MANAGEMENT OF MEDICATION OVERUSE HEADACHES

HEADACHE ACADEMY

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Disclosures

Treasurer International Headache Society
Treasurer, Anglo-Dutch Migraine Association
Trustee British Association for the Study of Headache
Chair of the headache specialty group Association of British Neurologist

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Reviewer for Cephalalgia, The Journal of Headache Pain, European Journal of Neurology, Neurotherapeutics, Headache

Editorial board – Practical Neurology

SUMMARY OF PRESENTATION

- WHAT IS MEDICATION OVERUSE AND MEDICATION OVERUSE HEADACHE
- ISSUES AROUND DEFINITION, DIAGNOSIS, CLASSIFICATION
- MANAGEMENT
- CONTROVERSIES

MEDICATION OVERUSE

- 10 DAYS OR MORE FOR OVER THREE MONTHS
  - ERGOTAMINE
  - TRIPTAN
  - OPIOIDS
  - COMBINATION WITH OPIOIDS
- 15 DAYS OR MORE FOR EVER THREE MONTHS
  - SIMPLE ANALGESICS

Negro et al TJHP 2017, Skajaa et al Headache 2019

MEDICATION OVERUSE HEADACHES

Classified as a secondary headache disorder

Headache occurring on **15 or more days/month** in a patient with a **pre-existing primary headache** and developing as a consequence of **regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month**, depending on the medication) for more than **three months**. It usually, but not invariably, resolves after the overuse is stopped.

Diagnostic criteria:

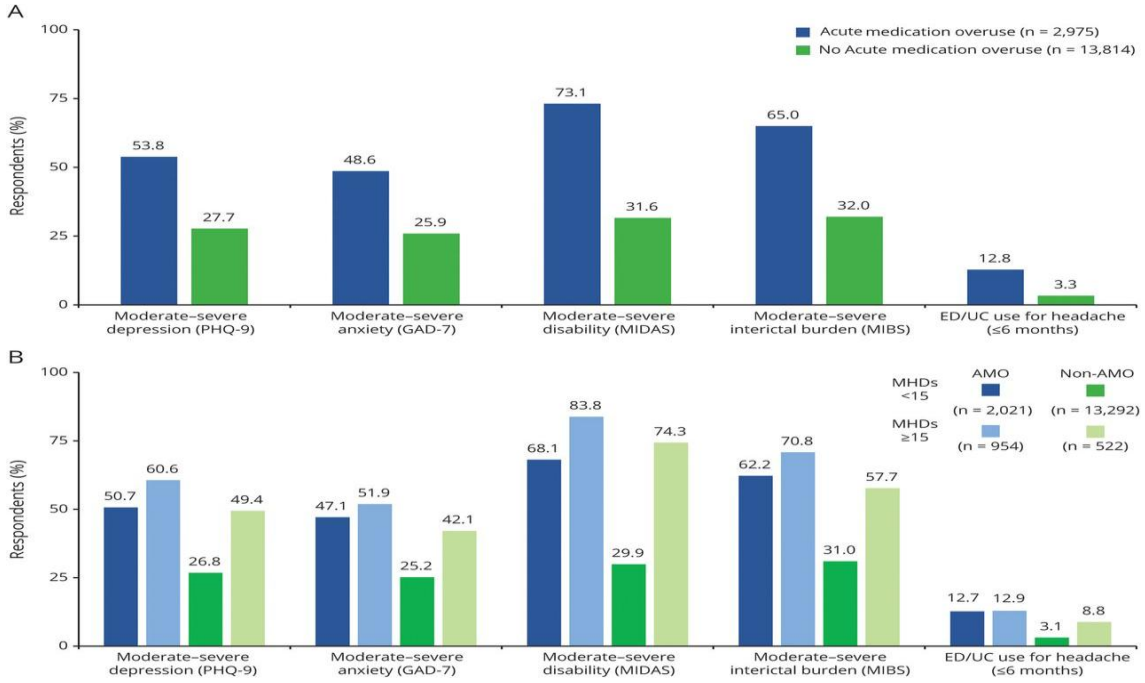
A. Headache occurring on 15 days/month in a patient with a pre-existing headache disorder

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. as a secondary headache disorder

MO VS MOH

- CaMEO Study
  - 16789 patients
  - 17.5% met criteria for medication overuse
  - Of these 68% reported < 15 headache days per month



Schwedt et al Neurol clinical practice 2021

HISTORY AND SYNONYMS

- 1951 FIRST DESCRIBED; PETERS AND HORTON
  - Ergotamine headaches resolved on discontinuation
- 1980 CONCEPT OF TRANSFORMED MIGRAINE
- 2004 ICHD-2
  - Should resolve or revert to episodic within 2 months of discontinuation
  - The clause removed in 2006
- SYNONYMS
  - Rebound headaches
  - Drug overuse headaches
  - Drug induced headaches
  - Medication misuse headaches
  - Medication adaptation headaches

Peters G, Horton B 1951; Proc Staff meet Mayo Clinic 25, 153-161
Olesen et al 2006 Cephalalgia 26;742-746

