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Medication Overuse Headache

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Disclosures: Farnaz Amoozegar, MD, MSc, FRCPC

Consultant/Advisory Boards: AbbVie, Eli Lilly, ICEBM, Lundbeck, Novartis, Pfizer, Teva

Speakers Bureau/Honoraria: AbbVie, Aralez, Eli Lilly, Novartis, Organon, Teva

Educational Grants (research or education): AbbVie, CIHR, Eli Lilly, Teva, Pfizer

Other: Research grants from charitable organization – Spinal CSF Leak Canada

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Learning Objectives

Upon completion of this activity, learners will be able to

- Define Medication Overuse Headache (MOH)
- Describe the pathophysiology of MOH
- Become familiar with an approach to management
- Discuss the various treatment options for MOH

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Case Introduction - Sandra

- 47F
- Long history of migraine dating back to teenage years
  - Initially low frequency and often associated with menstruation
  - Previously relieved by OTC medications and never needed help from HCP
- In 30s, after 2nd child, headaches became more frequent
  - Currently experiencing some symptoms of perimenopause
  - Feels increasing need for headache treatment days over the last few years

Sandra

- Currently:
  - 17 Total Monthly Headache Days
  - 10 Monthly Migraine Days
  - 13 Headache Free days
- Medications:
  - Sertraline 50mg (started for mood during perimenopause)
  - ASA/Caffeine/Acetaminophen – using 12-15 days per month
  - Ibuprofen 400mg – additional 3-5 days per month
- She has not previously tried acute therapies specific to migraine, nor preventives for migraine

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Discussion

Dr. Kingston, what are you worried about in this patient?

How is Medication Overuse Headache (MOH) diagnosed?

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What is Medication Overuse Headache?

ICHD-3 Diagnostic Criteria for Medication Overuse Headache

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

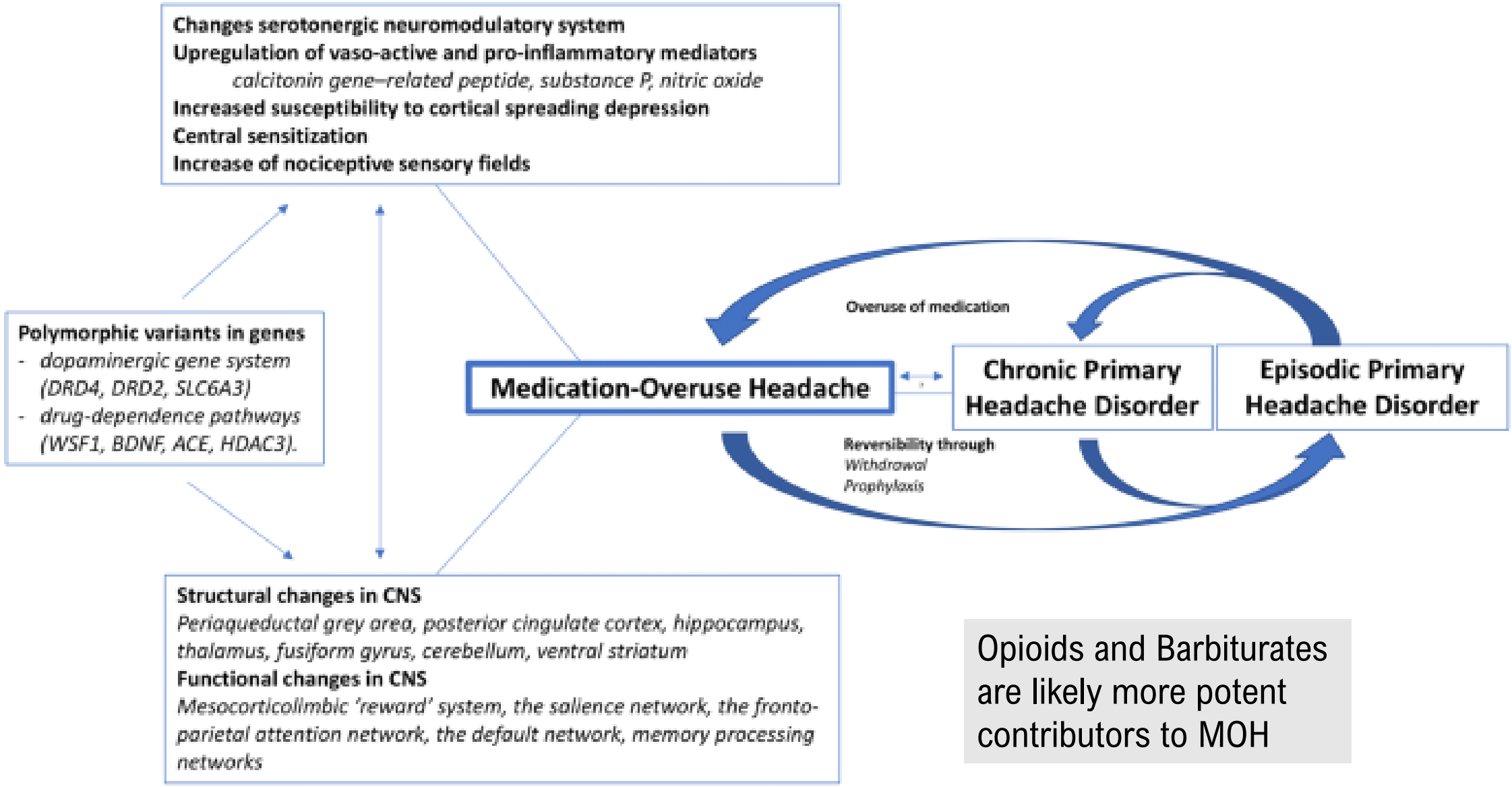
Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

