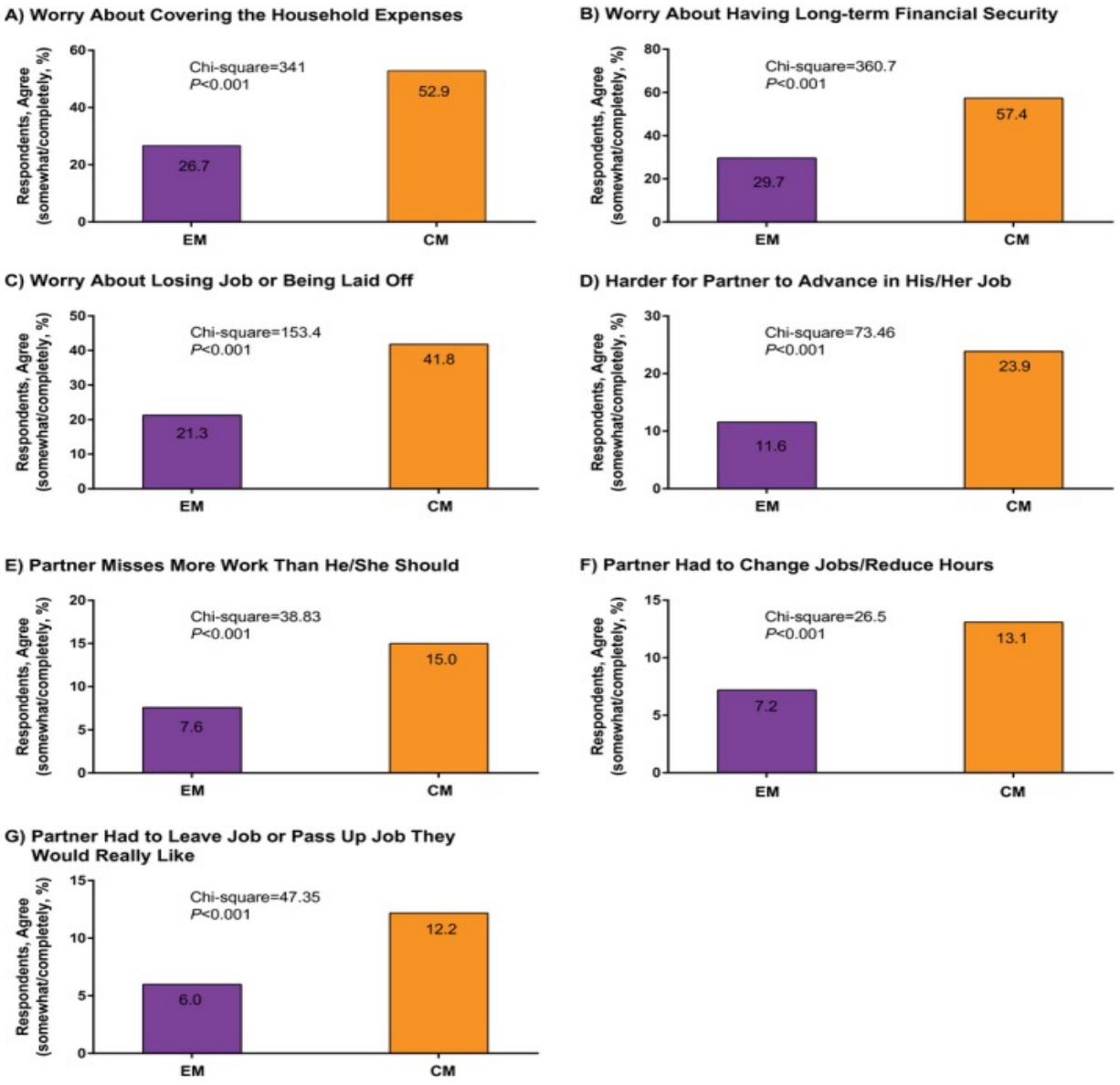


Young et al, Plos One 2013

Patient related factors

- Headache history, including medication history
- Social aspects
- Job requirements
- Patient preferences
- Finances (can they afford a particular therapy)
- Personal and family history of responses to various meds, “nocebo by proxy” and “placebo by proxy”, etc.
- Other

Life with migraine



Buse et al, Headache, 2019 - CAMEO

Disease related factors

- Genetics?

primary CNS dysfunction

- Structural?

neuroplasticity

- Systems functional?

trigemino-vascular activation, central sensitization, heightened pain sensation?

- Pharmacological?

undiscovered targets

Goadsby, Hargreaves, Headache 2008

Objectives

Definitions: chronic migraine (CM) and refractory chronic migraine

Potential factors involved in CM refractoriness

Explore therapeutic approaches

Why are headache patients so difficult to treat?

- Cognition is impaired during pain
- Judgment is impaired during pain
- Memory is impaired during pain
- Pain makes people desperate
- Most pain patients' expectations are both jaded and unrealistic

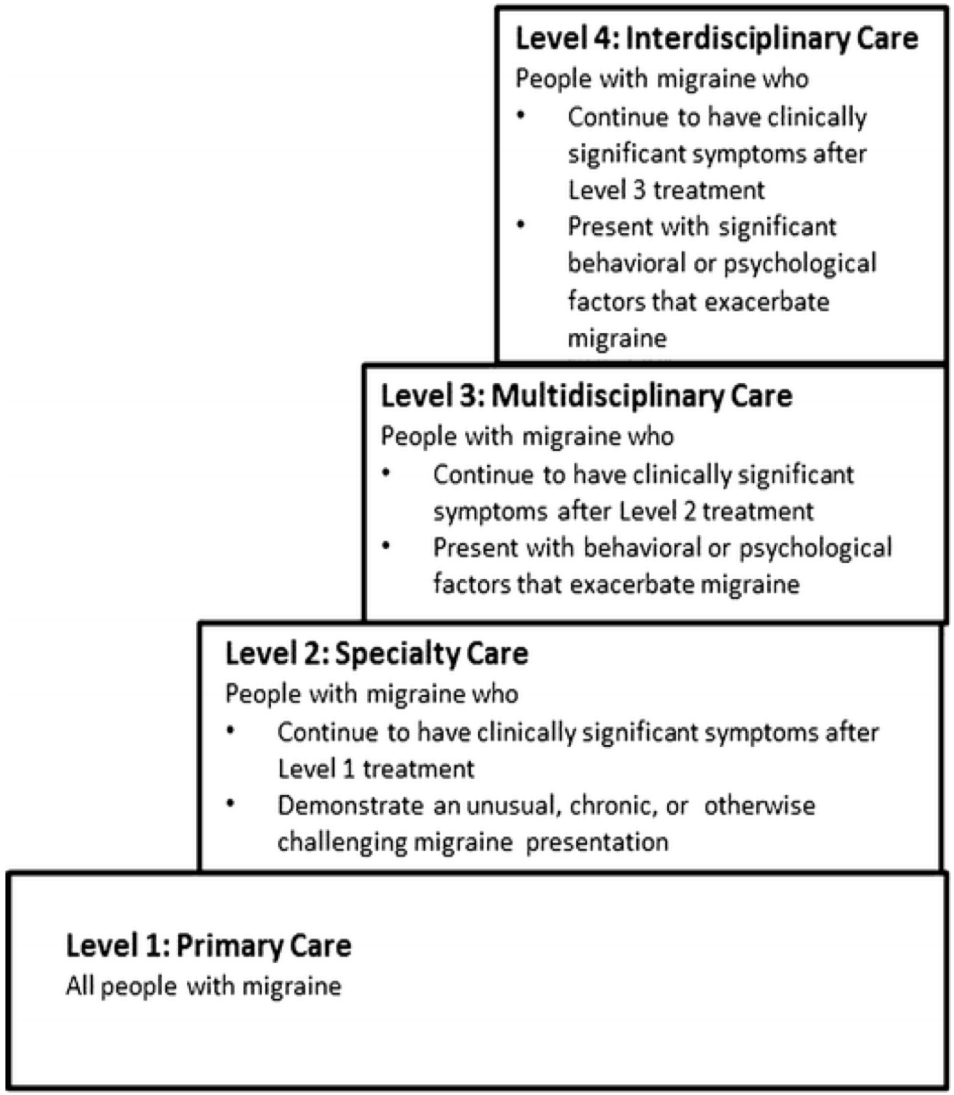
  All of which complicate the history
- Central Sensitization/Cutaneous Allodynia complicate the exam
- Psychiatric comorbidities