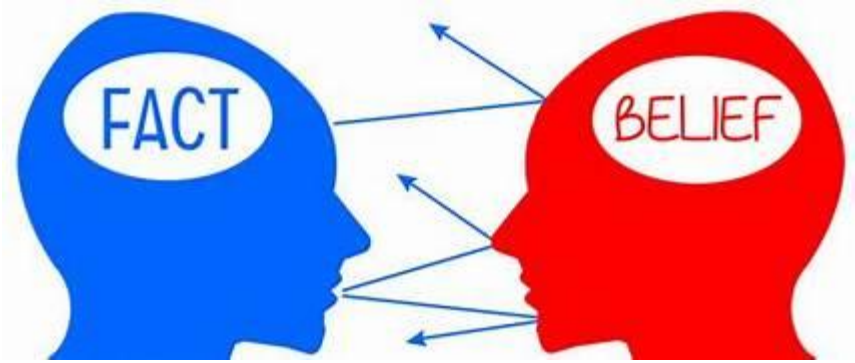
MOH - STATS

- PREVALENCE: 1-3% (as high as 7%)
- FEMALE: MALE: 2:1 to 5:1
- VARIABLE REPORTS
  - HIGH IN RUSSIA
  - LOW IN INDIA
  - HIGH LOWER SOCIOECONOMIC GROUPS
  - INCREASED PREVALENCE AGE 30-50 YEARS
  - 50-80% IN HEADACHE CENTRES

Diener et al, Lancet 2004;3:475-483

MOH - DOGMA

- IN MOH PROPHYLACTIC MEDICATIONS DON'T WORK
- STOPPING MEDS IS ESSENTIAL POSSIBLY THERAPEUTIC
- MOH IS A SECONDARY HEADACHE
- EVERY PRIMARY HEADACHE PATIENT IS PRONE TO MOH



MOH – CLINICAL OBSERVATION

- SEEMS TO OCCUR ONLY IN MIGRAINE AND TTH
- THOSE WITH CLUSTER INVARIABLY H/O MIGRAINE
- REDUCING THE USE INITIALLY TEND TO MAKE HEADACHE WORSE
- HIGH IMPACT ON QOL
- PHYSICAL AND PSYCHOLOGICAL DEPENDENCEY MANY CO-OCCUR

Hagen K et al, Pain 153(1):56-61

MOH – PATHOPHYSIOLOGY

- IMAGING FINDINGS
  - Reduced grey matter in orbitofrontal, mid-occipital, parietal, cingulate, insula, amygdala, hippocampus
  - Functional studies shows hypometabolism in orbitofrontal cortex, thalamus, anterior cingulate, insula and inferior parietal lobule

- CSF IN MOH
  - Raised levels of substance P, CGRP, glutamate, nitrate, orexin-A, cortocotrophin-releasing factor and cyclical guanosine monophosph

- SERUM
  - CGRP levels not raised
  - No markers identified

- Genetics: none identified – candidate gene proposed

Muksgaard SB et al, Acta Neurol Scand 2019;139:269-275

MOH – POSSIBLE MECHANISM

- PRIMING EFFECTS OF FREQUENT MIGRAINE ATTACKS

- PROLONGED EXPOSURE TO ANALGESICS
  - Increased activity in the TN
  - Lowering of trigeminal nociceptive threshold
  - Upregulation of CGRP levels and receptor expression
  - Changes in 5-HT receptor expression
  - Alteration of cortical neuronal exceitability
  - Genetic susceptibility

- PROLACTIN-DEPENDENT MECHANISM FOR NOCICEPTIVE SENSITISATION (Porreca lab data)

Ikegami et al, Cephalalgia 2022

MOH – ADDICTION

- Is there an overlap between MOH and addiction

- Both have dopaminergic mechanisms.
  - Psychiatric disorder
  - Drug seeking behaviour
  - Sensitisation
  - Habit
  - Genetic predisposition
  - Lower education
  - Impaired decision making power

Takahashi et al 2021 22:32

MOH – DIAGNOSIS

- DD between MOH,CM, CTTH, NDPH is challenging
- Morphology – not helpful
  - Similar to the primary headache
  - Holocranial
- Clue – headache severe when offending drug is troughing
- Taking off the offending drug may resolve headaches

MOH – WHY DIAGNOSIS IMPORTANT?

- Address treatment priorities- 1st step detox
- Help patient to understand previous Rx failures
- Research into mechanisms relies on correct diagnosis
- Testing new treatment relies on correct diagnosis
- Patients to feel blamed
- Wrong diagnosis leads to undertreatment
- Emphasis on MOH can divert research funds/energy
- Misdiagnosis can distract from efficient preventive therapies

MOH – ARE ALL SAME?

PATIENTS

- Some patient improve reducing from 4 days to 3 days/week
- Some do well on daily intake
- Some patients are prone to get worse with some and not others
- Patients have different types of MO headaches

MEDICATIONS

- Opioids
- Ergotamine
- Barbiturates
- Caffeine containing comb
- #Triptans
- NSAID, paracetamol
- Antihistamines
- Gepants

MOH – HOW COMMON?

