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Medication Overuse Headache

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Disclosures: Tommy Chan, MD

Consultant/Advisory Boards: Abbvie, Eli Lilly, Lundbeck, Miravo/Searchlight, Pfizer, Teva, Linpharma, Novartis

Speaker: None

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Meet Mary

45F office administrator, mother of 3 children

PMH: Migraine, lower back pain

“I get around 25-30 headache days a month, I take ibuprofen around the clock so I can go to work. It takes the edge off. For the severe days (around 12 days a month), I take rizatriptan and I get some relief from it, but I only get 12 pills a month”

“For my lower back pain, I take acetaminophen with codeine and caffeine everyday.”

“For some reason, I feel like my headache is more frequent now and the medications don’t work as well.”

“What is happening, doctor?”

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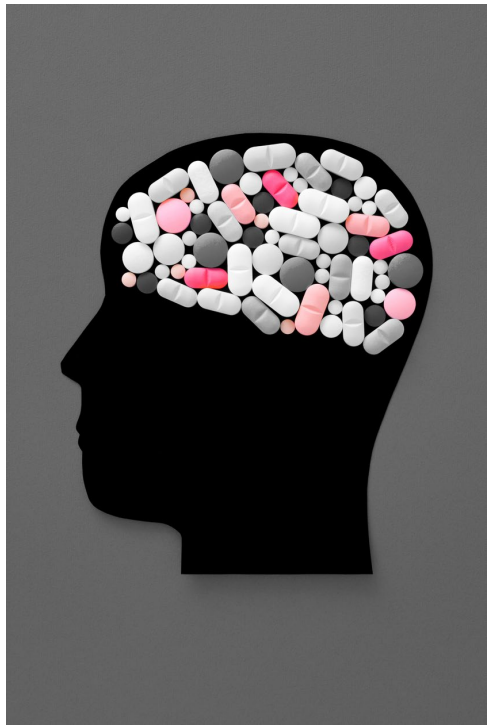
Learning Objectives

Upon completion of this activity, learners will be able to

- Identify the clinical features of medication overuse headache (MOH);
- Implement evidence-based strategies for the management and prevention of MOH.



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History

1951

Migraine patients developed daily headaches after daily use of ergotamine

1970-1980s

- Association of mixed analgesics with headache progression
- Transformed or evolutive migraine

1988-2018

- **ICHD (1988) -** Drug induced headache, ergotamine induced headache, analgesics abuse headache
- **ICHD-2 (2004) -** Medication overuse headache was introduced
- **ICHD-3 (2018) -** Updated diagnostic criteria for MOH

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Epidemiology

- 3rd most common cause of headache after migraine & tension type headache
- Prevalence: 1%–2%
  - As high as 20.6% in referrals to Canadian headache clinics (Becker et al. Cephalalgia 2008)
- Most common type of secondary headache disorder
- Most common: 30-50 years old, F > M
- Indirect and Direct Cost Burden: (Amoozegar et al. CJNS 2021)
  - Chronic Migraine: $25,669/patient/year

Scher AI, Lipton RB, Stewart WF, Bigal M (2010) Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study. Cephalalgia 30:321–328.
Becker WJ, Purdy RA. Medication overuse headache in Canada. Cephalalgia. 2008 Nov;28(11):1218-20.
Amoozegar F, Khan Z, Oviedo-Ovando M, Sauriol S, Rochdi D. The burden of illness of migraine in Canada: new insights on humanistic and economic cost. Canadian Journal of Neurological Sciences. 2022 Mar;49(2):249-62.

8.2 Medication-overuse headache (MOH)

IHS CLASSIFICATION ICHD-3

Diagnostic criteria:

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

B. Regular overuse for **>3 months (on 10 or more or 15 or more days/month,** depending on the medication)…

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

Olesen J. International classification of headache disorders. The Lancet Neurology. 2018 May 1;17(5):396-7.

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8.2 Medication-overuse headache (MOH)

IHS CLASSIFICATION ICHD-3

Previously used terms:

Drug-induced headache, medication misuse headache, rebound headache

When a patient develops a new type of headache, or a significant worsening of their pre-existing headache, **they should be given both this diagnosis and the diagnosis of the pre-existing headache.** e.g.: **Chronic migraine + Medication Overuse Headache**

Olesen J. International classification of headache disorders. The Lancet Neurology. 2018 May 1;17(5):396-7.

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Cutoff: 10-15 days

10 days	15 days
Ergotamine	Paracetamol (Acetaminophen)
Triptans	Non-steroidal anti-inflammatory drugs (NSAIDs)**
Opioids/Butalbital*	Acetylsalicylic acid
Combination	

American Migraine Prevalence and Prevention population-based study

- MOH risk: Odd Ratio (EM→CM): **2.06 butalbital, 1.48 opioids**
- ***Butalbital >5 days Opioids >8 days**
- **NSAIDs ?protective at low to moderate level of monthly headache days (<15)

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. Headache: The Journal of Head and Face Pain. 2008 Sep;48(8):1157-68.