Outpatient Therapy Options

- No good algorithm: everyone is different
- There is no specific treatment for RCM
- The “Art of Headache Medicine”: many factors go in…*
- “It takes a village”: Get other villagers involved!

Dr. Lawrence Robbins

Example of step care in migraine



Patient education

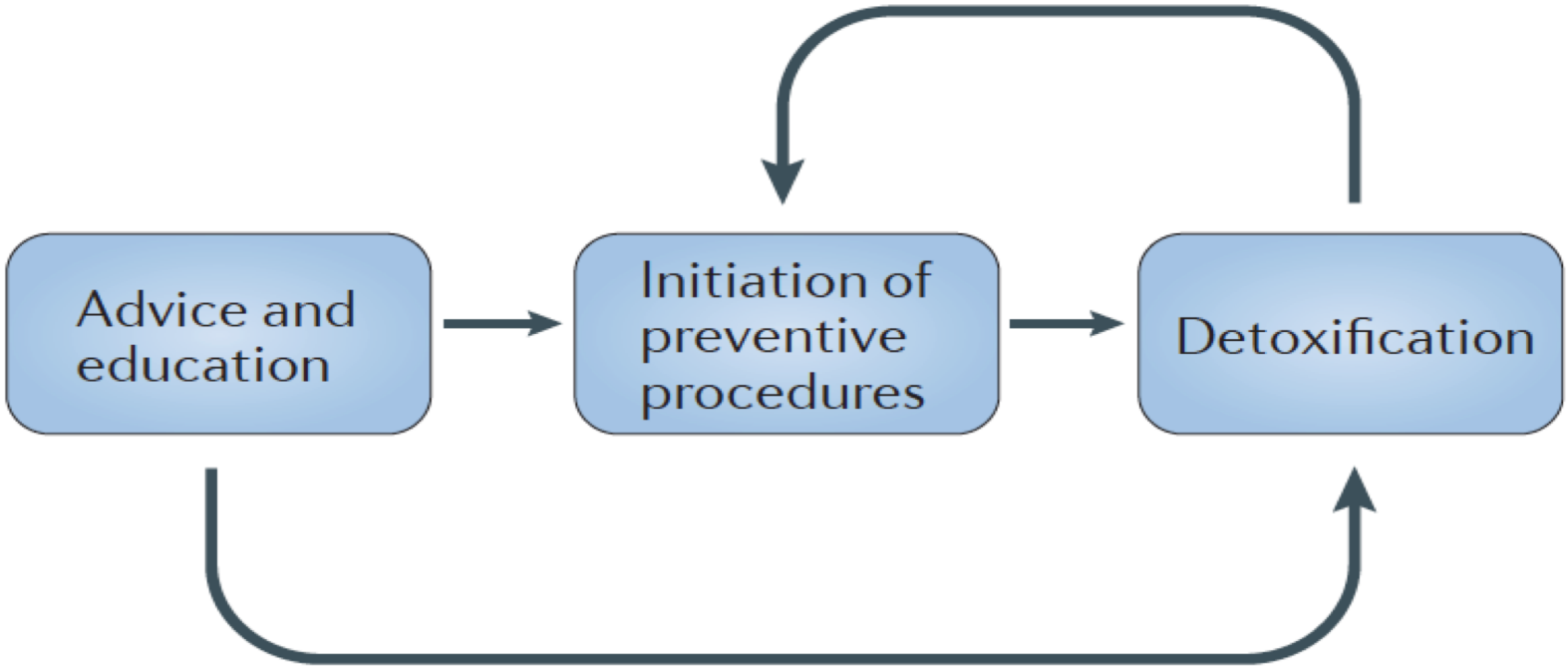
Patient education

Patient education

Patient education

Singer et al, Curr Neurol Neurosci Rep 2015

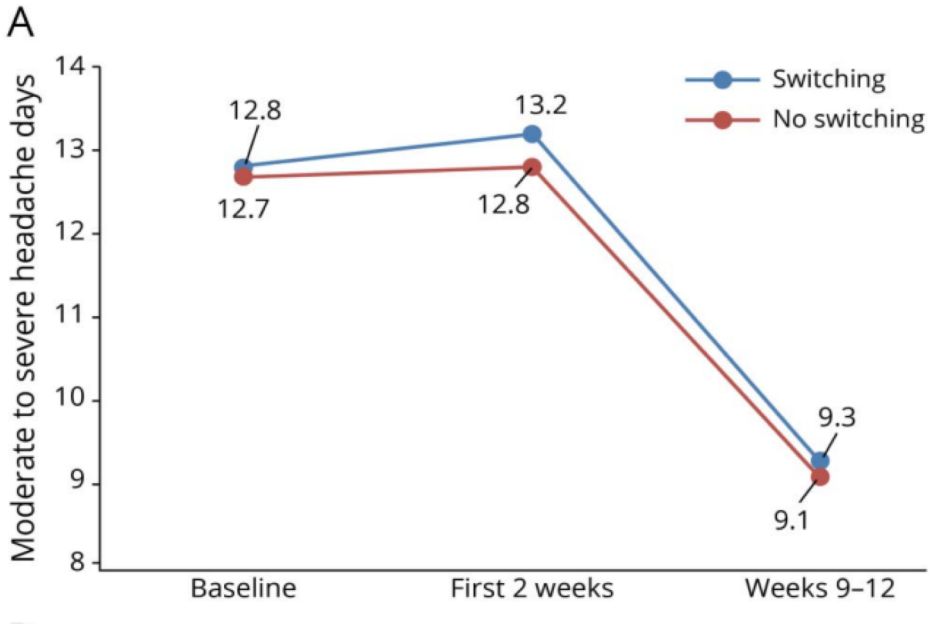
Treatment algorithm in medication-overuse headache (MOH)



Diener HC et al, Nature Reviews, 2016

Medication overuse treatment strategy (MOTS)

