MIGRAINE UPDATE

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Disclosures

- Non related to this talk
- Winter boots
- Confession

1. Extrapolate to a clinical setting the diagnostic criteria for migraines.
2. Classify different migraine phenotypes.
3. Categorize the treatment options for migraines.

Definition

- The ICHD-3 has a nice interactive website to review the criteria for headaches.
- https://ichd-3.org/1-migraine/

TIMELINE OF A MIGRAINE ATTACK

PRODROME
FEW HOURS TO DAYS

- IRRITABILITY
- DEPRESSION
- YAWNING
- INCREASED NEED TO URINATE
- FOOD CRAVINGS
- SENSITIVITY TO LIGHT/SOUND
- PROBLEMS IN CONCENTRATING
- FATIGUE AND MUSCLE STIFFNESS
- DIFFICULTY IN SPEAKING AND READING
- NAUSEA
- DIFFICULTY IN SLEEPING

AURA
5-60 MIN

- VISUAL DISTURBANCES
- TEMPORARY LOSS OF SIGHT
- NUMBNESS AND TINGLING ON PART OF THE BODY

HEADACHE
4-72 HRS

- THROBBING
- DRILLING
- ICEPICK IN THE HEAD
- BURNING
- NAUSEA
- VOMITING
- GIDDINESS
- INSOMNIA
- NASAL CONGESTION
- ANXIETY
- DEPRESSED MOOD
- SENSITIVITY TO LIGHT, SMELL, SOUND
- NECK PAIN AND STIFFNESS

POSTDROME
24-48 HRS

- INABILITY TO CONCENTRATE
- FATIGUE
- DEPRESSED MOOD
- EUPHORIC MOOD
- LACK OF COMPREHENSION

Setting realistic expectations

- Frequency of migraine days
- Intensity of headache pain during residual attacks
- Use of medication(s) for the acute treatment of migraine attacks.
- What is not
- Migraines will disappear
- Preventive medication timing to declare failure.

Diener HC, Tassorelli C, Dodick DW, Silberstein SD, Lipton RB, Ashina M, Becker WJ, Ferrari MD, Goadsby PJ, Pozo-Rosich P, Wang SJ, Houle TT, Hoek TCVD, Martinelli D, Terwindt GM; International Headache Society Clinical Trials Committee. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. Cephalalgia. 2020 Sep;40(10):1026-1044. doi: 10.1177/0333102420941839. Epub 2020 Jul 28. Erratum in: Cephalalgia. 2020 Aug 18;:333102420952270. PMID: 32722936.

One size fits all

- Around 50% of patients will reduce 50% migraine frequency
- Adherence is less than 25% after 1 year
- Trial and error process (Heterogeneity of the condition)
- Sense of ownership: set goals
- Reassure that many options are available

The perfect team

- Trigger identification. If your headaches are driven by poor sleep and you do not plan to improve this aspect, medications for prevention are not the solution.
- Win situation: frequency or magnitude reduction
- Keep a track.
    - Migraine Disability Assessment (MIDAS) (headaches.org/wp-content/uploads/2018/02/MIDAS.pdf)5,6 or the six-item Headache Impact Test (HIT-6) (headaches.org/wp-content/uploads/ 2018/02/HIT-6.pdf)
- I have headaches every day. Ask about headache free days
- Attacks are not treated with preventive. Conversely, daily attack treatment is not preventive.
- Treat attacks rapidly.
- Another common clinical question is when to consider withdrawing a patient from preventive treatment. Few studies are available to guide decision making in this area.

The real question is why are migraine specific medications not the first line?

WHY ARE WE USING OLD ANTISEIZURE DRUGS, HEART MEDICATIONS AND OLD ANTIDEPRESSANTS INSTEAD OF MIGRAINE SPECIFIC DRUGS?

Rationale

- Migraine is one of the leading causes of disability.
- New target-driven class of migraine preventive treatments that act by blocking calcitonin gene related peptide (CGRP) has been developed.
- CGRP is a neurotransmitter with an essential role in migraine pathophysiology.
  - CGRP monoclonal antibodies (CGRP-mAbs),
    - Erenumab which blocks CGRP receptor
    - Eptinezumab, fremanezumab, and galcanezumab that are CGRP blockers
  - Small molecule CGRP receptor antagonists, or gepants, including atogepant and rimegepant.