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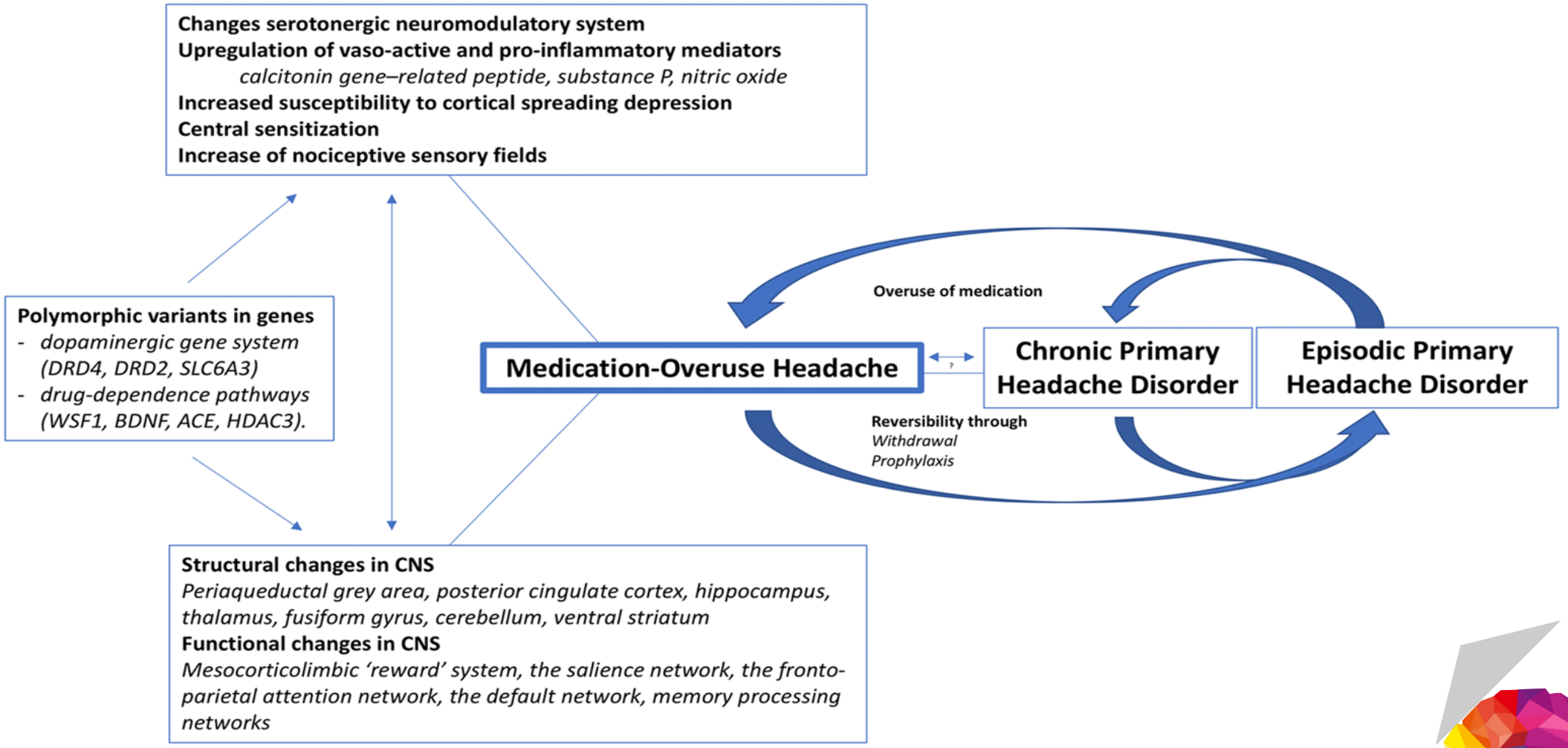
Pathophysiology



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Vandenbussche, N., Laterza, D., Lisicki, M. *et al.* Medication-overuse headache: a widely recognized entity amidst ongoing debate. *J Headache Pain* **19**, 50 (2018)

Features

Type of Headache: Worsening of the pre-existing primary headache disorder, such as migraine and/or tension-type headache. (Diener et al. 2016)

Daily/Almost Daily Headaches pattern (Diener et al. 2016, Silberstein et al. 1994, Rapoport et al. 1996, Bigal et al. Neurology 2008)

Withdrawal Symptoms: Temporary worsening of headache symptoms which can last from a few days to several weeks (Rossi et al. 2006)

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Risk Factors

- Combination of chronic musculoskeletal and gastrointestinal complaints
- Anxiety and Depression
- Physical inactivity
- Smoking
- High frequency headache
- Age <50
- Female sex
- Low socioeconomic status
- 2x increased risk if family history of MOH or substance abuse (Cevoli et al. 2009)

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Hagen K, Albretsen C, Vilming ST et al (2011) A 4-year follow-up of patients with medication-overuse headache previously included in a randomized multicentre study. J Headache Pain 12:315–322.
Cevoli S, D'amico D, Martelletti P, Valguarnera F, Bene ED, Simone RD, Sarchielli P, Narbone MC, Testa L, Genco S, Bussone G. Underdiagnosis and undertreatment of migraine in Italy: a survey of patients attending for the first time 10 headache centres. Cephalalgia. 2009 Dec;29(12):1285-93.