- Combination analgesics 39-42%
- Simple analgesics 29-38%
- Triptans 12-20%
- Opioids 6%
- Ergotamine 4-11%

- MOH develops faster with triptans and withdrawal symptoms are milder and resolve quicker with triptans

Relja et al Headache 2004, Zeeberg et al Cephalalgia 2006, Katsarava et al 2000

MOH – CONTROVERSIES
CURRENT DIAGNOSTIC CRITERIA

- KEEP THE CURRENT CRITERIA
- ALTER THE CRITERIA AND ADD MORE EVIDENCE
- TAKE IT OUT OF SECONDARY HEADACHE AND NAME IT AS A COMPLICATION OF MIGRAINE?
- DISCTONTINUE THE TERM ON THE BASES OF POOR EVIDENCE

MOH – CONTROVERSIES MANAGEMENT

- SHOULD WITHDRAWAL BE ABRUPT OR GRADUAL?
- INPATIENT OR OUTPATIENT
  - Is hospitalisation necessary or beneficial in some patients?
- WHAT IS THE ROLE OF BRIDGING THERAPY?
- SHOULD PREVENTIVE TREATMENT INITIATED BEFORE OR AFTER?
- WHAT IS THE BEST PREVENTIVE?
- IS WITHDRAWAL OF THE DRUG ALWAYS NECESSARY?

MOH – INPATIENT OR OUTPATIENT?

- 70% Patient improve on out-patient bases
  - Data from tertiary clinic
- 76% Stopped overusing medication at 18 month follow up
  - Community based clinic with short written advice

Rossi et al Cephalalgia 2006;26: 1097-1105
Grande RB Eur J Neurol 2011;18:129-137

MOH – COMPLETE OR PARTIAL WITHDRAWAL ?

- TERTIARY CARE CLINIC 2 MONTHS DETOX
  - Complete withdrawal
  - Reduction to 2 days per week
  - Follow up 12 months

	Reduction in headache	**Reversion to episodic headache**
No acute treatment	46%	70%
2 doses per week	22%	42%

Carlesen et al, Cephalalgia 2017

MOH – WITHDRAWAL BEFORE PREVENTIVE?

- Tertiary centre – CDH & MO refractory to Rx
- 30-40% became responsive to previously tried prophylactics
- Triptan overuse performed better

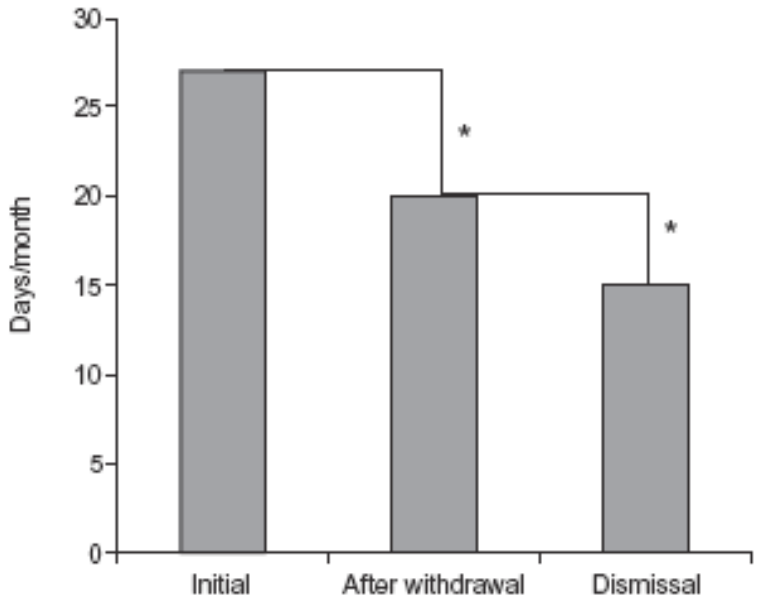
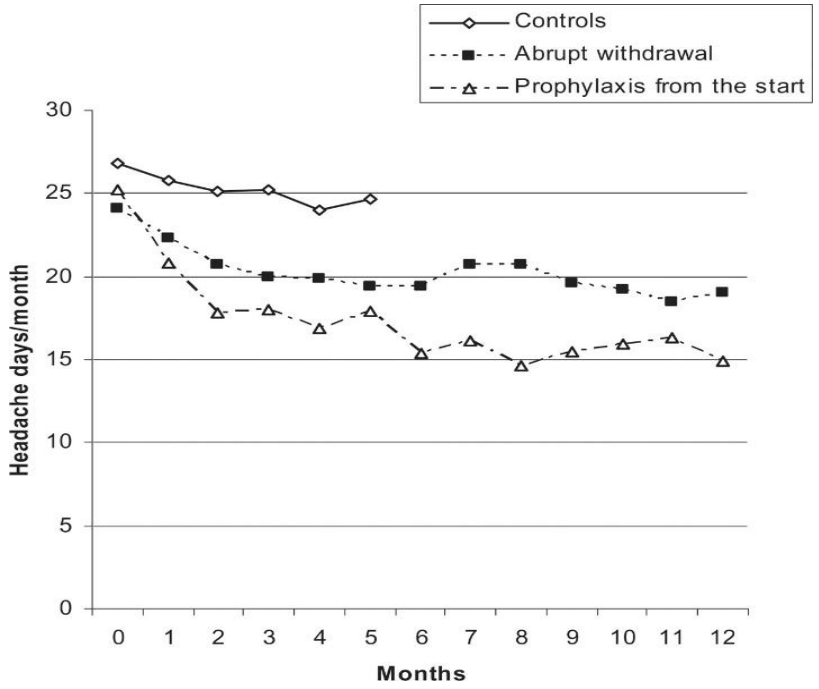
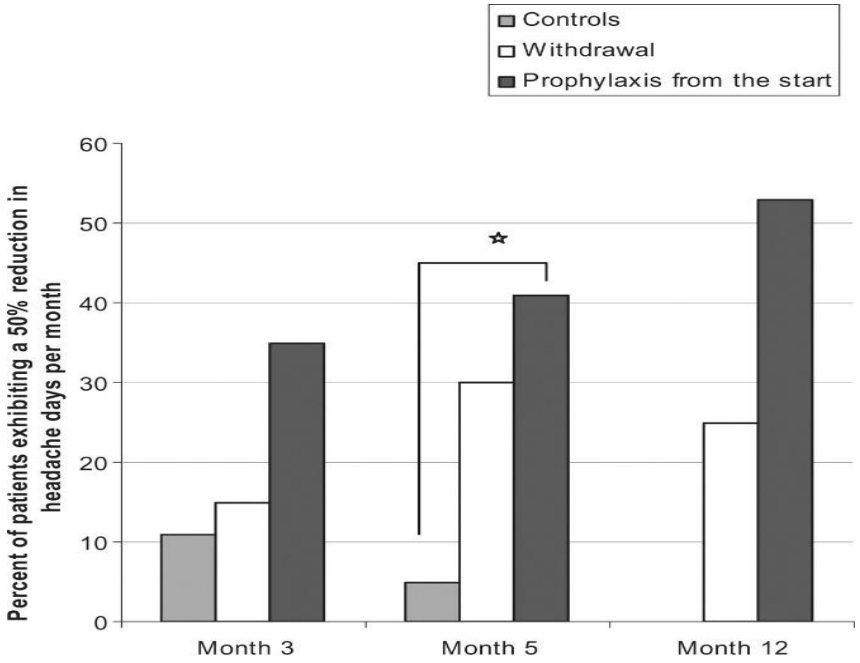