Not better accounted for by another ICHD-3 diagnosis

Recommended Monthly Maximums

Medication	Maximum days / month (ICHD-3 criteria)
Opioids	<10
Barbiturates (butalbital combinations)	<10
Triptans	<10
Ergotamines (DHE)	<10
Acetaminophen	<15
Combination analgesia	<10
ASA	<15
Nonsteroidal anti-inflammatory drugs	<15

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211.
Adapted from Migraine Matters slide deck.



Opioids and Barbiturates are likely more potent contributors to MOH

Vandenbussche N, et al. Medication-overuse headache: a widely recognized entity amidst ongoing debate. J Headache Pain. 2018 Jul 13;19(1):50.

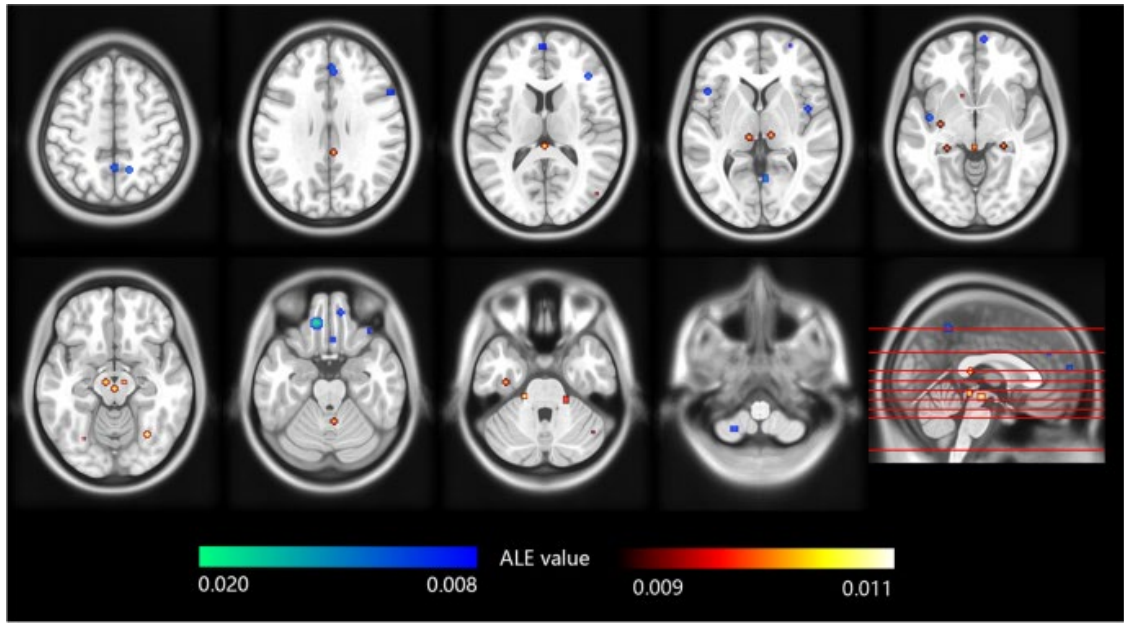
MOH Pathophysiology

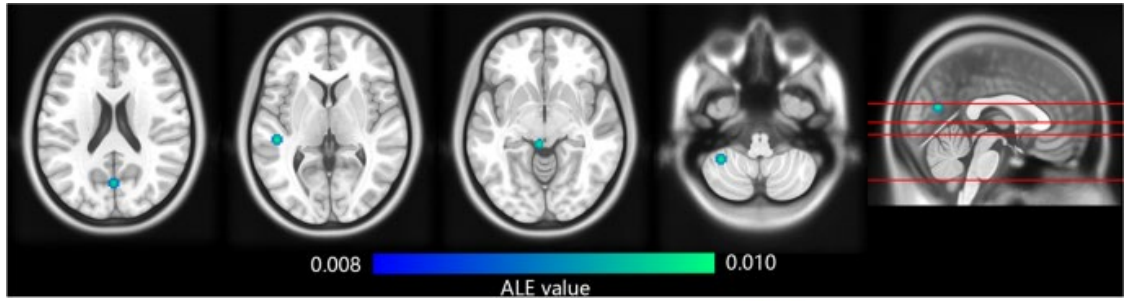
- Chronic exposure to acute headache medications leads to:
  - Altered descending pain modulation
  - Central sensitization
- Mediated by dysfunction in:
  - Endogenous antinociceptive systems
    - Serotonergic pathways
    - Endocannabinoid pathways
- Resultant increased excitability of trigeminal and cortical neurons.
- Facilitate the trigeminal nociceptive process and promote upregulation and release of calcitonin gene-related peptide (CGRP), which further sensitizes pain pathways.

Ashina S, et al. Medication overuse headache. Nat Rev Dis Primers. 2023 Feb 2;9(1):5.
Sun-Edelstein C, et al. The Evolution of Medication Overuse Headache: History, Pathophysiology and Clinical Update. CNS Drugs. 2021 May;35(5):545-565.

Imaging Changes in MOH

- Several studies (functional and structural) have identified differences in MOH brains compared with CM without MOH.
  - Reduced grey matter volume – most notably orbitofrontal cortex
    - May be linked to ”number of pills taken”
  - fMRI show reduced activity in right putamen