Who develops MOH?

- Overlapping pathophysiology: Migraine & MOH
- MOH develops in patients suffering from migraine or positive family history of migraine*, but not cluster headache patients**
- Patients with other chronic pain disorders who overuse analgesics for non-cephalic pain conditions do not seem to acquire chronic headache unless they have a pre-existing history of primary headache disorder***

*Paemeleire K, Bahra A, Evers S et al (2006) Medication-overuse headache in patients with cluster headache. Neurology 67:109–113.
**Paemeleire K, Evers S, Goadsby PJ (2008) Medication overuse headache in patients with cluster headache. Curr Pain Headache Rep 12:122–127
** Bahra A, Walsh M, Menon S, Goadsby PJ (2003) Does chronic daily headache arise de novo in association with regular use of analgesics? Headache 43:179–190.

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Management and Prevention

- Acute Withdrawal vs Gradual Reduction
- With or Without Preventatives

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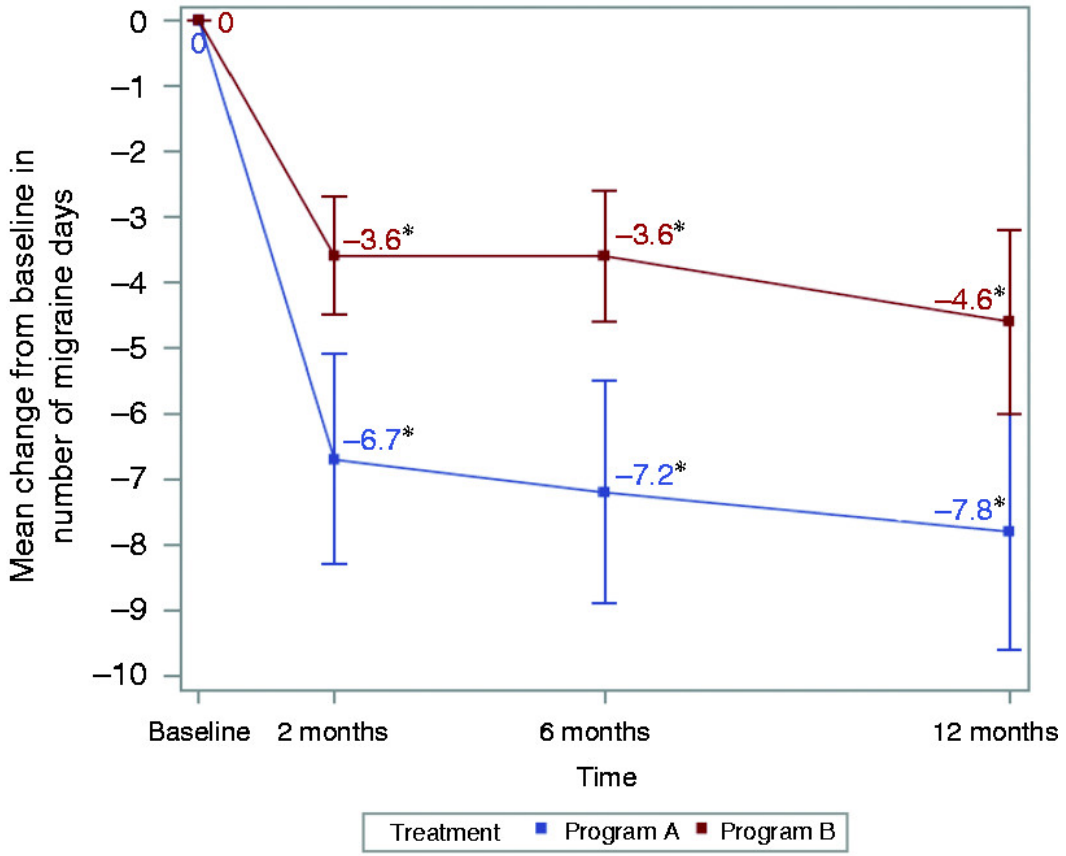
Acute Withdrawal vs Gradual Reduction

Randomized Controlled Trial > Cephalalgia. 2018 Feb;38(2):225-236.
doi: 10.1177/0333102417737779. Epub 2017 Oct 19.

Complete detoxification is the most effective treatment of medication-overuse headache: A randomized controlled open-label trial

Louise Ninett Carlsen [1], Signe Bruun Munksgaard [1], Rigmor Højland Jensen [1], Lars Bendtsen [1]

- **Program A:** Zero acute meds
- **Program B:** Acute meds <2days/week



At 6 months: (A vs B)

- 46% vs 22% reduction in HA days
- 50% vs 42% reverted from CM to EM
- -7.2 vs -3.6 migraine days

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Carlsen LN, Munksgaard SB, Jensen RH, Bendtsen L. Complete detoxification is the most effective treatment of medication-overuse headache: a randomized controlled open-label trial. Cephalalgia. 2018;38(2):225-236.