Figure 2 Change in Moderate to Severe Headache Days by Treatment Strategy

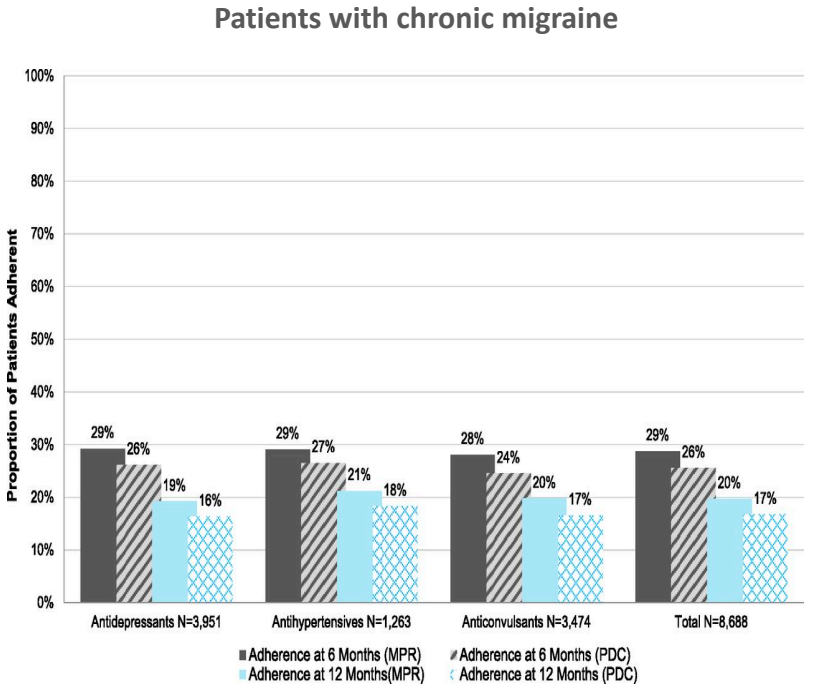


"Those using symptomatic medications with very high frequency **(>23 days per 4 weeks** in the MOTS Trial) may represent a subgroup who achieve better outcomes if they are switched off the overused medication to alternative symptomatic treatment used with a limited frequency"

Schwedt et al, Neurology 2022

Migraine preventives

Anticonvulsants	Antihypertensives	Antidepressants
Carbamazepine (Tegretol)	Candesartan (Atacand)	Amitriptyline (Elavil)
Gabapentin (Neurontin)	Irbesartan (Avapro)	Desvenlafaxine (Pristiq)
Lamotrigine (Lamictal)	Lisinopril (Zestril)	Duloxetine (Cymbalta)
Oxcarbazepine (Trileptal)	Metoprolol (Lopressor)	Milnacipran (Savella)
Pregabalin (Lyrica)	Propranolol (Inderal)	Nortriptyline (Pamelor)
Valproic acid (Depakote)	Timolol (Betimol)	Protriptyline (Vivactil)
Topiramate (Topamax, Trokendi)	Verapamil (Calan)	Venlafaxine (Effexor)
Zonisamide (Zonegran)		



Hepp, Cephalalgia 2014

Supplements: Boswellia (Gliacin)- Butterbur(Petadolex)- CoQ10- Dolovent-Feverfew- Melatonin-Magnesium- Migrelief- Vitamin B2 (Riboflavin)
Other prescriptions: Onabotulinum toxin A, Acetazolamide (Diamox); Baclofen (Lioresal); Indomethacin (Indocid); Memantine (Namenda); Metaxolone (Skelaxin); Methylergonovine (Methergine); Tizanidine (Zanaflex); Spironolactone (Aldactone)
Devices: eTNS (Cefaly); Gammacore (Sapphire); Transcranial Magnetic Stimulator (TMS, eNeura)

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Devices: eTNS (Cefaly); Gammacore (Sapphire); Transcranial Magnetic Stimulator (TMS, eNeura)

Migraine preventives

Anticonvulsants	Antihypertensives	Antidepressants	Anti CGRP Antibodies Monoclonal	Gepants Small molecules
Carbamazepine (Tegretol) Gabapentin (Neurontin) Lamotrigine (Lamictal) Oxcarbazepine (Trileptal) Pregabalin (Lyrica) Valproic acid (Depakote) Topiramate (Topamax, Trokendi) Zonisamide (Zonegran)	Candesartan (Atacand) Irbesartan (Avapro) Lisinopril (Zestril) Metoprolol (Lopressor) Propranolol (Inderal) Timolol (Betimol) Verapamil (Calan)	Amitriptyline (Elavil) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Milnacipran (Savella) Nortriptyline (Pamelor) Protriptyline (Vivactil) Venlafaxine (Effexor)	Erenumab-aooe (AIMOVIG) Fremanezumab (AJOVY) Galcanezumab-gnlm (EMGALITY) Eptinezumab (VYEPTI)	Atogepant (Qulipta) Rimegepant (Nurtec) Oral meds as abortive Ubrogepant (UBRELVY) Rimegepant (NURTEC)
Supplements: Boswellia (Gliacin)- Butterbur(Petadolex)- CoQ10- Dolovent-Fev (Riboflavin)				
Other prescriptions: Onabotulinum toxin A, Acetazolamide (Diamox); Baclofen (Namenda); Metaxolone (Skelaxin); Methylergonovine (Methergine); Tizanidine (				
Devices: eTNS (Cefaly); Gammacore (Sapphire); Transcranial Magnetic Stimulat				

?

Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study – “LIBERTY"