    - Altered functional connectivity between putamen, cingulate, lingual and precuneus
  - fMRI shows hypoperfusion in certain hypothalamic regions.
  - MRS – distinct metabolite profiles in anterior cingulate and thalamus





Chong CD. Brain Structural and Functional Imaging Findings in Medication-Overuse Headache. Front Neurol. 2020 Jan 28;10:1336.
Chen W, Li H, Hou X, Jia X. Gray matter alteration in medication overuse headache: a coordinates-based activation likelihood estimation meta-analysis. Brain Imaging Behav. 2022 Oct;16(5):2307-2319.

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Clinical Signs of Medication Overuse Headache

Increased headache frequency temporally associated with increase in acute medication use

Morning headaches signalling acute medication withdrawal

Predictable occurrence of headache when acute medication is delayed

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Adapted from Migraine Matters slide deck.

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Patient and Physician Perspectives on MOH

Patient perspective: Avoiding or delaying acute medications may lead to more severe and longer attacks

- "To treat or not to treat" is a constant concern for patients
- "I have to function" is what the patient is thinking

Physician Perspective: Frequent use of acute treatments can lead to or maintain chronic migraine

- Patient education is key
- Avoid the term "overuse" with patients, as may be stigmatizing
- Medication Induced Headache may be a better term when discussing with patients

In addition to increased frequency of acute medication use, other clues include:

- Behaviour associated with use (e.g., rituals, anxiety, use of medication before headache onset)
- Loss of effectiveness of acute medication over time – "the medication is not working as well as it used to."