Add a Preventive?

Sachielli et al., 2014

- RCT – 88 pts
- **Intervention**: Detoxification +Valproate acid vs. Detoxification alone
- **Results**:
  - -45.0% vs. -23.8% at 3 months

Hagen & Stovner, 2011

- Open label – 61 pts
- **Intervention**: Detoxification + any preventive medication vs. Detoxification alone
- **Results**: -7.2 days/month vs. -4.1 days/month at 3 months

Munksgaard et al., 2012

- Open label - 98 pts
- **Intervention:** Immediate & delayed initiation of preventive medication with Detox
- **Results**: 50% reduction
  - 48% response in both groups at 12 months

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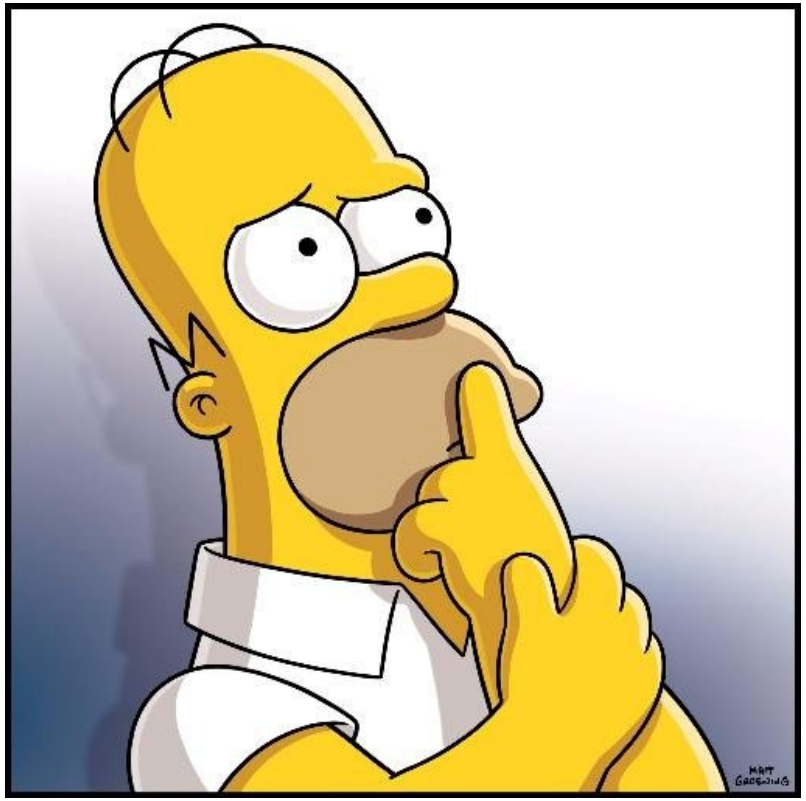
Sarchielli P, Messina P, Cupini LM, et al; SAMOHA Study Group. Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. Eur Neuropsychopharmacol. 2014;24:1289-1297.
Hagen K, Stovner LJ. A randomized controlled trial on medication-overuse headache: outcome after 1 and 4 years. Acta Neurol Scand Suppl. 2011;124(suppl 191):38-43.
Munksgaard SB, Bendtsen L, Jensen RH. Detoxification of medication-overuse headache by a multidisciplinary treatment programme is highly effective: a comparison of two consecutive treatment methods in an open-label design. Cephalalgia. 2012;32:834-844.

Is it necessary to go through detoxification?



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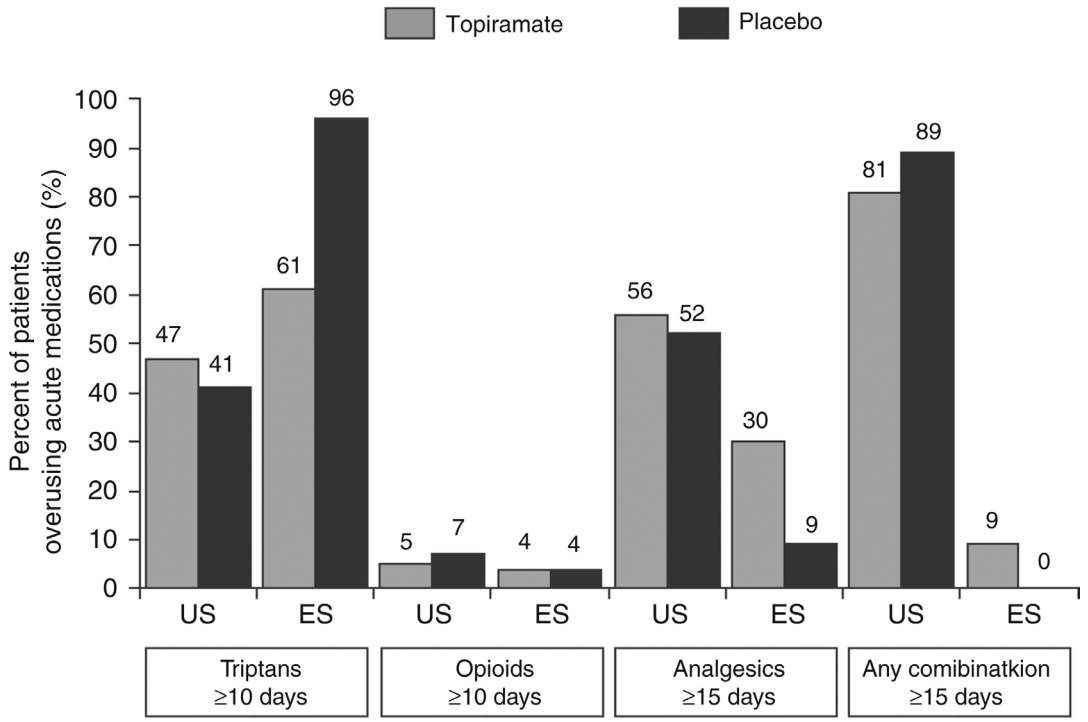
Detoxification is not necessary?