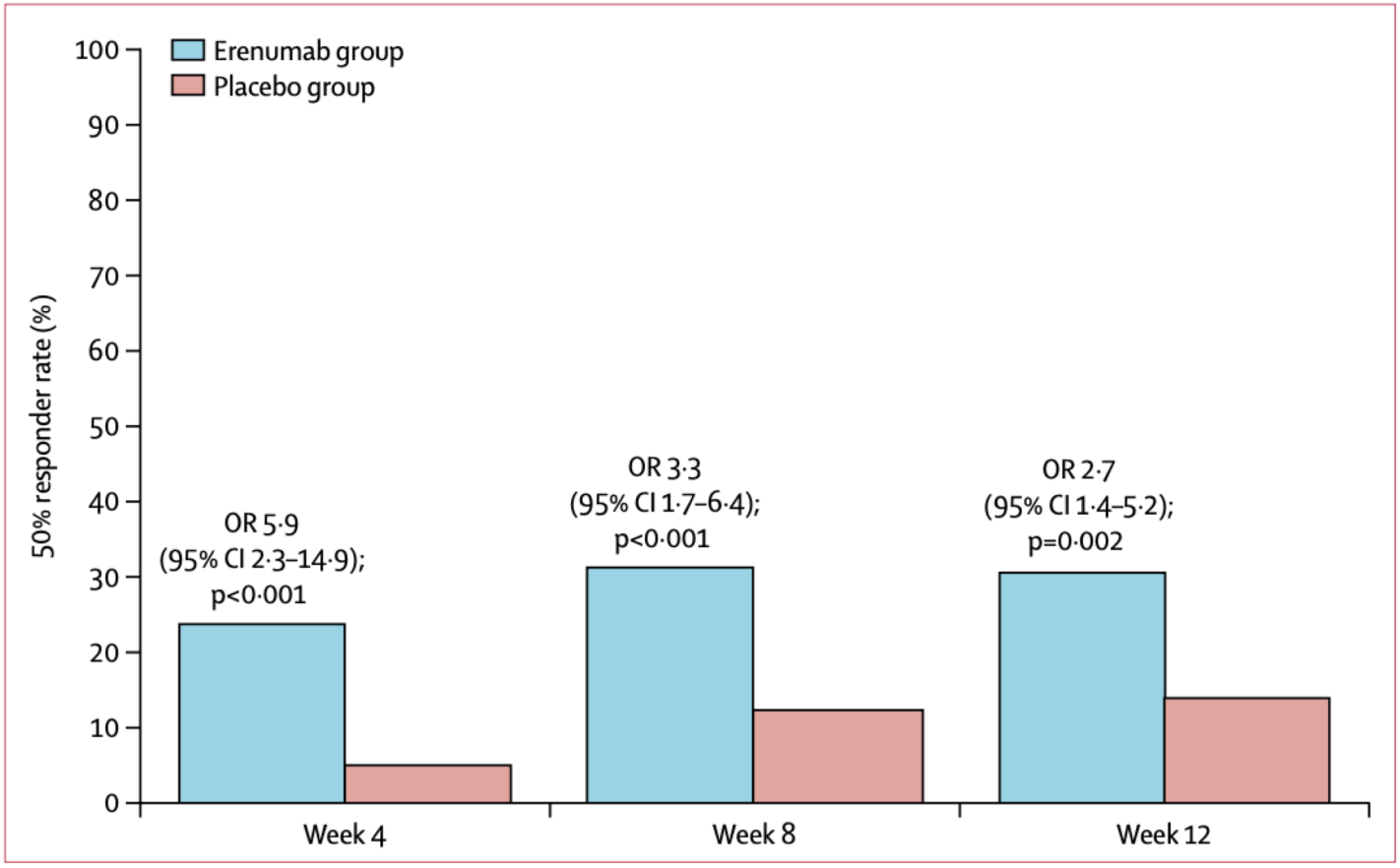


Figure 2: **Proportion of patients with a 50% or greater reduction in monthly migraine days in the erenumab and placebo groups**
OR=odds ratio.

Reuter et al, Lancet 2018

Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial

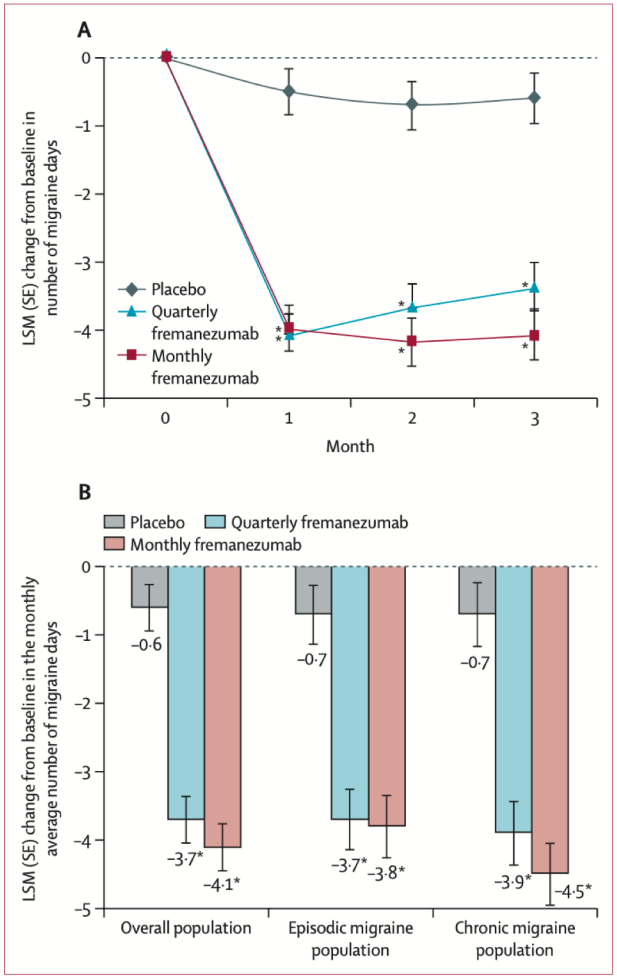


Figure 2: **Primary outcome analysis**
(A) LSM change from baseline in monthly number of migraine days during the double-blind treatment period. (B) LSM change from baseline in monthly average number of migraine days during the 12-week double-blind treatment period. LSM=least-squares mean. SE=standard error. *p<0·0001 versus placebo.

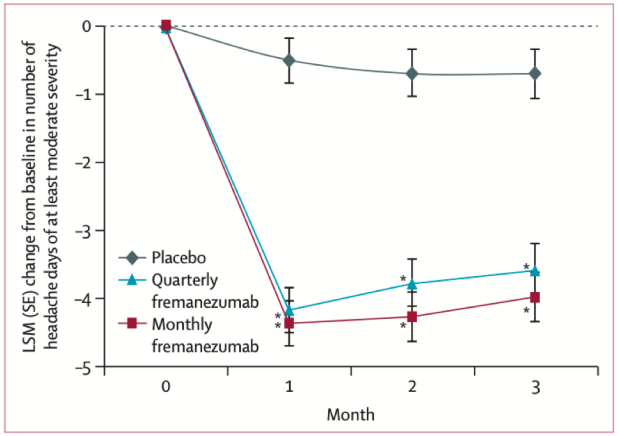


Figure 3: **LSM change from baseline in monthly number of headache days of at least moderate severity**
LSM=least-squares mean. SE=standard error. *p<0·0001 versus placebo.

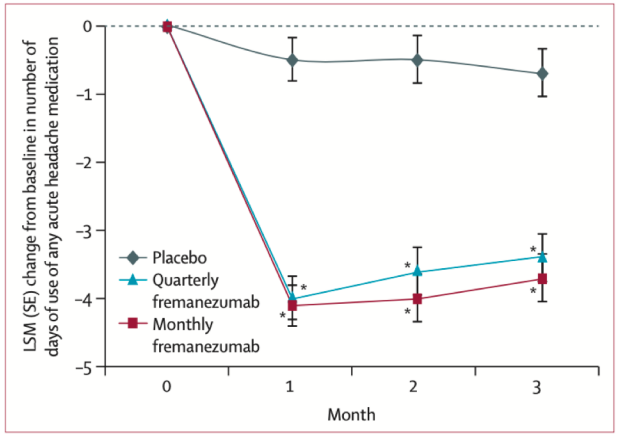


Figure 4: **LSM change from baseline in monthly number of days of use of any acute headache medication**
LSM=least-squares mean. SE=standard error. *p<0·0001 versus placebo.

