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A Comprehensive Systematic Review of The Relationship Between Excessive Analgesic Use and Migraine Chronicity

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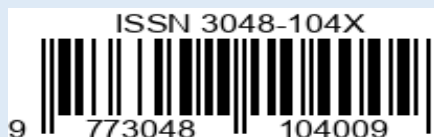
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ABSTRACT

Introduction: Medication overuse headache (MOH) is a significant complication in migraine management, where excessive use of acute analgesics paradoxically leads to increased headache frequency and chronicity. Understanding the bidirectional relationship between analgesic overuse and the transformation from episodic to chronic migraine (CM) is crucial for developing effective treatment strategies. This systematic review synthesizes evidence on this relationship and evaluates the efficacy of various interventions.

Methods: A systematic methodology was employed to screen and extract data from 80 relevant studies. Inclusion criteria focused on adult migraine populations, clear definitions of analgesic overuse and migraine chronicity, quantitative outcome data, and studies with adequate sample sizes. Data

extraction covered study design, definitions of key constructs, population characteristics, evidence of the analgesic-overuse-chronicity relationship, effects of interventions, and moderating factors.

Results: Analgesic overuse is highly prevalent (40-78%) in CM populations, with triptans, combination analgesics, and NSAIDs being most commonly overused. Evidence strongly supports a causal relationship from overuse to chronicity, demonstrated by significant improvements following medication withdrawal. Detoxification combined with preventive treatment achieved the highest success rates (up to 96.8% MOH cure). Anti-CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) showed consistent efficacy in reducing both migraine days and acute medication use, with 55-61% of patients reverting from overuse without formal detoxification. OnabotulinumtoxinA, gepants (e.g., atogepant), topiramate, and behavioral interventions (mindfulness, CBT) also demonstrated significant benefits. Outcomes varied by medication type overused, with triptan overuse associated with better prognosis, and were moderated by patient factors such as psychological comorbidities and pain catastrophizing.

Discussion: The findings highlight a complex, bidirectional relationship where overuse perpetuates chronicity through mechanisms like central sensitization and altered pharmacokinetics, while effective preventive treatment reduces the need for acute medication. The evidence supports stratified

treatment approaches: combined withdrawal and prevention for amenable patients, anti-CGRP therapies for those intolerant to withdrawal or with prior treatment failures, and integrated behavioral-pharmacological strategies for those with psychological comorbidities.

Conclusion: Excessive analgesic use is a key modifiable risk factor in migraine chronicity. A multimodal, patient-centered approach is essential, prioritizing medication withdrawal where feasible, leveraging the efficacy of newer preventive therapies like anti-CGRP agents, and addressing psychological moderators. Future research should focus on long-term outcomes, personalized medicine based on overuse medication type, and the neurobiological mechanisms underlying the overuse-chronicity cycle.

Keywords: Medication Overuse Headache; Chronic Migraine; Analgesic Overuse; Anti-CGRP Monoclonal Antibodies; Detoxification; Preventive Treatment; Migraine Chronicity.

INTRODUCTION

Background: Migraine is a prevalent and disabling neurological disorder characterized by recurrent episodes of headache, often accompanied by sensory and autonomic symptoms. A significant proportion of individuals with episodic migraine progress to chronic migraine (CM), defined as headache occurring on 15 or more days per month for more than three months, with at least eight days possessing migraine features (International Classification of Headache Disorders, 3rd edition). This transformation represents a substantial increase in disease burden, disability, and healthcare costs (Lanteri-Minet et al., 2011). Among the most critical and modifiable risk factors for this progression is the excessive use of acute headache medications, leading to a secondary condition known as medication overuse headache (MOH). MOH affects a substantial subset of CM patients, with prevalence estimates ranging from 40% to 78% (Bigal et al., 2004). The paradoxical cycle wherein acute medications taken for relief ultimately exacerbate and perpetuate headache chronicity presents a major clinical challenge, complicating treatment and worsening patient outcomes.