Topiramate

Mean Change From Baseline(Endpoint)	Week 24 p Value
Frequency of headache days	<0.001
Frequency of migraine days	<0.001
Frequency of moderate/servere of headache days	<0.001
Total cumlative headache hours on headache days	<0.001
Frequency of headache episodes	0.028
% Paints with servere (≥60) HIT-6 score	<0.001

OnabotulinumtoxinA

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Diener HC. Detoxification for medication overuse headache is not necessary. Cephalalgia. 2012 Apr;32(5):423-7.
Silberstein S, Joel R, Saper J, et al. OnabotulinumtoxinA for treatment of chronic migraine: 56-week analysis of the PREEMPT chronic migraine subgroup with baseline acute headache medication overuse. *62nd Annual Meeting of the American Academy of Neurology*; 2010

Key Trials on CGRP mabs in CM with MOH

	Erenumab 70mg, 140mg	(Galcanezumab 120mg, 240mg	(Fremanezumab 225mg, 675mg	(Eptinezumab 100mg, 300mg
Medication Overuse (% of patients)	41%	64%	52%	40.2%
MMD reduction	70mg: 6.6 days 140mg: 6.6 days	120mg: 4.8 days 240mg: 4.6 days	225mg: 5.0days 675mg: 4.9 days	100mg: 7.7 days 300mg: 8.2 days
Reduction in Acute Medication Use	5.4 and 4.9 days	>33%	55-60%*	>49%

*reverted to no medication overuse

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Tepper SJ, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology*. 2019;92:e2309–e2320.
Dodick DW, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia*. 2021;41:340–352.
Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology. 2018 Dec 11;91(24):
Silberstein SD, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain*. 2020;21:114

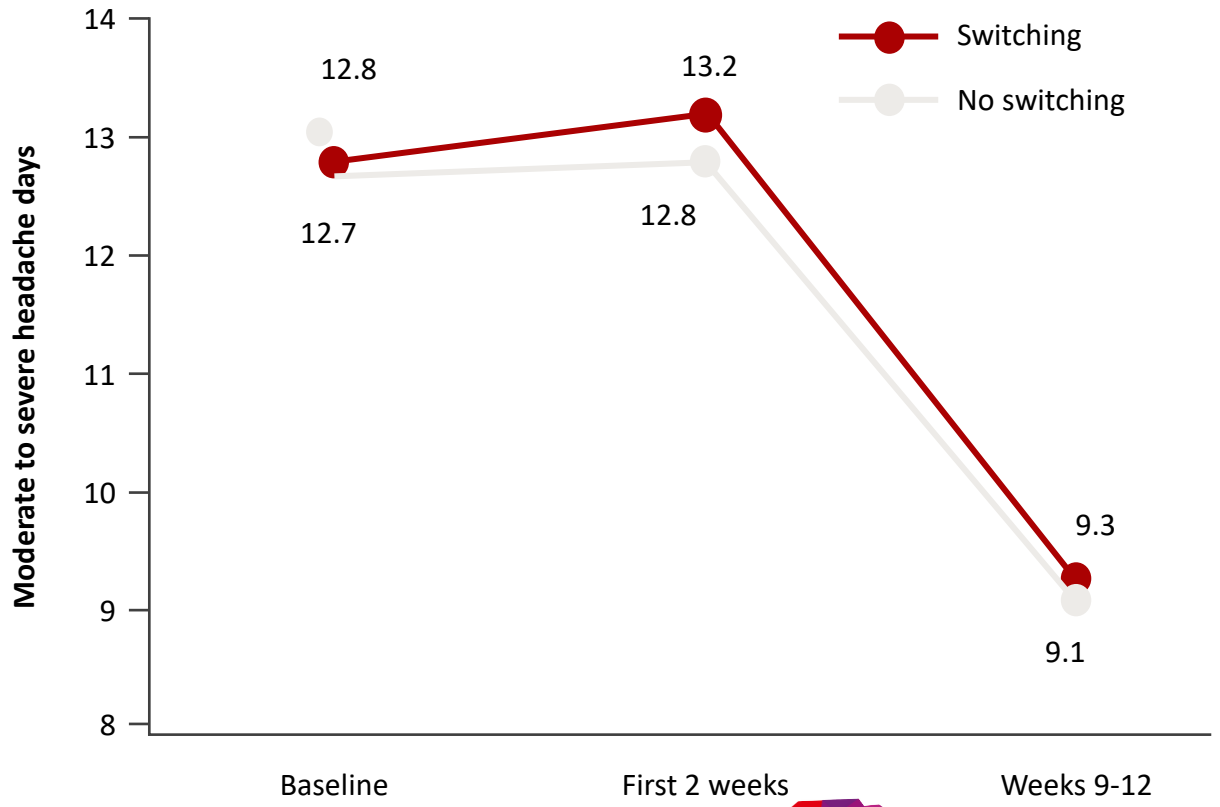
MOTS Study: Preventive Therapy Without Switching/Limiting Overuse Medication vs With Switching to Alternative Medication