Ferrari et al, Lancet 2019

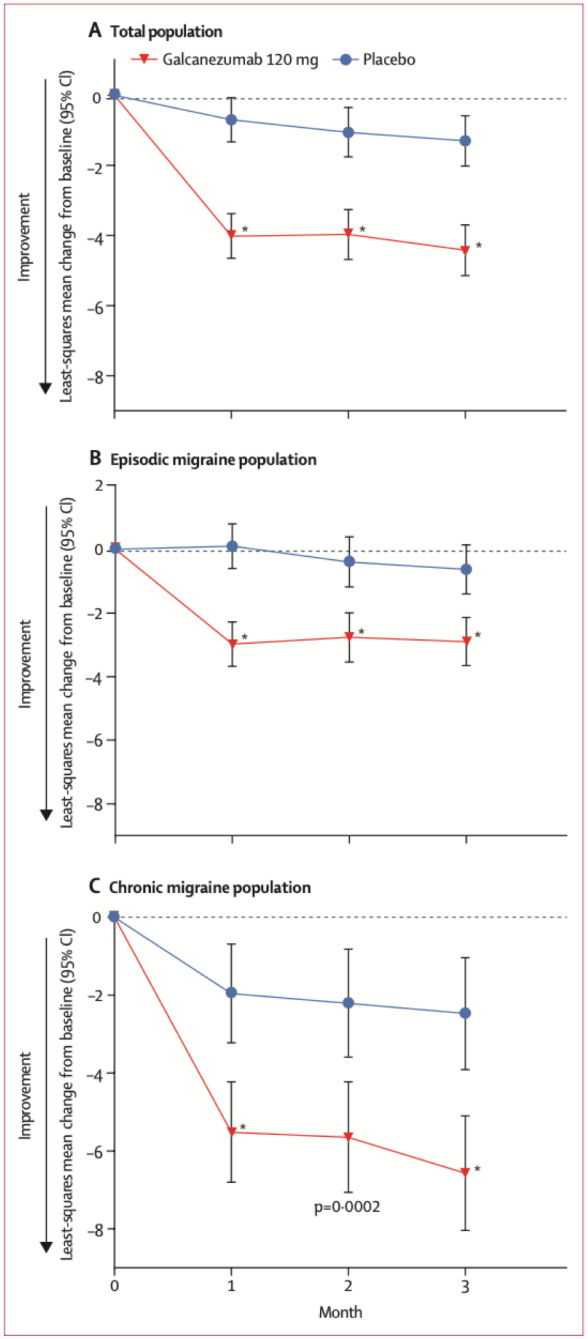


Figure 3: Change from baseline in the number of monthly migraine headache days in the total, episodic migraine, and chronic migraine populations
*p<0·0001 *vs* placebo.

Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial

Mulleners et al, Lancet 2020

Rational polypharmacy for migraine/refractory headache

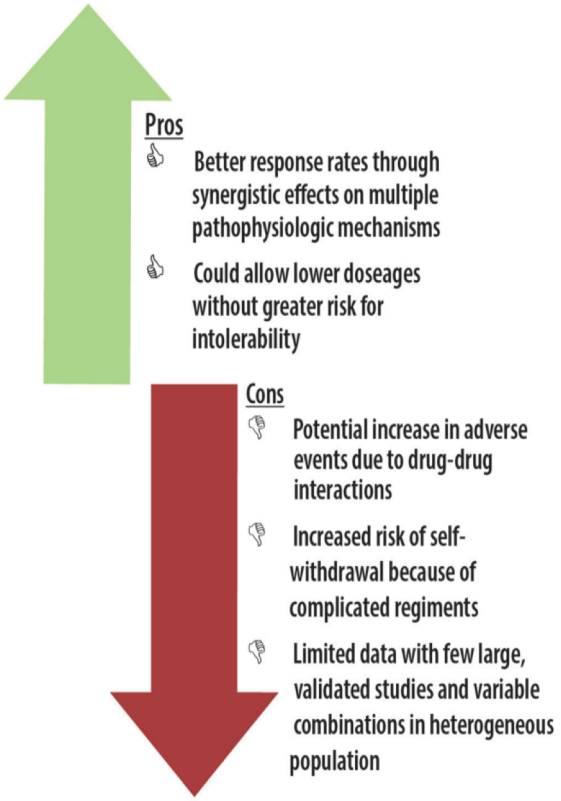


Figure. Advantages vs disadvantages of using polypharmacy in migraine management.

TABLE 2. CURRENT AND POTENTIAL POLYPHARMACY FOR PREVENTIVE MIGRAINE TREATMENT

Combination	Examples	Level of Evidence
β-blocker + ASM	Propranolol + divalproex sodium; propranolol + topiramate	Few small studies with different combinations have shown a > 50% reduction in headache frequency as compared to monotherapy[17-18]
β-blocker + TCA	Propranolol + nortriptyline	A small randomized controlled trial showed that the combination did not result in higher intolerance or more frequent side effects[19]
ASM + TCA	Topiramate + amitriptyline or nortriptyline	A small randomized controlled trial showed a > 50% reduction in headache frequency with dual vs monotherapy[21] and another showed no significant difference in frequency, but dual therapy resulted in higher patient satisfaction[22]
CGRP Mab + onabotulinumtoxinA	Erenumab + onabotulinumtoxinA	Multiple small studies have shown a greater reduction in mean headache/migraine days with combination[26-27]
CGRP Mab + gepants	Galcanezumab + rimegepant;	Small studies with combinations were well tolerated with no increase in adverse effects[31,32]
CGRP Mab + oral migraine preventive medication	Erenumab + topiramate; fremanezumab + propranolol	Post-hoc analysis of 2 randomized placebo-controlled studies showed a greater decrease in monthly migraine days, mean monthly days with moderate-severe headaches, and mean days with acute medication use.[29-31]
Behavioral therapy + oral migraine preventive	Behavioral management + propranolol; biofeedback + flunarizine	Few studies have shown that combination improved outcomes of optimized acute treatment more so than monotherapy[32] and leads to superior long-term management of migraine with analgesic overuse[33]
Neuromodulation + oral migraine preventive	No studies to date, but given different mechanisms combination would be a great option in those who prefer non-pharmacologic options or are unable to tolerate higher doses	

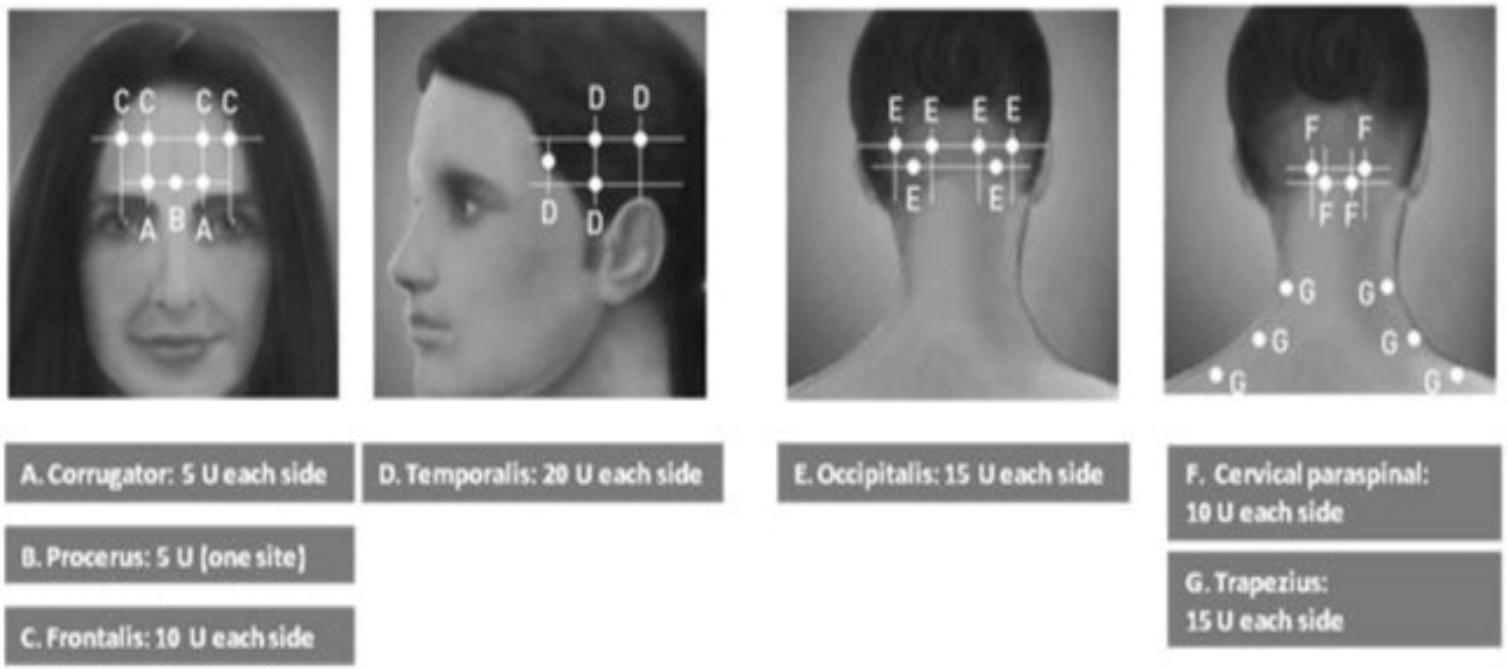
Abbreviations: ASM, antiseizure medication, CGRP, calcitonin gene-related peptide; MAb, monoclonal antibody; TCA, tricyclic antidepressant.