Figure 1 Development in headache frequency for patients withdrawn from medication overuse ($N = 175$). ■, Headache frequency. *$P < 0.0001$.

Zeeberg et al Cephalalgia 2006

MOH – WITHDRAWAL WITH PREVENTIVE?





THOSE WITH SIMULTANEOUS PROPHYLAXIS DID BETTER AT 3,6 AND 12 MONTHS

Hagen et al Cephalalgia 2009

Steroids in Medication Withdrawal Headaches

- DB RCT (n=18) Pageler et al Cephalalgia 2007
  - Prednisolone 100mg vs Placebo
  - 50% reduction in moderate to severe headache days in the steroid group
- DB RCT (n = 100 CM = 65) Bose et al Neurology 2007
  - Prednisolone 60 mg vs Placebo
  - No difference between steroid and Placebo
- DB RCT (n=96) Rabe et al Cephalalgia 2013
  - Prednisolone 100 mg vs Placebo
  - No benefit of steroids
- SB RCT (N=83) Cevoli et al Headache Pain 2017
  - 5 days of IVMEP or placebo
  - No benefit of steroids

MOH – WHAT TO EXPECT AFTER WITHDRAWAL ?

- 70% get worse
- Nausea, Vomiting, Sleep & Autonomic symptoms
- Duration of withdrawal symptoms:
  - Triptan 4 days
  - Ergotamine 7 days
  - Other 10 days

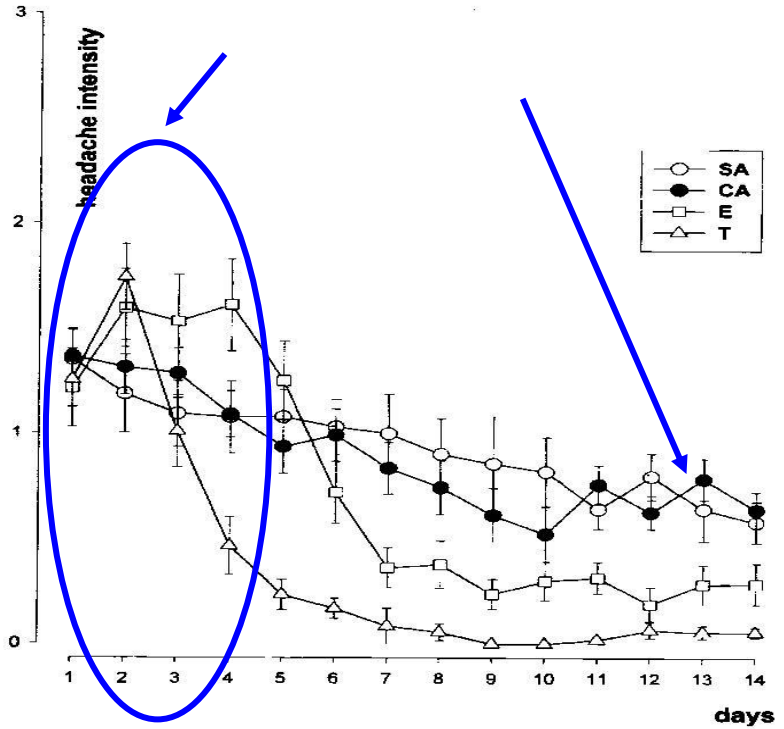


Figure 2. Mean daily intensity (four-point scale from 0 = no headache to 3 = severe headache) of withdrawal headache (given as mean value and SEM) during 14 days of withdrawal therapy in patients overusing single analgesics (SA), combination analgesics (CA), ergots (E), and triptans (T).

Katsavara et al 2002

MOH – PROGNOSIS ?