Patient-Centered Treatment of Chronic Migraine With Medication Overuse

A Prospective, Randomized, Pragmatic Clinical Trial

- 720 patients randomized to:
  - Migraine preventive medication AND **NO SWITCHING** of acute meds

  OR
  - Migraine preventive medication AND **SWITCHING** of overused medication to another one ≤2 days per week



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Schwedt TJ, Hentz JG, Sahai-Srivastava S, Murinova N, Spare NM, Treppendahl C, Martin VT, Birlea M, Digre K, Watson D, Leonard M. Patient-centered treatment of chronic migraine with medication overuse: a prospective, randomized, pragmatic clinical trial. Neurology. 2022 Apr 5;98(14):e1409-21.

Thoughts on MOH

- Evidence of cause and effect is equivocal
- Medication withdrawal does not help everyone with MOH *(the other 40-60%)*
- 15-day threshold for chronic migraine is arbitrary
- Thresholds for overuse (10-15 days) are arbitrary
- NSAIDs can be protective?
- Anxiety provoking
- Withdrawal effect

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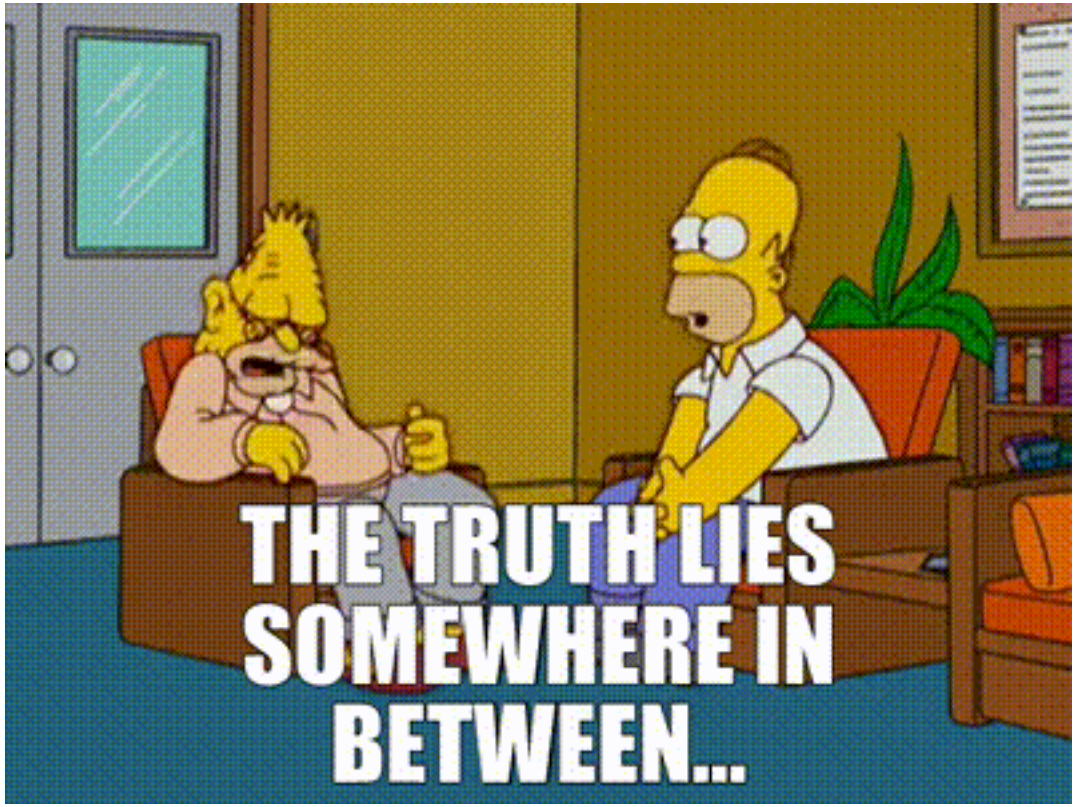