Research Gap: Despite recognition of MOH as a clinical entity, significant gaps remain in the understanding of its precise pathophysiological mechanisms, the differential impact of various analgesic classes, and the optimal sequence and combination of treatment strategies. While traditional management hinges on detoxification (medication withdrawal), this approach is often challenging due to withdrawal symptoms and high relapse rates. The advent of novel targeted preventive therapies, particularly anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) and gepants, has transformed the therapeutic landscape, yet their role within the overuse-chronicity cycle—specifically whether they can reverse overuse without formal detoxification—requires comprehensive synthesis. Furthermore, heterogeneity in study designs, definitions, and patient populations across the literature necessitates a systematic review to reconcile evidence and provide clear clinical guidance.

Novelty: This systematic review offers a contemporary and exhaustive synthesis of evidence from 80 studies, incorporating the latest data on cutting-edge CGRP-targeted therapies (erenumab, fremanezumab, galcanezumab, eptinezumab, atogepant) within the context of MOH. It moves beyond merely cataloging treatment efficacy to dissect the nuanced, bidirectional relationship between overuse and chronicity, examining how different intervention modalities (pharmacological withdrawal, preventive biologics, neuromodulation, behavioral therapy) interact with this cycle. The review also provides a detailed analysis of moderating factors—such as the type of overused medication, psychological comorbidities, and patient adherence—that critically influence outcomes, paving the way for a more personalized treatment paradigm.

Research Objectives: The primary objectives of this review are: 1) To systematically evaluate the evidence for a causal and bidirectional relationship between excessive analgesic use and the development or maintenance of chronic migraine. 2) To compare and synthesize the efficacy of various intervention strategies—including detoxification, preventive pharmacotherapy (anti-CGRP mAbs, onabotulinumtoxinA, topiramate), and non-pharmacological approaches (behavioral therapy, neuromodulation)—in breaking the cycle of medication overuse and reducing migraine chronicity. 3) To identify patient-specific, medication-specific, and treatment-specific factors that moderate the success of interventions for MOH.

Hypothesis: It is hypothesized that excessive analgesic use plays a causative role in promoting and sustaining migraine chronicity through mechanisms such as central sensitization and altered pain modulation. Consequently, interventions that directly address overuse (detoxification) or effectively prevent migraine attacks (thereby reducing the need for acute medication) will be most successful in reversing chronicity. Specifically, it is hypothesized that newer CGRP-targeted therapies will demonstrate significant efficacy in reducing both headache frequency and acute medication overuse, potentially offering a viable alternative or adjunct to traditional detoxification protocols.

Research Benefits: The findings of this review hold significant clinical and scientific value. Clinically, they will provide evidence-based guidance for healthcare professionals in managing the complex interplay between medication overuse and chronic migraine, supporting stratified treatment decisions. By clarifying which patients benefit most from specific interventions (e.g., withdrawal vs. immediate preventive therapy), the review can help improve treatment efficacy, reduce disability, and lower healthcare resource utilization (Adams et al., 2015; Ambrosini et al., 2022). Scientifically, synthesizing this broad evidence base will highlight consistent mechanistic pathways, identify key areas for future research, and contribute to the development of more precise diagnostic and therapeutic frameworks for MOH and CM.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between excessive analgesic use and migraine chronicity.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Migraine Population:** Does the study include participants diagnosed with migraine (episodic or chronic)?
- **Analgesic Overuse Definition:** Does the study examine analgesic use patterns with a clear definition of "excessive" or "overuse" (e.g., ≥ 10 -15 days per month depending on medication type)?

- **Migraine Chronicity Outcome:** Does the study measure migraine frequency, chronicity, or transformation from episodic to chronic migraine as an outcome?
- **Quantitative Data:** Does the study provide quantitative data on the relationship between analgesic use and migraine outcomes?
- **Adult Population:** Does the study involve adult participants (≥ 18 years)?
- **Migraine-Specific Analysis:** If the study includes multiple headache types, does it provide migraine-specific analysis (or does it focus exclusively on migraine)?
- **Adequate Sample Size:** Is the study design something other than a case report or case series with fewer than 10 participants?
- **Overuse Pattern Assessment:** Does the study assess analgesic overuse patterns or chronicity (rather than focusing only on acute migraine treatment effectiveness)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Chronic migraine patients	Analgesic overuse	Normal analgesic use	Migraine chronicity
Keyword 2	Adults with migraine	Medication overuse headache (MOH)	Episodic migraine	Headache frequency increase
Keyword 3	Migraine sufferers	Excessive painkiller use	Controlled analgesic use	Transformation to chronic migraine