Yuan H, Spare NM and Silberstein SD. Targeting CGRP for the prevention of migraine and cluster headache: a narrative review. Headache 2019; 59: 20–32

Useful terminology

Chronic 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.

Episodic less than 15

Responder: no clear definition.

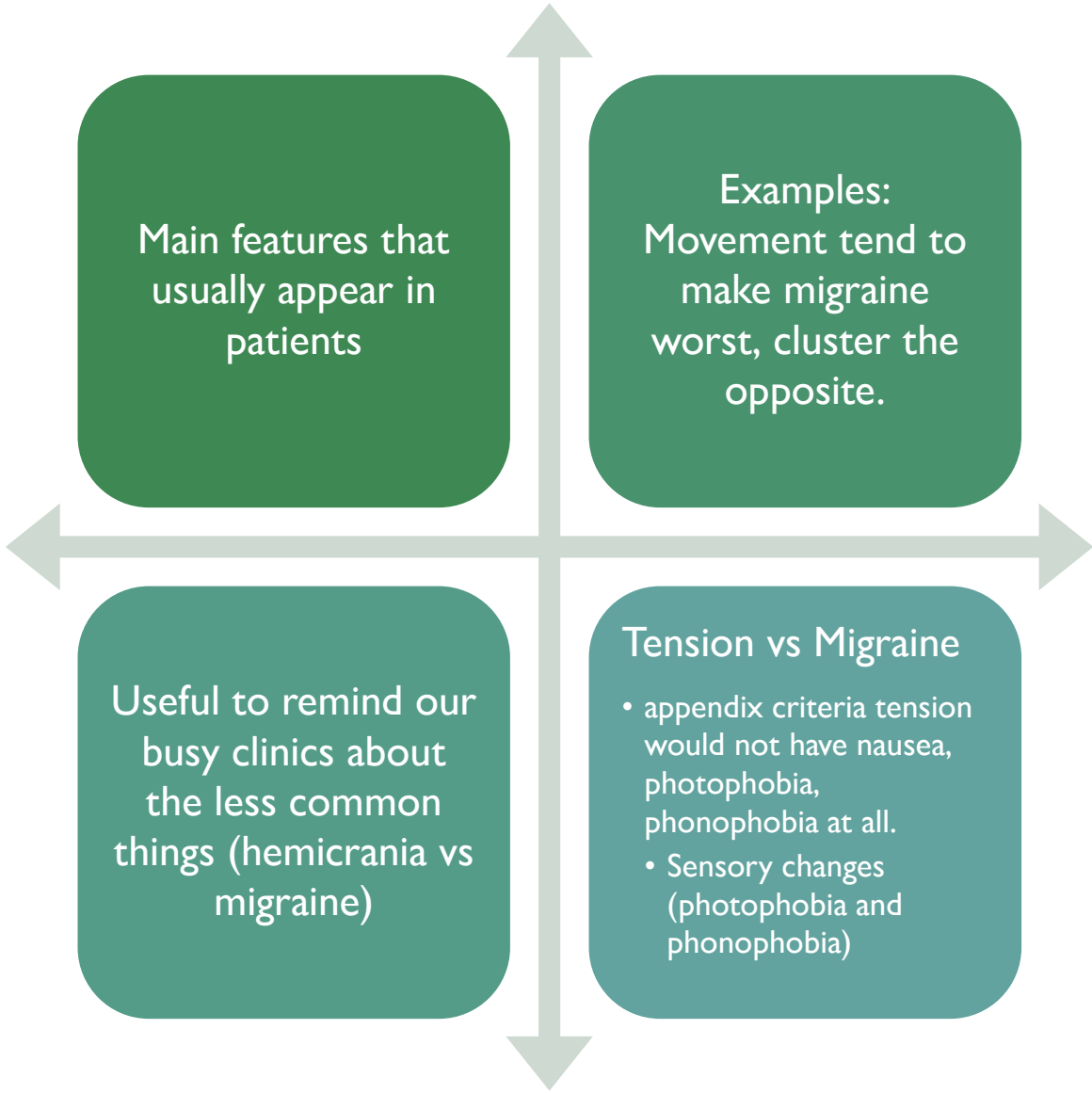
- Patients with migraine who achieved pain freedom within 2 hours of acute treatment in ≥4 of 5 attacks.
- EM and CM responders defined as a reduction of ≥ 2 or ≥ 4 monthly migraine days, respectively.
- Treatment benefits evaluated included reductions in monthly migraine days, acute headache medication use, and headache-related disability, and changes in health-related quality of life