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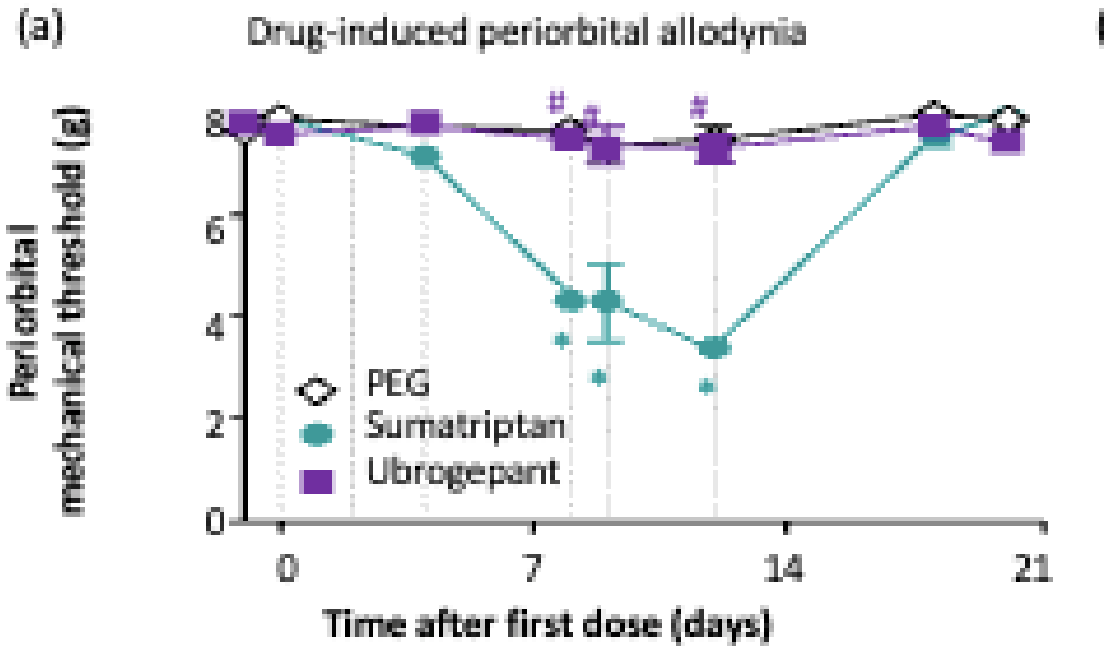
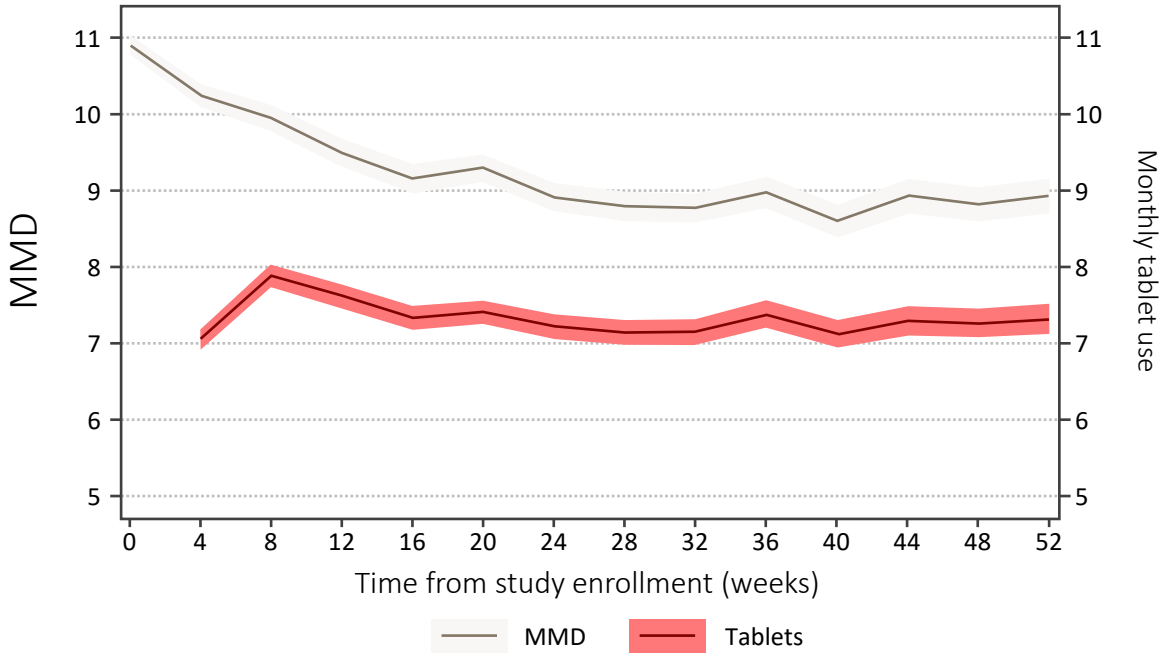
What About Newer Therapies - Gepants?