Keyword 4	Episodic migraine patients	Rebound headache	Preventive treatment alone	Medication overuse resolution
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The Boolean MeSH keywords inputted on databases for this research are: (*"Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients"*) AND (*"Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache"*) AND (*"Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone"*) AND (*"Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution"*)

Data extraction

- **Study Design:**

Extract the study design and methodology used to investigate the relationship between excessive analgesic use and migraine chronicity, including:

- Study type (RCT, cohort, cross-sectional, case series, etc.)
- Follow-up duration if longitudinal
- Control/comparison groups
- Blinding status
- Sample size and power considerations
- Any specific methodological features relevant to studying analgesic overuse and migraine chronicity

- **Analgesic Overuse Definition:**

Extract how excessive/overuse analgesic use is defined and measured in this study, including:

- Specific threshold criteria for overuse (frequency, quantity, duration)

- Types of analgesics included in the definition (simple analgesics, triptans, opioids, combination medications, etc.)
- Assessment method (patient report, diary, prescription records)
- Whether different thresholds are used for different medication types
- Any distinction between medication overuse headache (MOH) vs. simple overuse

- **Migraine Chronicity Definition:**

Extract how migraine chronicity is defined and measured, including:

- Specific criteria for chronic vs. episodic migraine (headache frequency thresholds, duration requirements)
- Diagnostic criteria used (IHS/ICHD, clinical judgment, etc.)
- Assessment tools and measurement instruments
- Time periods for assessment
- Any transformation/transition criteria between episodic and chronic migraine

- **Population Characteristics:**

Extract key characteristics of the study population relevant to understanding analgesic overuse and migraine chronicity, including:

- Demographics (age, gender, migraine duration)
- Baseline migraine patterns (frequency, severity, type)
- Baseline analgesic use patterns (types, quantities, duration of overuse)
- Comorbid conditions affecting headache or medication use
- Prior treatment history
- Setting (headache clinic, community, etc.)

- **Relationship Evidence:**

Extract evidence about the relationship between excessive analgesic use and migraine chronicity, including:

- Direction of relationship studied (overuse→chronicity, chronicity→overuse, bidirectional)
- Statistical associations found (correlations, odds ratios, risk ratios with confidence intervals)
- Temporal patterns or causal evidence
- Dose-response relationships
- Whether relationship varies by analgesic type
- Strength and significance of associations
- Any evidence of causality vs. correlation

- **Intervention Effects:**

Extract details about interventions targeting analgesic overuse or migraine chronicity and their effects on the relationship, including:

- Type of intervention (detoxification, preventive medication, education, etc.)
- Intervention protocol and duration
- Effects on analgesic use patterns
- Effects on migraine frequency/chronicity
- Success rates for breaking the overuse-chronicity cycle
- Factors predicting intervention success or failure
- Long-term maintenance of effects

- **Primary Outcomes:**

Extract the primary outcomes and their results specifically related to analgesic overuse and migraine chronicity, including:

- Main outcome measures (headache frequency, analgesic consumption, disability scores, etc.)
- Baseline and follow-up values with statistical comparisons
- Effect sizes and clinical significance
- Time course of changes
- Rates of conversion between chronic and episodic patterns
- Rates of successful medication overuse cessation

- **Moderating Factors:**

Extract factors that appear to modify or influence the relationship between analgesic overuse and migraine chronicity, including:

- Patient characteristics that affect outcomes (age, gender, headache duration, psychological factors)
- Medication-related factors (type, dose, duration of overuse, number of different medications)
- Treatment-related factors (setting, approach, adherence, support)
- Environmental or contextual factors
- Predictors of relapse or sustained improvement

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients") AND ("Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache") AND ("Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone") AND ("Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution")	10
Semantic Scholar	("Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients") AND ("Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache") AND ("Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone") AND ("Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution")	63
Springer	("Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients") AND ("Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache") AND ("Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone") AND ("Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution")	14
Google Scholar	("Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients") AND ("Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache") AND ("Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone") AND ("Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution")	1,930
Wiley Online Library	("Chronic migraine patients" OR "Adults with migraine" OR "Migraine sufferers" OR "Episodic migraine patients") AND ("Analgesic overuse" OR "Medication overuse headache (MOH)" OR "Excessive painkiller use" OR "Rebound headache") AND ("Normal analgesic use" OR "Episodic migraine" OR "Controlled analgesic use" OR "Preventive treatment alone") AND ("Migraine chronicity" OR "Headache frequency increase" OR "Transformation to chronic migraine" OR "Medication overuse resolution")	17