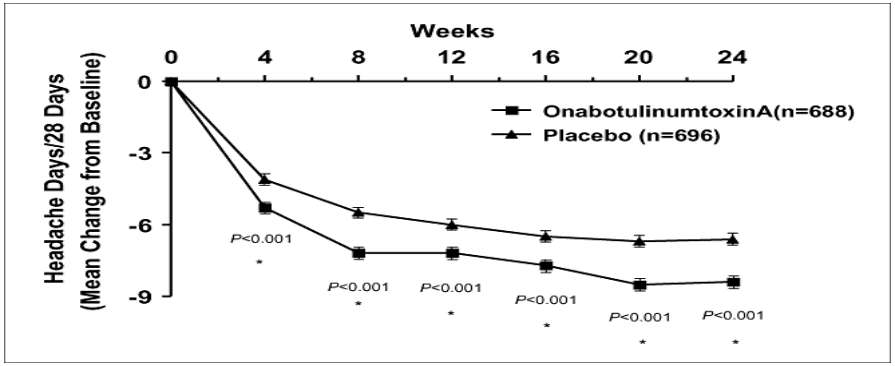
Alex&Armand, Practical Neurology, 2016

Other therapeutic options

- Other medications:
  - Methylergonovine
  - Namenda
  - Ketamine: nasal spray, outpatient infusions
  - Frequent triptans (ie Naratriptan)
  - Opioids
- Behavioral interventions: ACT, biofeedback, etc
- Cannabis, psychedelics
- Ketogenic diet
- Procedures
- Non-invasive and invasive neuromodulations
- Decompressive surgery: controversial
- Revisit previously tried therapies

Onabotulinum toxin A: PREEMPT





Dodick et al, Headache 2010

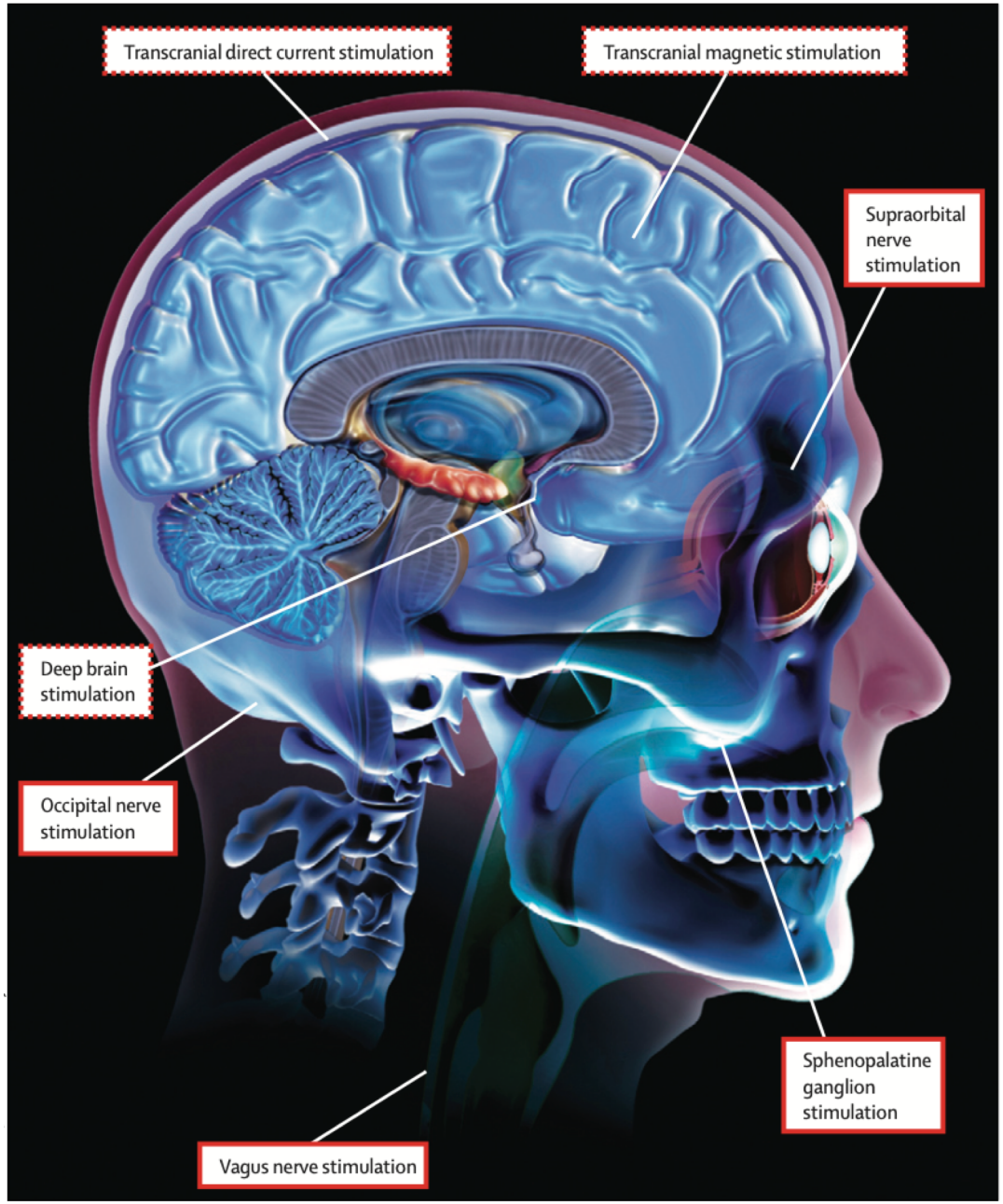


Figure: **Stimulation sites for headache treatment**
Dashed lines represent central neuromodulation techniques and continuous lines are peripheral techniques.