Monthly migraine days (MMD)

Responder rate (>50%)

Tassorelli C, Diener HC, Dodick DW, Silberstein SD, Lipton RB, Ashina M, Becker WJ, Ferrari MD, Goadsby PJ, Pozo-Rosich P, Wang SJ; International Headache Society Clinical Trials Standing Committee. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. Cephalalgia. 2018 Apr;38(5):815-832. doi: 10.1177/0333102418758283. Epub 2018 Mar 4. PMID: 29504482.

- Classification of headache disorders
- Encompass most things
- Not designed to nail every headache
- Never get in the way of clinical judgement
- It is not as a rigid jacket


Main features that usually appear in patients
Examples: Movement tend to make migraine worst, cluster the opposite.
Useful to remind our busy clinics about the less common things (hemicrania vs migraine)
Tension vs Migraine
• appendix criteria tension would not have nausea, photophobia, phonophobia at all.
• Sensory changes (photophobia and phonophobia)

- Not perfect the elephant in the room Migraine vs. Tension
- We need structural discussions to define rare headaches disorders.
- Distinction between episodic and chronic?? <14
- Messy terms like low frequency, continuos, intractable and refractory. It means different things to different physicians.

What is Aura and What is not

Discrete neurologic event, usually visual.

Starting at the center and moving outside or vice versa.

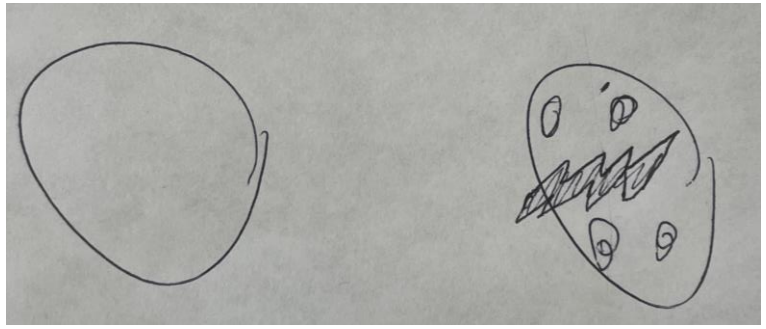
Floaters or blurry not aura.

Ask them to draw the aura

Zigzag line in my right side (occipital in origin)

Flashes of light followed by floaters= be careful retinal detachment.

Blurry vision preceding headaches is common, pain related phenomena. Reported during, before or after. Poorly understood phenomena.



Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021; 17: 501–514.

What is a retinal migraine

To be honest there is no consensus on this term

Vasospasm transient visual loss. Can be observed in fundoscopy. Is it a real migraine? Or a different event.

Ocular migraine is not in the ICHD3. Often referred to as migraine with aura.

Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021; 17: 501–514.

Light that is normal light should not be painful, unless you have migraines. It is a very common debilitating symptom.

Mechanism interesting different pathways. Visual forming system, rods and cones projecting ganglion cells, axons to lateral geniculate body and so on to occipital. This system is connected to the pain system.

Intrinsically photosensitive ganglion cells and project to posterior olivary nuclei, pupillary reflex, suprachiasmatic nuclei, other brainstem, and posterior thalamus (pain).

Connection to the limbic system, aka the system related to anxiety and mood. Could explain why photophobia is related to this disorders.

Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021; 17: 501–514.