- 2 weeks
  - Triptan 85%
  - Ergot 57%
  - Analgesic 23%
- 1 Year
  - 30% relapse
- 5 Year
  - 50% relapse

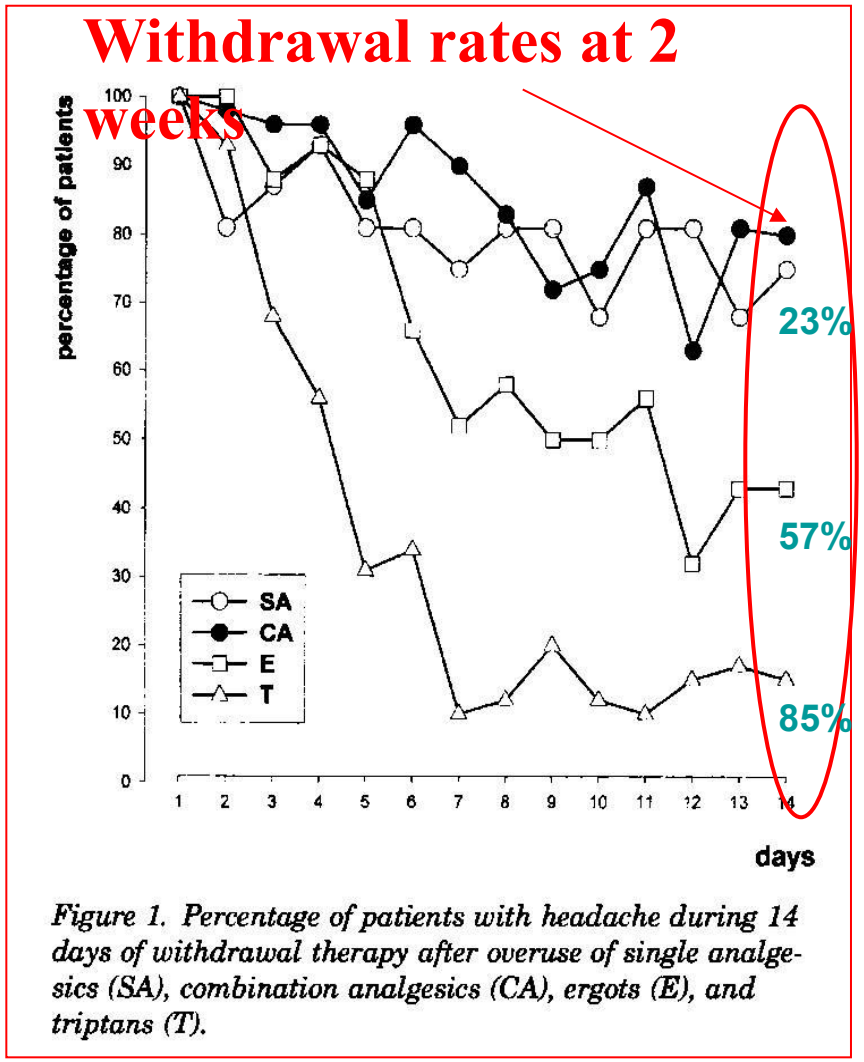
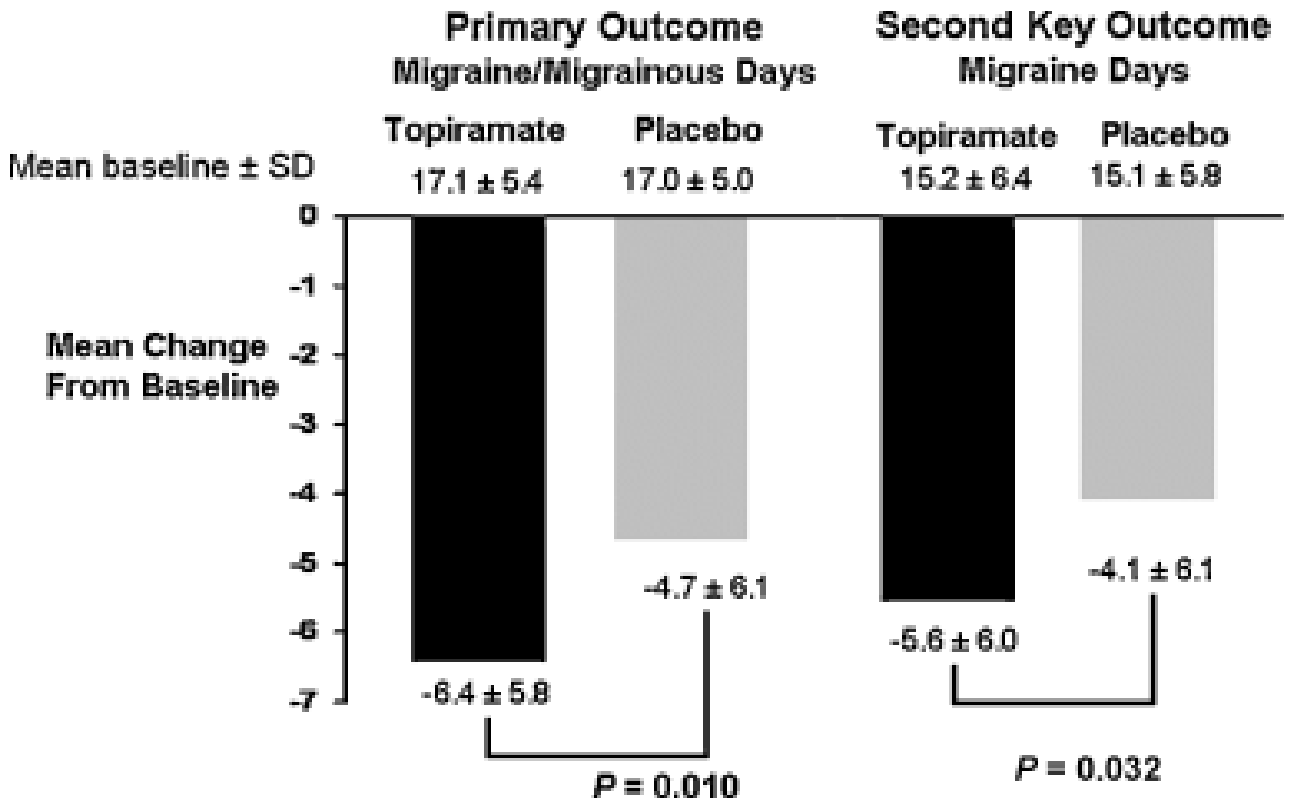