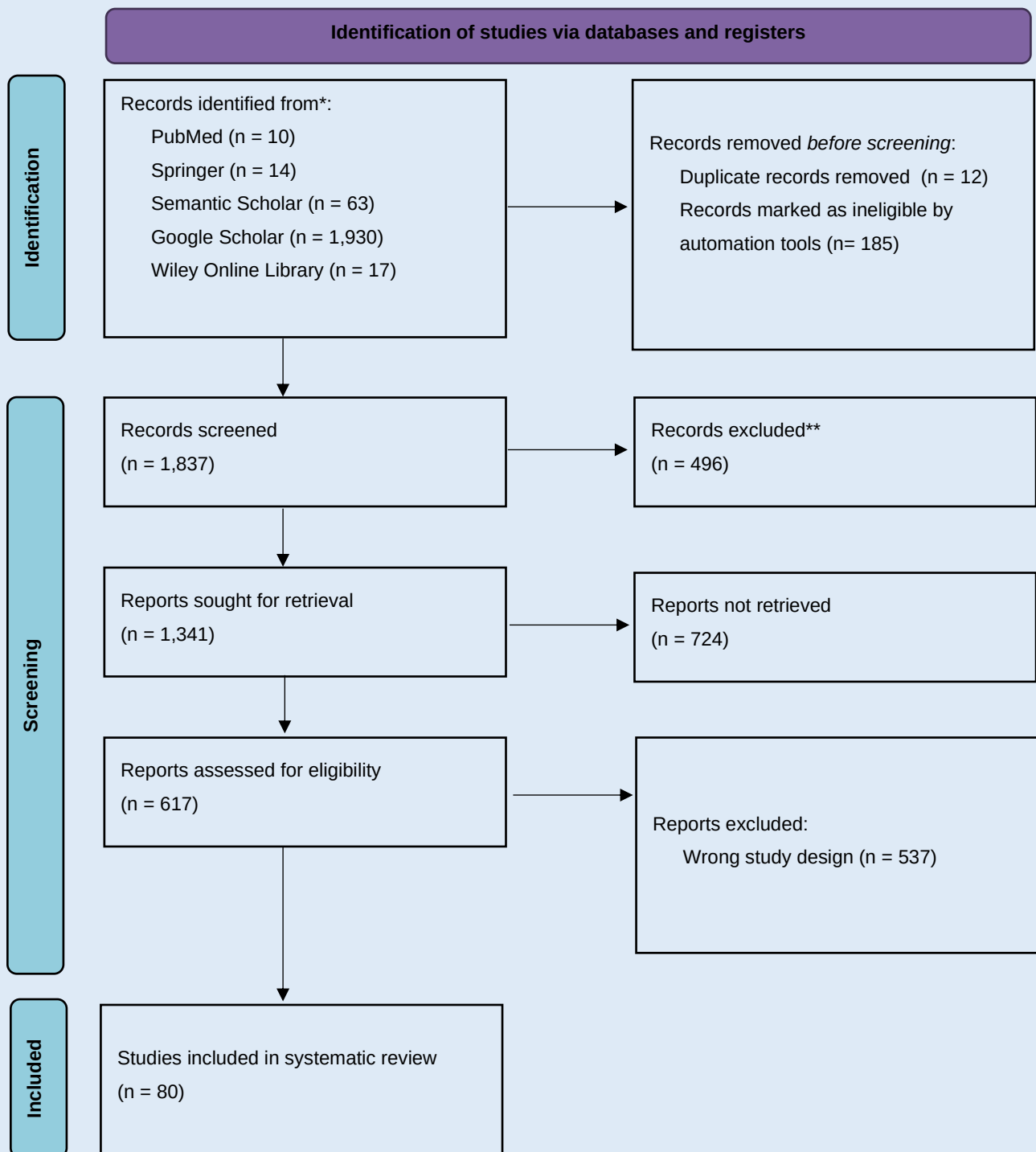


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
M. Bigal et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Andrasik et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Caronna et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Silberstein et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Silberstein et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Biagianti et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Kanki et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Tepper et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Silberstein et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Dodick et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Guerzoni et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Dodick et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Schwedt et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Caronna et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓

P. Goadsby et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Valguarnera et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Krymchanski et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Cowan et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Negro et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Viganó et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Goadsby Peter et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Ambrosini et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Tobin et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Krymchanski et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓

L. Grazzi et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Marmura et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
S D Silberstei n et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Bártková et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Cevoli et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Cowan et al., 2022a	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Halker et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Michele Alessiani et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Frank Andrasik et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Tepper et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Riachi et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓

R. Jensen et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shuu-Jiun Wang et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
SISC et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Ashina et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Mei et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Schiano di Cola et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Divya Mehta et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Sergeev et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Curone et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Samita Giri et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Carlsen et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Mansour et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

Nhan Nguyen et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sirilertme kasakul et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
AV Krymcha ntowski et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Krymcha ntowski et al., 2023a	✓	✓	✓	✗	✓	✗	✓	✓	✓
DR Williams et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
Z. Katsarava et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Lanteri-Minet et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Renato Oliveira et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ami Z. Cuneo et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

Samita Giri et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Carlsen et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Oliveira da Silva et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Tepper et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Pijpers et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. A. Guziy et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
V. Golovach eva et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Ornello et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Barbanti et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Grazzi et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Piero Barbanti et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

L. Grazzi et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Rizzoli et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
T.H. Черныха et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. G. Renouil et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Ferrari et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓
H. Diener et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Adams et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Bigal et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review encompasses 80 sources examining the relationship between excessive analgesic use and migraine chronicity.

Study	Population Size	Follow-up Duration	Primary Focus
M. Bigal et al., 2004	456	1 year	Detoxification outcomes in transformed migraine
F. Andrasik et al., 2010	84 initially, 58 at follow-up	5 years	Long-term disability in CM with MO
E. Caronna et al., 2018	139	6 months	OnabotulinumtoxinA efficacy in CM-MO
S. Silberstein et al., 2019	587 with MO	12 weeks	Fremanezumab impact on MO
S. Silberstein et al., 2013	904 CM+MO subgroup	24 weeks	OnabotulinumtoxinA in CM+MO
B. Biagianti et al., 2014	63	1 year	Dependency behaviors and relapse predictors
R. Kanki et al., 2008	47-276	3 months	MOH characteristics in Japan
S. Tepper et al., 2019	667	3 months	Erenumab in CM with MO
S. Silberstein et al., 2020	1130	12 weeks	Fremanezumab subgroup analysis
L. Grazzi et al., 2017	44	1 year	Mindfulness vs pharmacological prophylaxis
D. Dodick et al., 2020	Not specified	3-6 months	Galcanzumab in MO subgroup
S. Guerzoni et al., 2017	90	3 years	Long-term OnabotulinumtoxinA efficacy
D. Dodick et al., 2019	349	3 months	Erenumab in MO with prior treatment failure
T. Schwedt et al., 2022	720	12 weeks	Treatment strategies for CMMO
E. Caronna et al., 2021	139	6 months	Anti-CGRP mAbs real-life effectiveness

Study	Population Size	Follow-up Duration	Primary Focus
P. Goadsby et al., 2024	755	12 weeks	Atogepant in CM with/without MO
F. Valguarnera et al., 2010	52	6 months	Withdrawal therapy with topiramate/amitriptyline
A. Krymchantowski et al., 2023	172	6 months	Anti-CGRP mAbs vs conventional treatment
R. Cowan et al., 2022	1072	24 weeks	Eptinezumab AHM use changes
A. Negro et al., 2015	155	2 years	OnabotulinumtoxinA long-term efficacy
A. Viganó et al., 2018	17 CM, 19 HV	1 month	GON block neurophysiology
L. Grazzi et al., 2016	44	12 months	Mindfulness vs pharmacology preliminary
Goadsby Peter et al., 2023	778	12 weeks	Atogepant efficacy in MO
A. Ambrosini et al., 2022	462	6 months	Galcanezumab AHM and HCRU
J. Tobin et al., 2022	1113	12 months	Galcanezumab AHM and HCRU (REGAIN)
A. Krymchantowski et al., 2016	149	8 months	Daily vs near-daily headache outcomes
L. Grazzi et al., 2018	29	12 months	Catecholamine changes with mindfulness
M. Marmura et al., 2023	Not specified	24 weeks	Eptinezumab in CM+MOH
S D Silberstein et al., 2020	435 with MO	12 weeks	Fremanezumab in treatment-resistant patients