Ashina S, et al. Medication overuse headache. Nat Rev Dis Primers. 2023 Feb 2;9(1):5.
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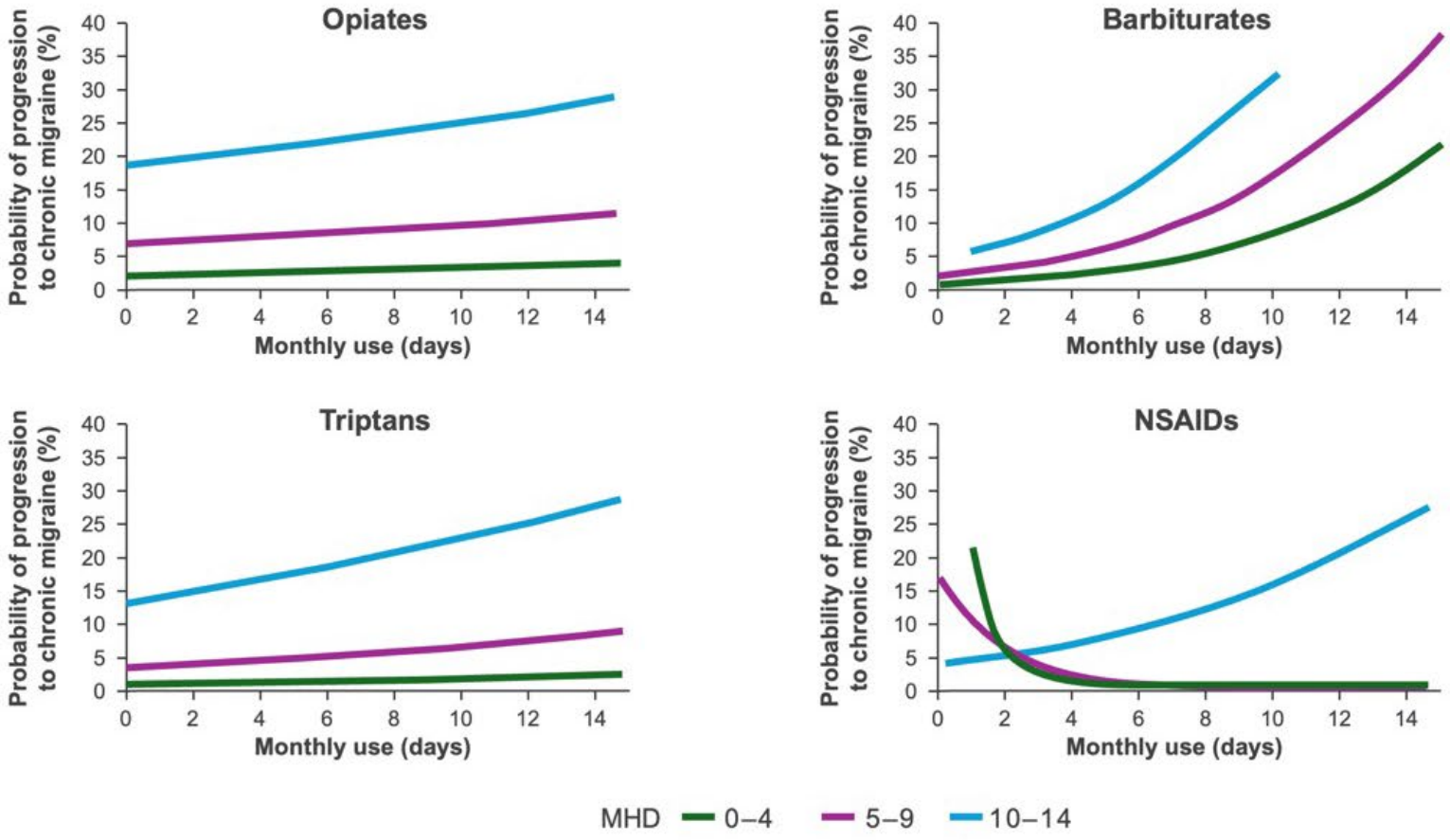
Medication Overuse and Associated Progression to Chronic Migraine

Overuse of opioids, barbiturates, and triptans are associated with progression to chronic migraine



MHD, monthly headache days.

Bigal ME et al. *Headache* 2008;48:1157-1168.

Sandra - Update

- We see Sandra 6 months later
- At the previous visit, she had been counselled to reduce her acute medications, started on a sumatriptan and Candesartan
- Fatigued with sumatriptan & lightheaded with Candesartan; stopped them
- Now experiencing
  - Daily Headache
  - Less responsiveness to acute treatments (both Ibuprofen and Excedrin)
  - Headaches worse in the morning
  - More absenteeism/presenteeism
- Medications:
  - ASA/Caffeine/Acetaminophen – 20 days per month
  - Ibuprofen 5 days per month

Sandra - Update

- She is now wondering about next steps
- Her family MD expressed concern about her frequent medication use
- She wonders whether any treatments can help her reduce her medication use and her headache frequency.

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Discussion

Dr. Amoozegar, what is your approach to managing MOH?