Figure 1. Percentage of patients with headache during 14 days of withdrawal therapy after overuse of single analgesics (SA), combination analgesics (CA), ergots (E), and triptans (T).

MOH – ADDITIONAL RX OPTIONS

- TOPIRAMATE
- BOTOX
- CGRP MABS
- GEPANTS

MOH – TOPIRAMATE



Deiner et al Cephalalgia 2007
Silberstein et al Headache 2007

MOH – BOTOX

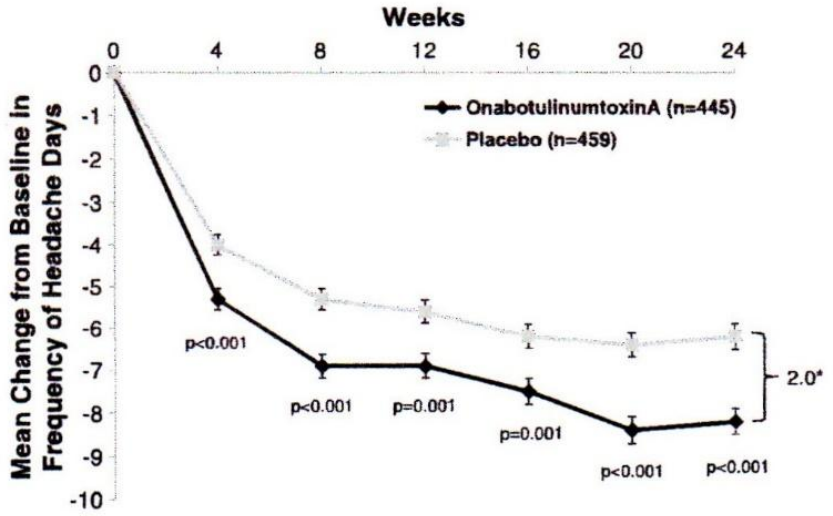


Fig. 2. Mean (SE) change in headache days from baseline in the chronic migraine with acute headache medication overuse subgroup. $p \leq 0.05$ is statistically significant. *Exceeds 1.0, the established minimally important between-group difference [36].

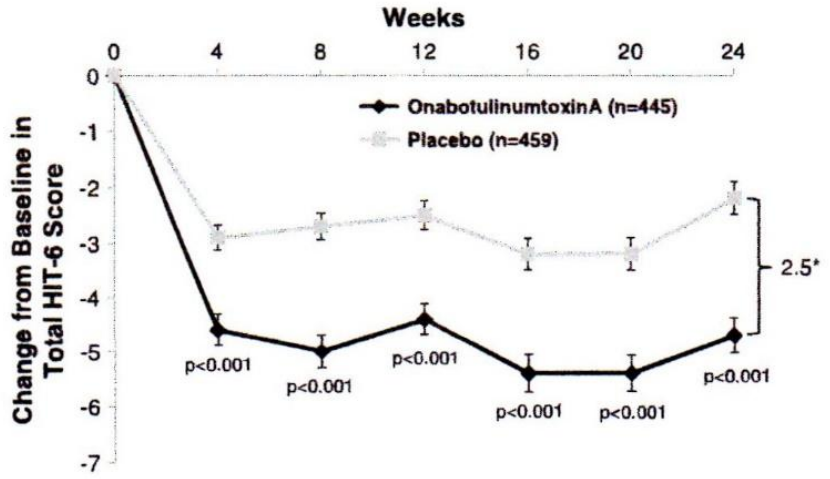
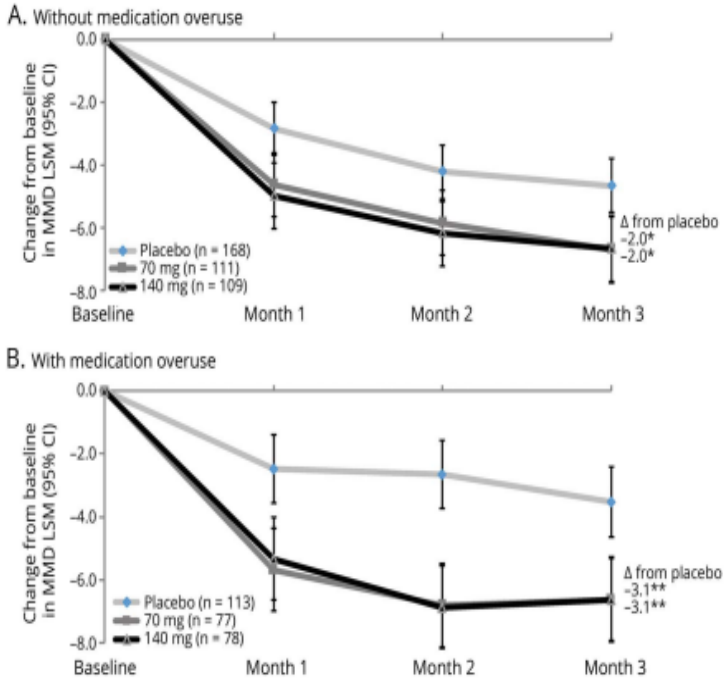