My algorithm photophobia

- Different types of headaches.
- Central process, meningeal, pituitary, by history.
- Look into the eye. Some neuroophtalmologists use eye drop anesthetics to determine if the photophobia is related to the eye (surface eye pain). Dry eyes with a schimmer strips paper too.
- In migraines photophobia is a debilitating symptom, probably second after the headache.
- Blepharospasm, squeezing eyes all the time. It can be reflexive in response to light.
- Retinitis
- If it is not one of those things the answer is migraines.
- Some evidence for FI41 dark glasses if the main problem is photophobia (blue green wave length)

Kumar A, Bhatia R, Sharma G, Dhanlika D, Vishnubhatla S, Singh RK, Dash D, Tripathi M, Srivastava MVP. Effect of yoga as add-on therapy in migraine (CONTAIN): A randomized clinical trial. Neurology. 2020 May 26;94(21):e2203-e2212. doi: 10.1212/WNL.0000000000009473. Epub 2020 May 6. PMID: 32376640.

Interesting add-on tips

- The efficacy of yoga therapy for migraine remains controversial.
- Meta-analysis.
- yoga therapy was associated with substantially reduced headache frequency headache frequency (SMD = -1.43; 95% CI = -2.23 to -0.64; P = 0.0004) and HIT-6 score (SMD = -2.19; 95% CI = -4.09 to -0.28; P = 0.02), but revealed no obvious influence on pain intensity (SMD = -1.37; 95% CI = -2.76 to 0.01; P = 0.05) or McGill Pain Questionnaire (SMD = -2.09; 95% CI = -6.39 to 2.22; P = 0.34).
- Reduced frequency.
- This study provides Class III evidence that for patients with episodic migraine, yoga as adjuvant to medical therapy improves headache frequency, intensity, impact, and disability.

Anheyer D, Klose P, Lauche R, Saha FJ, Cramer H. Yoga for Treating Headaches: a Systematic Review and Meta-analysis. J Gen Intern Med. 2020 Mar;35(3):846-854. doi: 10.1007/s11606-019-05413-9. Epub 2019 Oct 30. PMID: 31667736; PMCID: PMC7080891.

Acupuncture

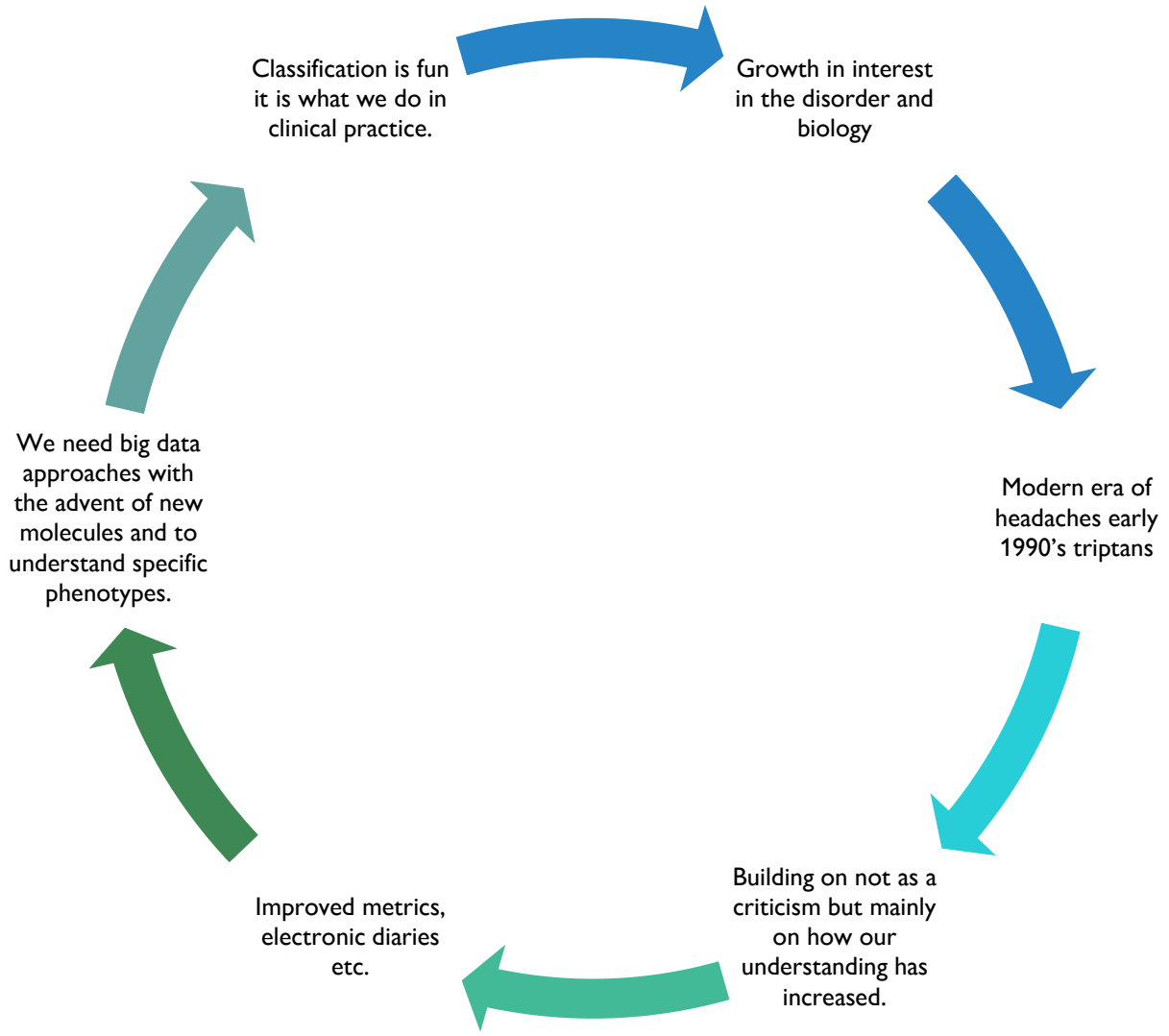
- Preparing my presentation, I found this regarding TH.