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



Neither rimegepant nor ubrogepant PRN have been associated with increased headache frequency (medication overuse)

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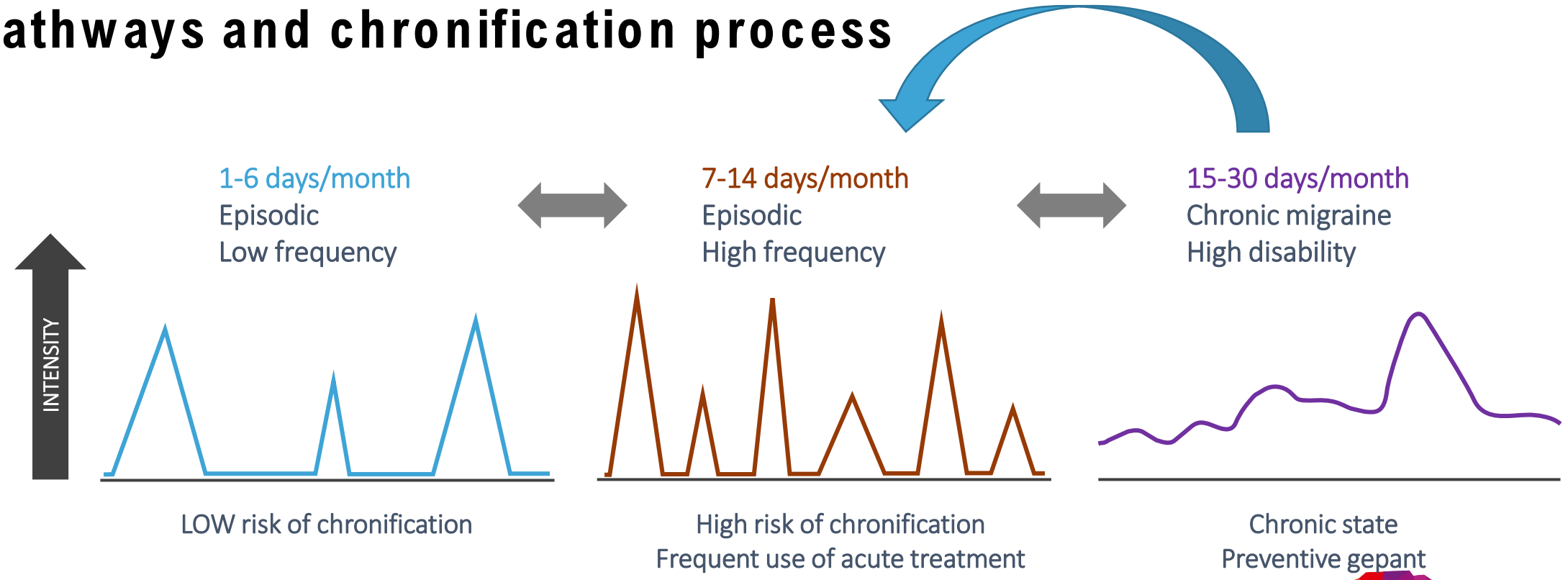
Navratilova E, Behravesh S, Oyarzo J, Dodick DW, Banerjee P, Porreca F. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. Cephalalgia. 2020 Aug;40(9):892-902.
Ailani J, Lipton RB, Hutchinson S, Knievel K, Lu K, Butler M, Yu SY, Finnegan M, Severt L, Trugman JM. Long-term safety evaluation of ubrogepant for the acute treatment of migraine: phase 3, randomized, 52-week extension trial. Headache: The Journal of Head and Face Pain. 2020 Jan;60(1):141-52.
Johnston K, Harris L, Powell L, Popoff E, Coric V, L'Italien G, Schreiber CP. Monthly migraine days, tablet utilization, and quality of life associated with Rimegepant–post hoc results from an open label safety study (BHV3000–201). The journal of headache and pain. 2022 Dec;23(1):10.

Gepants: Treating More Often = Preventive Effect?

Acute gepant use may block CGRP pathways and chronification process



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Meet Mary Again

45F office administrator, mother of 3 children

PMH: Migraine, lower back pain

"I get around **25-30 headache days** a month, I take **ibuprofen around the clock** so I can go to work. It takes the edge off. For the severe days (around **12 days a month**), I take **rizatriptan** and I get some relief from it, but I only get 12 pills a month"

"For my **lower back pain,** I take **acetaminophen with codeine and caffeine everyday.**"

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My Detoxification Program for Mary

- Education
- Counselling (Behavioral therapy and psychological support)
- Abrupt (Triptans, simple analgesics) vs Gradual (Opioids, Barbiturates) vs Add Gepants
- Bridging Therapy (NSAIDs, steroids, long acting triptans, nerve blocks)
- Preventive Medications (anti-hypertensives, anti-seizures, anti-depressants, CGRP-based treatment, onabotulinumtoxin A)
- Follow up (Relapse rate can be up to 20-40%)

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THANK YOU