Neuromodulation targets:

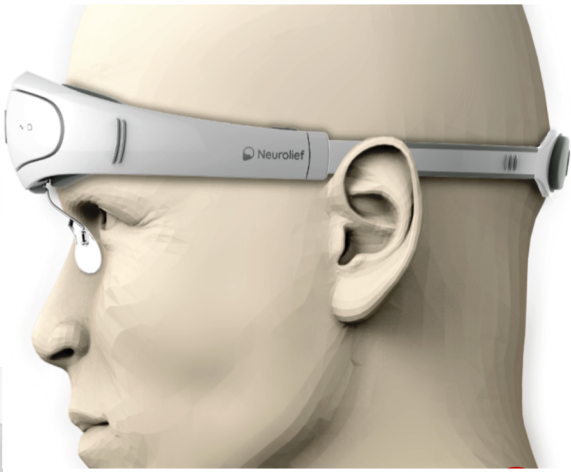
Peripheral and Central

Magis&Schoenen, Lancet Neurology 2012

Devices- FDA cleared

eTNS (Cefaly)

TMS (eNeura)



Multi - channel stimulation (Relivion)

Vagal nerve stimulator (Gammacore)

Remote electrical neuro stimulation (Nerivio)

Inpatient Therapy Options

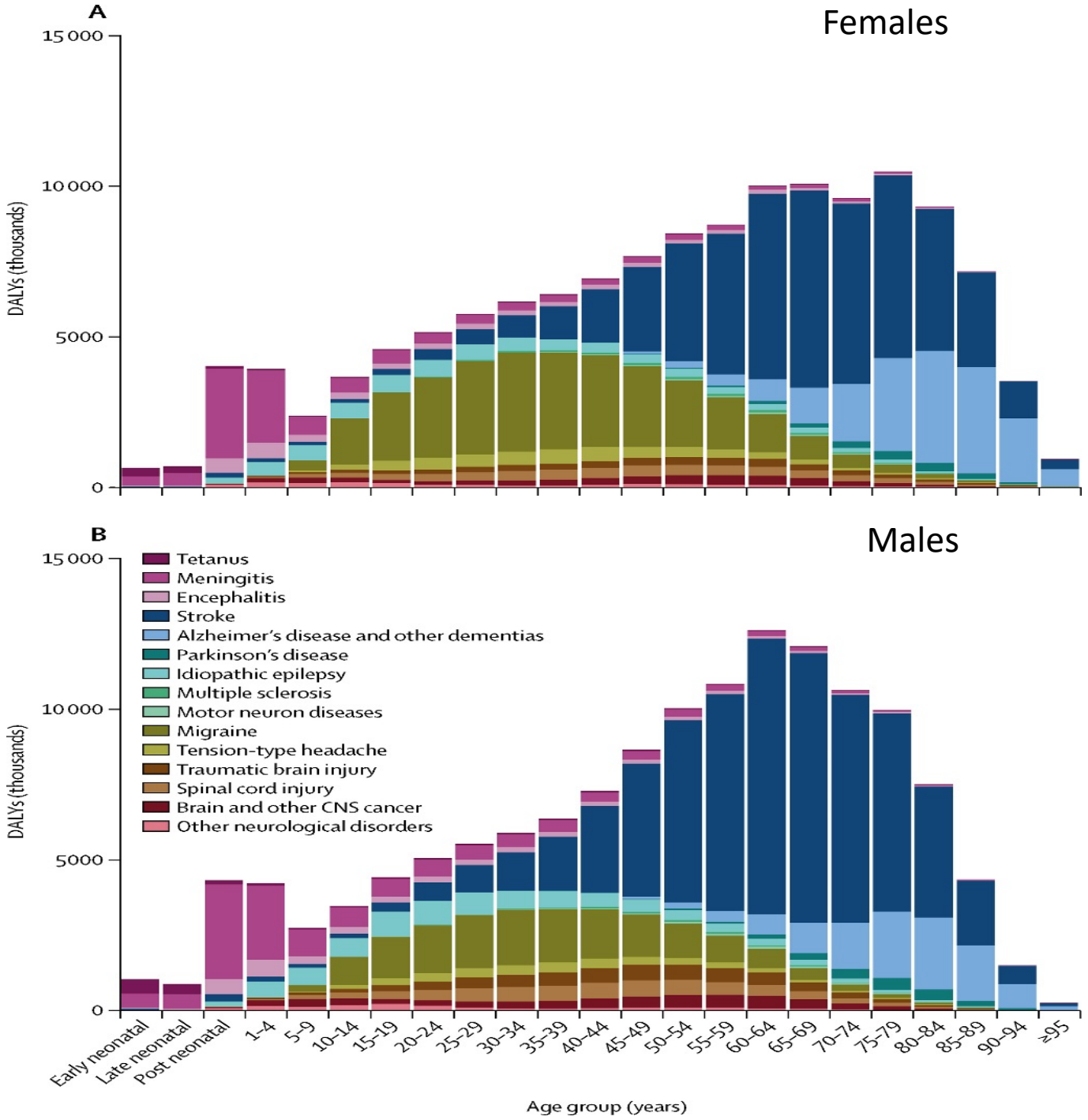
- Dihydroergotamine IV
- Ketamine IV
- Lidocaine IV
- Other

Mojica et al, Current Pain and Headache Reports, 2021

Summary

- Definition of refractory CM is an evolving concept
- Refractoriness is not irreversible
- Many factors are involved in making CM refractory
- Need to account for both patient and provider factors
- Relationship patient-provider is critical
- Therapeutic options can always be tried
- New developments are promising
- It is critical to maintain hope

THANK YOU VERY MUCH!



Global, regional, and national burden of neurological disorders, 1990-2016:

a systematic analysis for the Global Burden of Disease Study 2016.

Lancet Neurol. 2019

Complications of migraine

- Status migrainosus: debilitating migraine attack >72 hours
- Persistent aura (>1 week) without infarction
- Migrainous infarction (aura >60 min and stroke)
- Migraine aura-triggered seizure (within 60 minutes of aura)

ICHD 3, Cephalalgia, 2018

Available definitions for migraine that is difficult to treat

Intractable migraine - Goadsby, 2006

Criteria	Definition
Diagnosis	Migraine (any, criteria not specified)
Medication overuse	-
Refractory definition	Failure of at least four classes, where three should come from 1–4 1 Beta-blockers 2 Anticonvulsants 3 Calcium channel blockers 4 Tricylic antidepressants 5 Other treatments with at least one positive randomized controlled trial 6 Non-steroidal anti-inflammatory drugs 7 Metabolic enhancers, such as vitamin B2 or coenzyme Q10
Adequate trial definition	Appropriate dose Appropriate length of time Consideration of medication overuse
Failed trial definition	No therapeutic or unsatisfactory effect Intolerable side-effects Contraindications to use

Refractory migraine – American Headache Society, 2008

Criteria	Definition
Diagnosis	Episodic or chronic migraine with significant disability, as defined by MIDAS >10
Medication overuse	With or without
Refractory definition	1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: a. Beta-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers 2. Failed adequate trials of abortive medicines from the following classes, unless contraindicated: a. Both a triptan and DHE intranasal or injectable formulation b. Either nonsteroidal anti-inflammatory drugs or combination analgesics
Adequate trial definition	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum tolerated dose, unless terminated early due to adverse effects
Additional criteria	Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy

DHE = dihydroergotamine; ICHD = International Classification of Headache Disorders; MIDAS = Migraine Disability Assessment.