Zheng H, Gao T, Zheng QH, Lu LY, Hou TH, Zhang SS, Zhou SY, Hao XY, Wang L, Zhao L, Liang FR, Li Y. Acupuncture for Patients With Chronic Tension-Type Headache: A Randomized Controlled Trial. Neurology. 2022 Jun 22:10.1212/WNL.0000000000200670. doi: 10.1212/WNL.0000000000200670. Epub ahead of print. PMID: 35732505.

FL41

Patient may show with dark glasses.
Tinted lenses have been used (England orphanage treated children)
Wavelentgh blue green area 480 520 wavelength
Children had marked improvement of headaches
Blepharospasm and migraines
For some people work
Not everything work for everyone.
Pure blue, black, green tinted. If possible, just try it.
Sometimes a combination of migraine and dry eye.
Chronic migraine a study found that over 90% had dry eyes.

Why was there a new update on the guidelines for migraines



Ailani J, Burch RC and Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache 2021; 61: 1021–1039

CGRP overview

- Fascinating discovery
- 1985 trigeminovascular reflex
- CGRP released during migraine attacks
- Trigeminal CGRP containing neurons are equipped with receptors for estrogens and oxytocin. Females preponderance?
- Genetic differences GWAS studies 400,000 predominant link to X chromosomes. Loci 123 spread evenly, it appears to be no genetic difference.
- Estrogen receptors, numerous in neurons containing CGRP receptors, some nuclear.
- Oxytocin receptor in trigeminal ganglia.
- Blood brain barrier trigeminal system lacks, estrogen oxytocin come in freely and modify it. Females dynamic changes during hormone cycle.
  - Nature paper catamenial migraine estrogen, oxytocin, progesterone diminish before menstruation was associated with migraine attacks.
  - What happens in males; who has more debilitating symptoms unanswered questions.

CGRP signaling

- Observation, trigeminovascular reflex.
- Inducing vasocontriction, sensory fibers release CGRP to control vessel tone.
- CGRP antivasconstricor
- Brain vessels from patients who died from stroke had no detectable CGRP levels. Other substance P were normal
- Helps vasodilation and prevents vasoconstriction.
- Subarachnoid hemorrage? Could it reverse vasospasm
- Non responders try a different one or a higher dose. Down the pipeline another alternative will be gepants.

	Anti CGRP rec AB	Anti CGRP antibodies	CGRP receptor antagonist	Route	Dose	Administration
Erenumab	X			SC	70mg 140mg	Monthly
Framenezumab		X		SC	225mg	Monthly 675mg every 3 months
Galcanezumab		X		SC	120mg	Requires loading dose 240mg, then 120mg monthly
Eptinezumab		X		IV	100mg 300mg	Infusion
Rimegepant			X	Oral	75mg	Every other day
Ubrogepant	ATTACK MEDICATION NOT PREVENTIVE		X	Oral	50mg and 100mg	Option for attacks (triptan unresponsive patients?)