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Approach to Management of MOH

- Patient education is key
- Work on reducing/removing or tapering overused medication as appropriate (concerns beyond MOH, e.g. systemic effects)
- Offer alternative acute therapies if possible
- Offer bridge/transitional therapy when appropriate
- Provide preventive therapy
- Set realistic expectations, including possible initial worsening before improvement
- Provide support to patient throughout the process

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CHS Statements on MOH from 2024 Guidelines

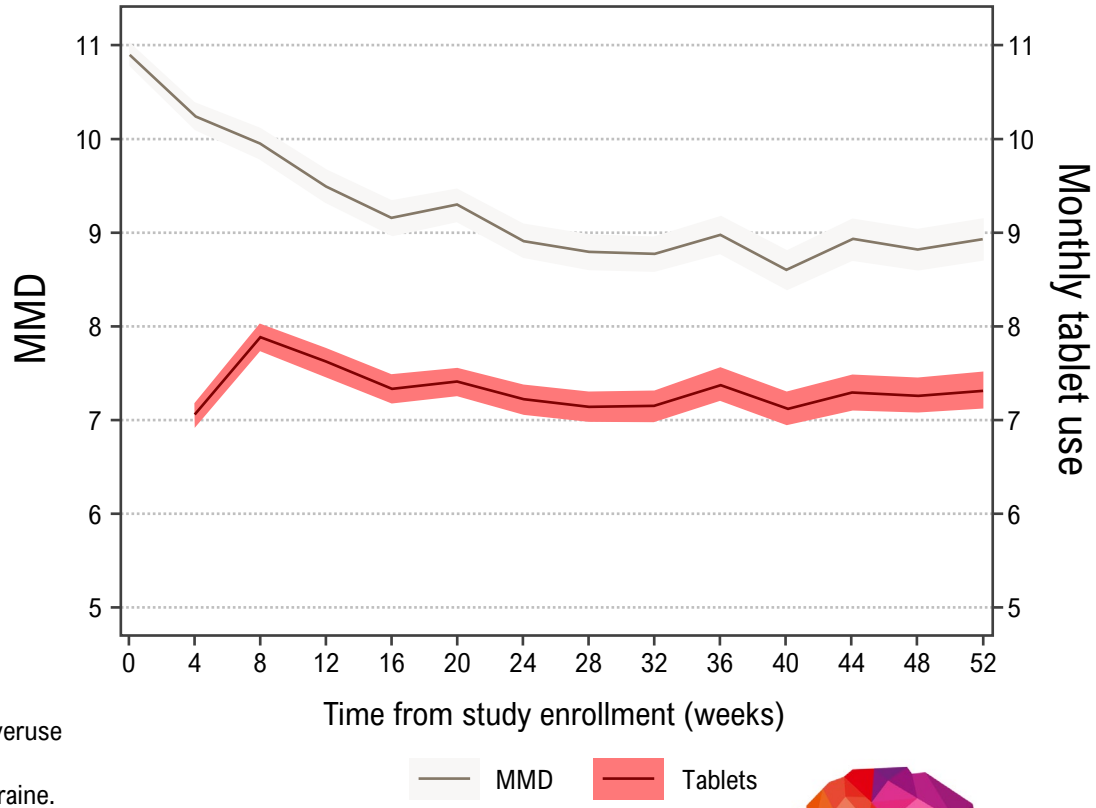
- Patients should be evaluated for MOH and instructed regarding the appropriate amount of medication to use monthly
- Frequency of acute medication use should be followed.
- *"To avoid MOH, commonly accepted recommendations are to:*
  - *Limit use of acetaminophen, ASA, and NSAIDs to a maximum of 14 days per month.*
  - *Limit use of triptans, ergotamine, opioids and combination analgesics to a maximum of 9 days a month."*
- "Evidence suggests that in many cases, a withdrawal may not be necessary and starting preventive therapy alone may be adequate."
- "As opioid and barbiturate-induced MOH is more likely, and in clinical experience may be less likely to respond to prevention, we recommend taper in these situations."

Medrea I, et al. Updated Canadian Headache Society Migraine Prevention Guideline with Systematic Review and Meta-analysis. Can J Neurol Sci. 2024 Nov 7:1-23

What About Gepants for Acute Therapy?

- Gepants do not lead to MOH based on preclinical and clinical data
- Preclinical data show that repeat treatment with ubrogepant does not produce MOH-like sensitization (seen with repeat treatment with sumatriptan)
- In one-year trials, neither rimegepant nor ubrogepant use as needed were associated with increased headache frequency

Mean (SE) MMD and PRN rimegepant 75 mg tablet use over time in 1-year safety study



Navratilova E, et al. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. Cephalalgia. 2020 Aug;40(9):892-902.
Croop et al. A multicenter, open-label long-term safety study of rimegepant for the acute treatment of migraine. Cephalalgia. 2024 Apr;44(4):3331024241232944.
Ailani J, et al. Long-Term Safety Evaluation of Ubrogepant for the Acute Treatment of Migraine: Phase 3, Randomized, 52-Week Extension Trial. Headache. 2020 Jan;60(1):141-152.