Fig. 3. Change in mean total HIT-6 score from baseline for chronic migraine with acute headache medication overuse subgroup. $p \leq 0.05$ is statistically significant. *Exceeds 2.3, the established minimally important between-group difference [27]. HIT = Headache Impact Test.

PREEMPT SUBGROUP ANALYSIS FOR MOH

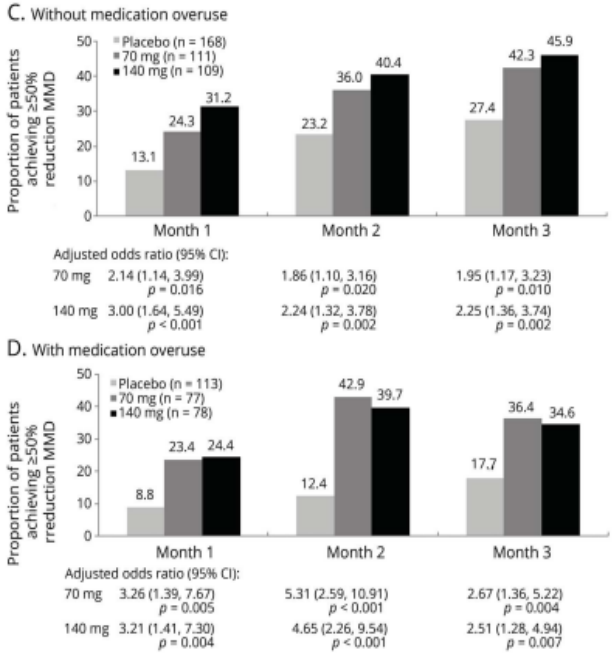
Silberstein et al 2013

MOH – ERENUMAB



WOMO

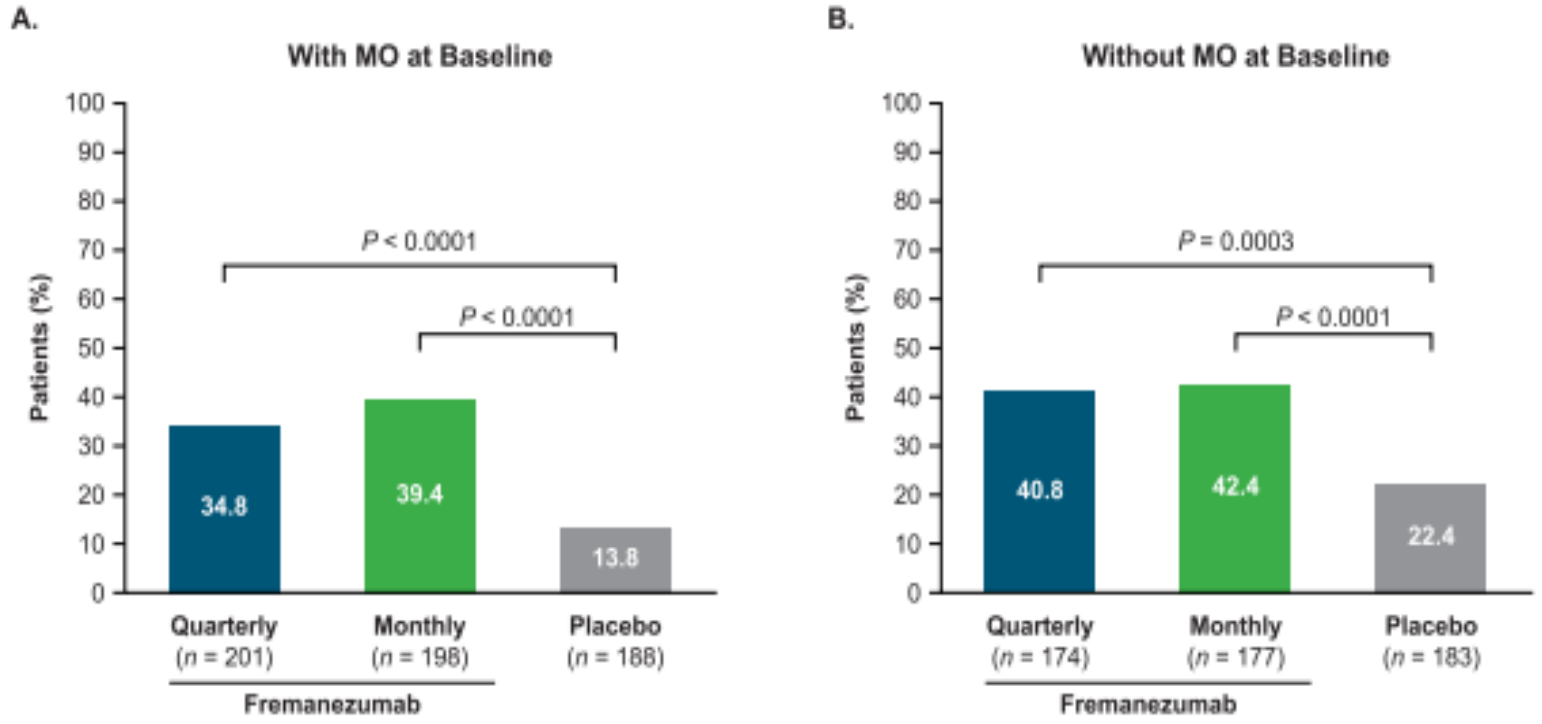
WMO



ERENUMAB SUBGROUP ANALYSIS FOR MOH

Tepper et al 2019 Neurology

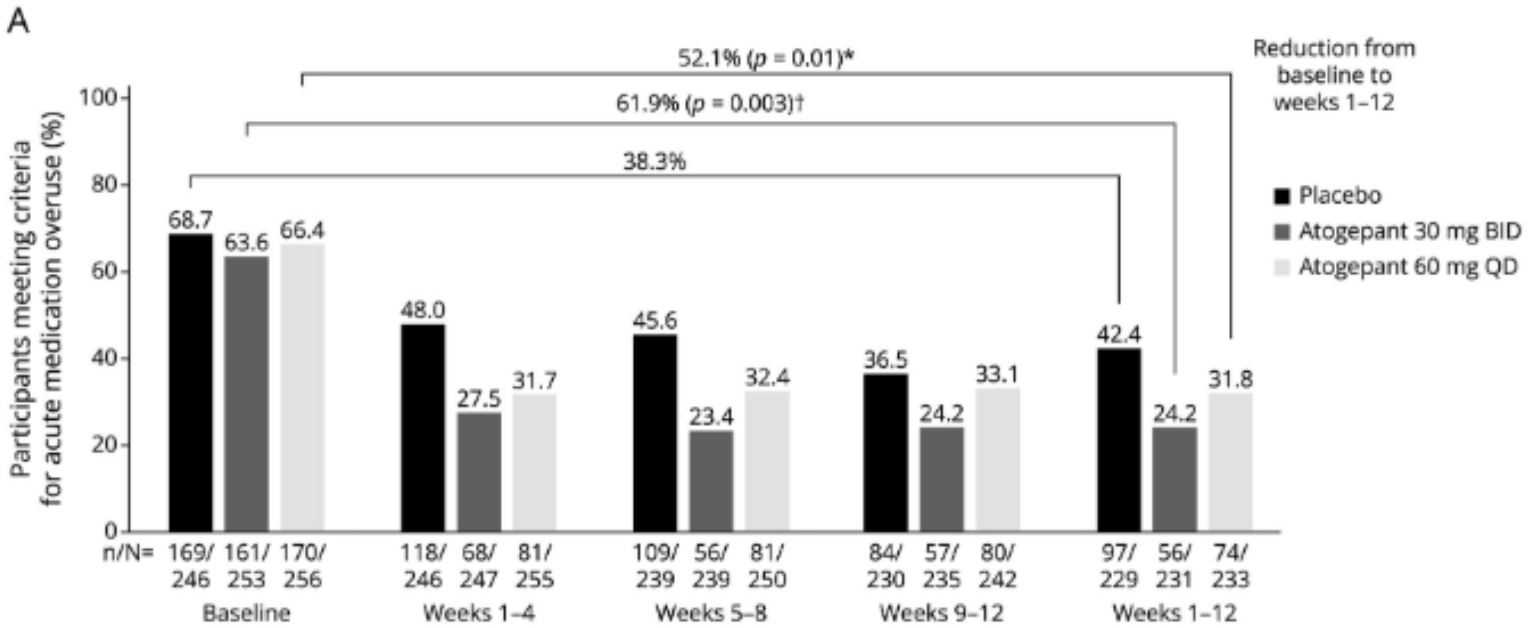
MOH – FREMANEZUMAB



FREMANEZUMAB HALO STUDY SUBGROUP ANALYSIS FOR MOH

Silberstein et al 2020 TJHP

MOH – ATOGEPANT



ATOGEPANT PROGRESS STUDY SUBGROUP ANALYSIS FOR MOH

Goadsby et al 2024 Neurology

MOH – TOPIRAMATE, BOTOX, MABS, PANTS

- TOPIRAMATE IS CURRENTLY NOT AN OPTION
- BOTOX AND MABS ARE BOTH EFFECTIVE
  - MABS HAVE BETTER OUTCOME
- DATA LIMITED TO POSTHOC ANALYSIS OF SUBGROUP FROM THE ORIGINAL RCT
- MORE EVIDENCE REQUIRED TO ASCERTAIN THE BEST CHOICE

MOH – CONCLUSIONS

- MO AND MOH ARE TOTALLY DIFFERENT ENTITIES
- DD BETWEEN MOH, CM, CTTH, NDPH IS CHALLENGING
- MOH DEFINITION, CLASSIFICATION AND DIAGNOSIS IS BASED ON POOR EVIDENCE
- DETOX BEFORE OR WITH PREVENTIVES IS THE OPTION
- MEDICATION OVERUSE DOES NOT MATTER