The main difficulty is that they are new

- No long-term data
- No evidence for specific phenotypes (e.g., migraine with aura hemiplegic, catamenial)
- Pregnancy?
- Medication overuse
- Sounds compelling to try a different mechanism if one fails.
- Side effects: skin reactions and hypersensitivity. Erenumab has been around longuer hypertension and constipation.

Consensus statement

- Major finding: there is solid literature data from high quality trails to prevent episodic and chronic migraines for all Moloclonal AB.
- Significantly reduction in migraines days.
- Placebo control trials statistically significant to meet definition of responder
- Safe high quality data
- Also quality data for Botulinum toxin injections

Ailani J, Burch RC and Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache 2021; 61: 1021–1039

Clinic trials not rigorous as now.

Head to head trial topiramate vs Erenumab.

Erenumab non inferior: demonstrated a favourable tolerability and efficacy profile compared to topiramate.

Seven hundred and seventy-seven patients.

In the erenumab group, 10.6% discontinued medication due to adverse events compared to 38.9% in the topiramate group (odds ratio, 0.19; 95% confidence interval 0.13-0.27; $p < 0.001$).

More patients achieved a ≥50% reduction in monthly migraine days from baseline with erenumab (55.4% vs. 31.2%; odds ratio 2.76; 95% confidence interval 2.06-3.71; $p < 0.001$).

Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S, Hours-Zesiger P, Nickisch J, Sieder C, Hentschke C, Maier-Peuschel M. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia. 2022 Feb;42(2):108-118. doi: 10.1177/03331024211053571. Epub 2021 Nov 7. PMID: 34743579; PMCID: PMC8793299.

European Headache Federation

- Also updated evidence.
- At some point it was question why they were released in the middle of the release of new molecules.
- There was substantial quality data to show.
- Number of systematic reviews and meta-analysis
- Giving a better sense that they are very effective for both episodic and chronic.
- How to help guide clinicians
- Not aimed to force medications
- They support older medications, but if you feel these new drugs are a better choice push for the patient.
- Clinicians should have the right to choose with the patient a medication
- Statement of medical attestation

Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R, Katsarava Z, MaassenVanDenBrink A, Martelletti P, Mitsikostas DD, Ornello R, Reuter U, Sanchez-Del-Rio M, Sinclair AJ, Terwindt G, Uluduz D, Versijpt J, Lampl C. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022 Jun 11;23(1):67. doi: 10.1186/s10194-022-01431-x. PMID: 35690723; PMCID: PMC9188162.

What to do if insurance to not want to cover migraine specific treatments

- Cite the consensus
- Letter of medical necessity
- Encourage a conversation of treatment options.
- Highlight the excellent tolerability and compared poor side effects of migraine-non-specific medications.
- Tolerability is an important topic to review with the patient.
- In clinical practice, guidelines are a good starting point.
- Efficacy is one part of the pie, but tolerability and adherence are central.
- Understanding and extrapolating the evidence to the patient leads to right decision which improve outcomes

Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R, Katsarava Z, MaassenVanDenBrink A, Martelletti P, Mitsikostas DD, Ornello R, Reuter U, Sanchez-Del-Rio M, Sinclair AJ, Terwindt G, Uluduz D, Versijpt J, Lampl C. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022 Jun 11;23(1):67. doi: 10.1186/s10194-022-01431-x. PMID: 35690723; PMCID: PMC9188162.

CONTINUE

- Guidelines should consider costs.
- Healthcare economics.
- Sometimes we cannot backup evidence with insurance companies
- We cannot always do what we sometimes aim to prescribe.
- Medical attestation
- Run the extra mile
- In a patient with no comorbidities it is reasonable to try the older medications

Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R, Katsarava Z, MaassenVanDenBrink A, Martelletti P, Mitsikostas DD, Ornello R, Reuter U, Sanchez-Del-Rio M, Sinclair AJ, Terwindt G, Uluduz D, Versijpt J, Lampl C. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain. 2022 Jun 11;23(1):67. doi: 10.1186/s10194-022-01431-x. PMID: 35690723; PMCID: PMC9188162.