Adapted from Migraine Matters slide deck.

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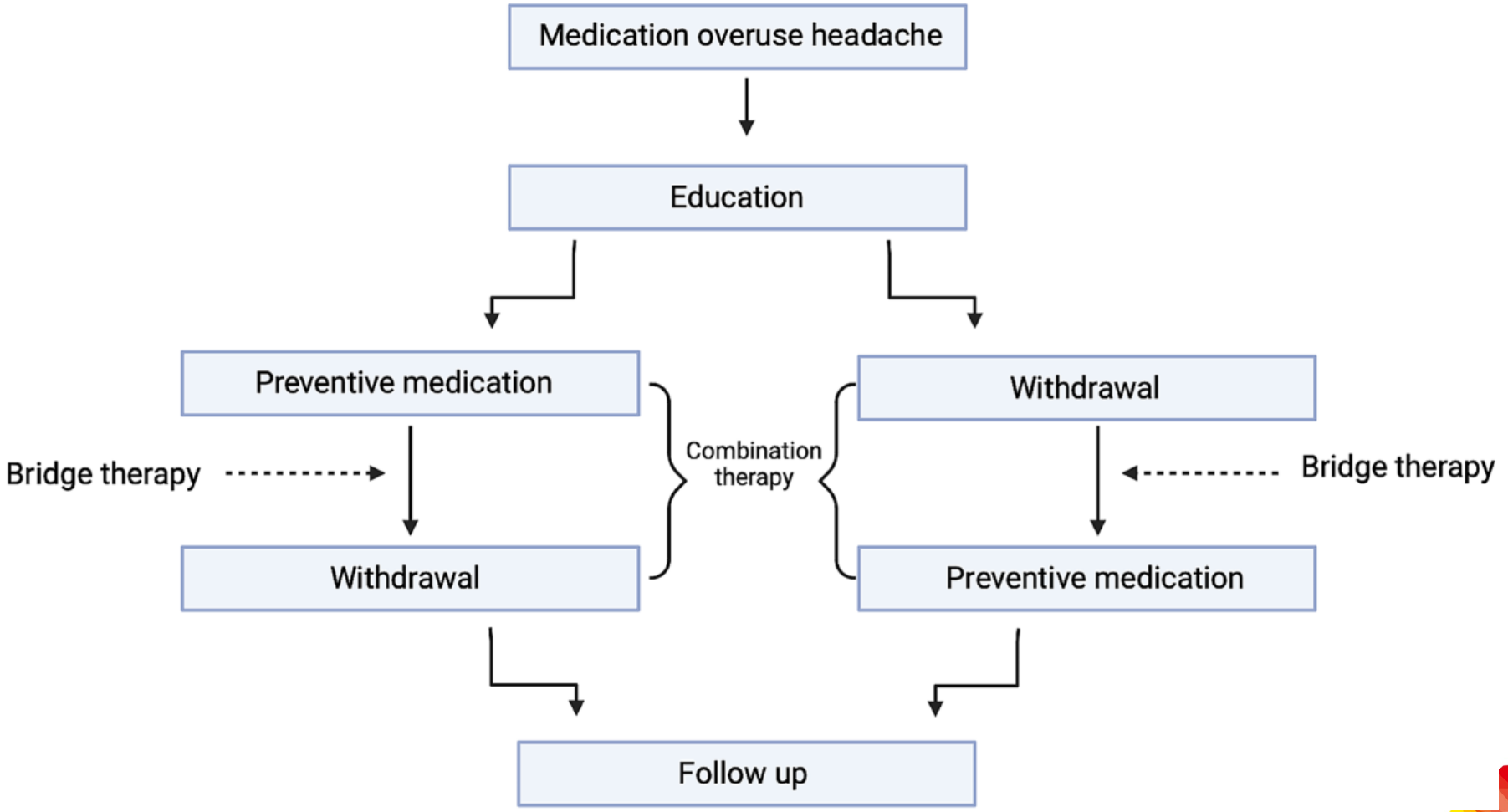
Bridge/Transitional Therapies if Needed

- Can often be done as an outpatient
- In severe or complex cases, consider inpatient management

- Cranial nerve blocks
- DHE protocol
- Course of steroids
- Gepants
- NSAID taper
  - Long acting NSAIDs (Nabumetone or Naproxen) favoured

Barad et al, 2021. Percutaneous interventional strategies for Migraine Prevention: A Systemic review and Practice Guideline. Pain Medicine 23(1): 164-188

Management of MOH



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Discussion

Dr. Kingston, is there a big difference in stopping the medication overuse or not while starting a preventive?