Intractable headache – Silberstein, 2010

Criteria	Definition
Diagnosis	Migraine
Definition of refractory	1. Acute treatment - Class I (mild): Failure of adequate response to 2 different classes of non-specific acute treatments (eg, NSAIDs, combination analgesics) - Class II (moderate): Above plus failure to respond to triptans or ergot derivatives.† If contraindicated, failure to respond to oral dopamine antagonists or parenteral NSAID - Class III (severe): Above plus failure to respond to oral or parenteral opioids or corticosteroids or parenteral dopamine antagonists in adequate doses and appropriate formulation 2. Preventive treatment - Class I (mild): Failure of adequate treatment trial of any of the below reported drugs (may not be contraindication) - Class II (moderate): Failure of adequate treatment trials of 2 of the below reported drugs where 1 must be from a to f - Class III (severe): Failure of adequate treatment trials of 3 of the below reported drugs* where 2 must be from a to f - Class IV (very severe): Above plus failed aggressive infusion or inpatient treatment and/or failure to respond to detoxification treatment in subjects with acute headache pain medication overuse
Prophylactic therapies	(a) Beta-blockers; (b) Tricyclic antidepressants; (c) Verapamil or flunarizine; (d) Sodium valproate (or divalproex sodium); (e) Topiramate; (f) Combination therapy that includes at least 1 drug of type; a-e; the second drug can be from any type (a-e or g-j); The drugs must be of different types (eg, a combination of 2 anticonvulsants is not acceptable); (g) Gabapentin; (h) Other treatments with at least 1 positive; placebo-controlled trial; (i) Non-steroidal anti-inflammatory drugs; (j) Metabolic enhancers (ie, Vitamin B2 or CoQ10)

†Ergot derivatives include dihydroergotamine (DHE). NSAID = non-steroidal anti-inflammatory drug. **Failed medical management, defined as failure or contraindication (1 medicine only) to 3 preventive medications, where 2 must be of different types from a to f below. Failure is contingent on the headache disorder. For episodic migraine it is often defined as <50% reduction in frequency of headache days or attacks. For chronic migraine, treatment failure is defined as <30% reduction in headache days.

Refractory migraine – Austrian Consensus Group, 2014

Criteria	Definition
Diagnosis	Chronic migraine according to ICHD-3-beta for at least 24 months causing significant impairment of quality of life and/or socio-economic burden
Medication overuse	Outpatient or inpatient detoxification and diagnostic re-evaluation after two months of follow-up is mandatory
Refractory definition	Failure of at least 3 adequate treatments with prophylactic medication; use of drugs from at least three of the classes a-d (a) beta blockers: propranolol 80-160 mg, metoprolol 100-200 mg, bisoprolol 5-10 mg (b) anticonvulsants: topiramate 75-100 mg, valproic acid 600-1500 mg (c) tricyclics: amitriptyline up to 75 mg (d) flunarizine: 5–10 mg, (e) other drugs with at least one positive randomised controlled study - e.g. lisinopril 20 mg, candesartan 20 mg, onabotulinumtoxin A 155 – 195U according to PREEMPT
Adequate trial definition	Adequate treatment requires the intake of specific compounds (a) from certain classes of drugs, (b) in an effective dosage, (c) over a period of at least three months
Failed trial definition	(a) no or insufficient efficacy (based on patient report and recordings in a headache diary), (b) intolerable adverse effects, (c) contraindications
Additional criteria	Modification of trigger factors and lifestyle and treatment of comorbid disorders did not improve the headache

Other primary headaches such as hemicrania continua and new daily persistent headache as well as secondary headaches apart from medication overuse headache must be excluded by history, clinical examination and laboratory analyses. (b) Cranial MRI including the cranio-cervical region, MR-angiography and MR-venography do not show a disorder explaining the headache. (d) CSF pressure should be measured in patients with evidence of sinus stenosis in MR-venography

Refractory migraine - European Headache Federation, 2014

Criteria	Definition
Diagnosis	ICHD-III beta chronic migraine
Medication overuse	Excluded
Refractory definition	Contraindications or no effect of the following preventive medication with at least 3 drugs from the following classes: 1. Beta blockers: Propranolol up to 240 mg/d, Metoprolol up to 200 mg, Atenolol up to 100 mg, Bisoprolol up to 10 mg 2. Anticonvulsants: Valproate acid up to 1,5 g/d, Topiramate up to 200 mg/d 3. Tricyclics: Amytriptyline up to 150 mg/d 4. Others: Flunarizine up to 10 mg/d, Cardesartan 16 mg/d 5. OnabotulinumtoxinA: 155 - 195 U according to the PREEMPT protocol
Adequate trial definition	Prophylactic migraine medications in adequate dosages used for at least 3 months each
Additional criteria	Adequate treatment of psychiatric or other comorbidities by multidisciplinary team, if available

Notes:
- Secondary Headache must be excluded
- MRI provides no underlying cause
- Laboratory and CSF analyses within normal range, including CSF pressure
- Meaning of efficacy: reduction on HA days >50%
- Detoxification procedure (in/out hospital setting): intravenous, oral and advice only are all accepted

Refractory migraine - D'Antona and Matharu, 2019

Criteria	Definition
Diagnosis	ICHD-III chronic migraine
Medication overuse	Excluded[b]
Refractory definition	Failure to respond to 5 classes of preventive treatments (including 2 from 1 to 3[c]): 1. Topiramate 2. Minimum of two quarterly injections of Onabotulinumtoxin A 3. CGRP pathway monoclonal antibody 4. Betablockers (Propranolol, Metoprolol, Timolol) 5. Tricyclic antidepressant (Amitriptyline) 6. SNRI (Venlafaxine) 7. Sodium valproate/Divalproex sodium 8. Other pharmacological preventive treatments with established efficacy in migraine[f]
Adequate trial definition	At least 2 month trial at an optimum or maximum tolerated dose (excluding the time taken for the titration o the dose), unless terminated early due to side effects[d]
Failed trial definition	1. Failure to respond to drug (< 50% reduction in frequency and/or severity of monthly migraine days) 2. Intolerable side effects 3. Contraindication to use

CGRP calcitonin gene related peptide, ICHD International Classification of Headache Disorders, SNRI Serotonin-noradrenaline reuptake inhibitor
[b]Patients who overuse abortive treatments can be included provided medication overuse headache has been excluded
[c]Applicable if available in the local healthcare system
[f]2 class I or 2 class II based on American Academy of Neurology Scheme for classification of evidence
[d]Optimum dose defined as that used in the controlled trials demonstrating efficacy or as outlined by local treatment guidelines

Sacco et al. J Headache Pain 2020

Phylosophy and migraine

Without a philosophy…

- Locus of control rests with the doc or the meds
- Medication selection resembles “darts in the dark”
- Lifestyle modification is often negative

With a philosophy…

- Locus of control returns to the patient
- Medication selection is goal-directed and contextual
- Lifestyle modification is positive