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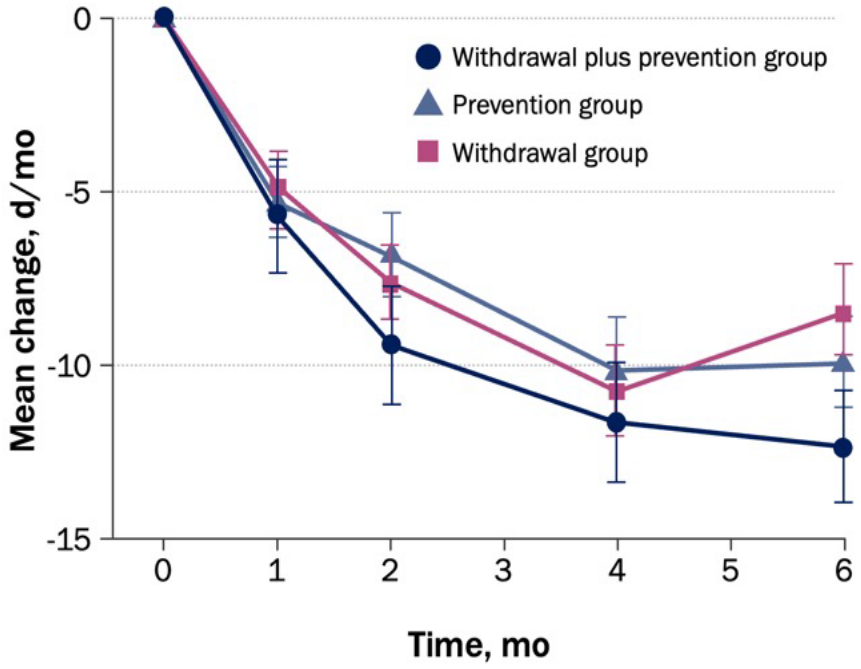
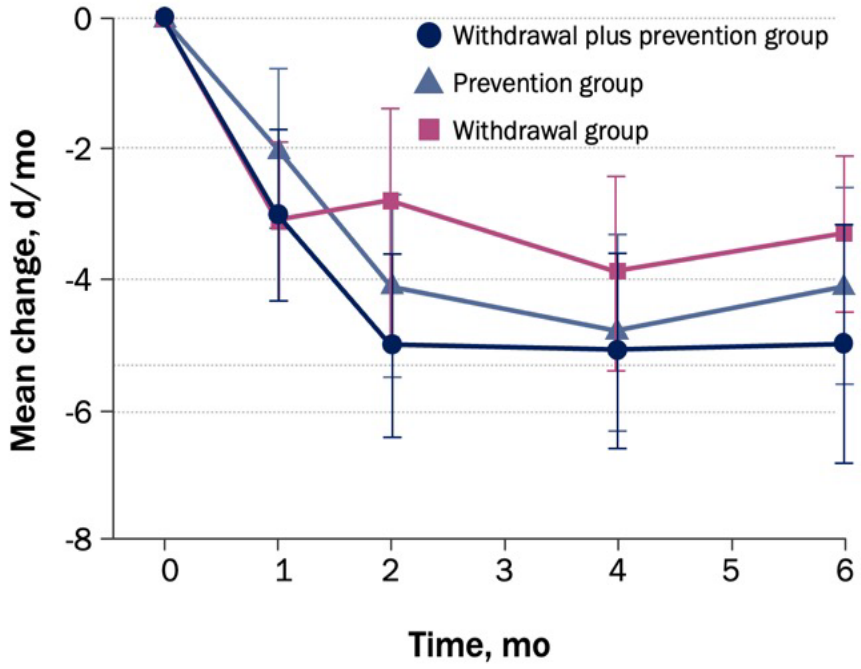
Comparison of MOH Treatment Strategies

Change in headache days



Change in migraine days



While "no difference", more patients in Prevention and withdrawal + prevention group reverted to EM.

Schwedt TJ et al. 2022. Patient-Centered Treatment of Chronic Migraine with Medication Overuse: A prospective, Randomized, Pragmatic Clinical Trial. Neurology 98(14): e1409-e1421.
Adapted from Migraine Matters slide deck.

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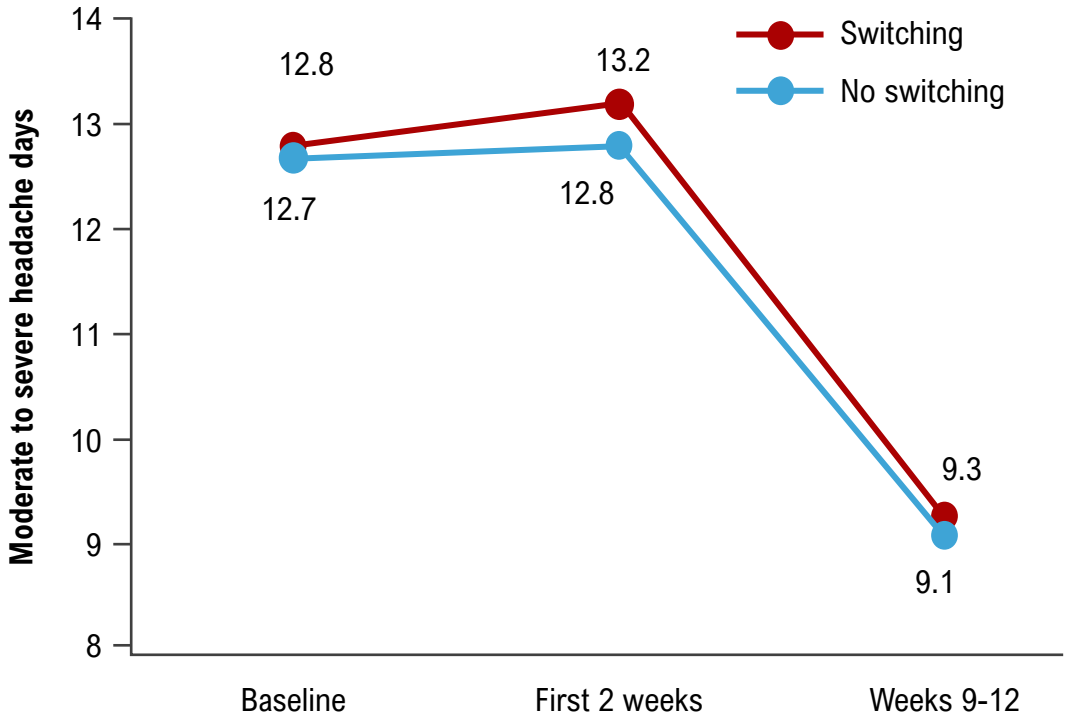
MOTS Study: To Switch or Not to Switch

- Study of 720 patients randomized to:
  - Migraine preventive medication + switching from overused medication to alternative

  Or
  - Migraine preventive medication and continuation of overused medication
- Outcomes are similar with both strategies
- Suggests that MOH is likely partly attributable to an under-treated problem and responds to treatment.



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Clinical Pearls: Strategies to Manage MOH

Paradigm shift toward proactive preventive treatment to manage MOH instead of relying solely on withdrawal

- Withdrawal may be appropriate in some patients, but is not a mandatory first step for all patients
- Should be done together with preventive treatment initiation
- Education & support should be provided to all patients
- Transitional therapy, as discussed, may be appropriate, especially in more difficult situations
- Gepants are a good option: their use does not appear to lead to chronification of migraine

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Sandra – Final Update

- Started Fremanezumab
- Advised to reduce ibuprofen and acetaminophen use
- Started the following acute treatments:
  - Almotriptan for severe attacks
  - Naproxen 500mg for moderate attacks

- At 4 month follow up
- Down to 6 monthly headache days
  - Using almotriptan 3-4 days monthly with excellent effect
  - Naproxen only modestly helpful for moderate attacks
  - Remainder of the month is headache free.

Take Home Points - MOH

- Headache occurring on ≥ 15 days/month in a patient with pre-existing headache disorder
- Regular overuse of > 3 months of an acute headache medication
  - Ergots, triptans, opioids, or combination analgesics use on ≥10 days a month
  - Simple analgesics (or a combination of drugs without single drug overuse) on ≥ 15 days a month
  - Gepants used for acute therapy do not appear to lead to MOH
- Patient education is key
- Reduce overused medication as appropriate
- Provide alternative abortive therapies if possible
- Offer transitional therapy when appropriate
- Provide preventive therapy
- Support the patient throughout the process

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THANK YOU