Study	Population Size	Follow-up Duration	Primary Focus
A. Bártková et al., 2015	58	24 weeks	OnabotulinumtoxinA feasibility
S. Cevoli et al., 2014	54	3 months	Withdrawal headache treatment
R. Cowan et al., 2022a	431 MOH	24 weeks	Eptinezumab AHM reductions in MOH
R. Halker et al., 2013	96	14 days	Steroids in MOH withdrawal
Michele Alessiani et al., 2020	150	12 months	STPP vs OnabotulinumtoxinA
Frank Andrasik et al., 2019	68	6 months	Catastrophizing changes with OnabotulinumtoxinA
S. Tepper et al., 2020	609	52 weeks	Long-term erenumab efficacy
N. Riachi et al., 2018	16	2 weeks	tDCS in MOH
R. Jensen et al., 2023	570 planned	36 weeks	Eptinezumab + BEI (RESOLUTION)
Shuu-Jiun Wang et al., 2019	179	12 weeks	BTA vs withdrawal alone
SISC et al., 2025	71	6 months	LDQ predictive value
S. Ashina et al., 2022	427 MO	OLE period	Fremanezumab MO reversion
D. Mei et al., 2006	50	12 weeks	Topiramate and triptans efficacy
F. Schiano di Cola et al., 2019	84	12 months	OnabotulinumtoxinA response predictors
Divya Mehta et al., 2023	98	12 weeks	DNA methylation and treatment response
A. Sergeev et al., 2024	44	12 months	Treatment strategy comparison

Study	Population Size	Follow-up Duration	Primary Focus
M. Curone et al., 2013	50	12 weeks	Duloxetine in CM-MO with depression
Samita Giri et al., 2023	3121 pooled	12-24 weeks	Topiramate, BoNTA, mAbs comparison
L. Carlsen et al., 2018	72	12 months	Detoxification strategies
A. Mansour et al., 2020	18	2 weeks	tDCS in MOH
Nhan Nguyen et al., 2025	769	≥3 months	Eptinezumab/erenumab safety and efficacy
L. Grazzi et al., 2022	177	3 months	Mindfulness added to TaU
Sirilertmekasakul et al., 2024	Not specified	Not specified	Anti-CGRP MO status transition
AV Krymchantowski et al., 2003	150	5 weeks	Outpatient detoxification strategies
A. Krymchantowski et al., 2023a	88	6 months	Three anti-CGRP mAbs comparison
DR Williams et al., 2003	71	6 months	IV lignocaine infusion
Z. Katsarava et al., 2005	96	4 years	Relapse rates and predictors
M. Lanteri-Minet et al., 2011	34 studies	N/A	QoL, disability, economic burden
Renato Oliveira et al., 2024	19 studies	3-12 months	CGRP-targeted medication review
L. Grazzi et al., 2020	135	12 months	tDCS with drug withdrawal

Study	Population Size	Follow-up Duration	Primary Focus
Ami Z. Cuneo et al., 2023	50	12 weeks	Biofeedback-VR device
Samita Giri et al., 2022	N/A	N/A	Topiramate, BoNTA, CGRP-antibodies
L. Carlsen et al., 2020	102	6 months	Three treatment strategies
R. Oliveira da Silva et al., 2025	875	≥3 months	Erenumab efficacy and tolerability
L. Grazzi et al., 2023	79	12 months	OnabotulinumtoxinA and catastrophizing
S. Tepper et al., 2021	955-667	24-52 weeks	Erenumab acute medication reduction
J. Pijpers et al., 2019	179	N/A	BTA in CM+MO
E. A. Guziy et al., 2024	140	9 months	Preventive therapy efficacy
V. Golovacheva et al., 2024	156	18 months	CBT efficacy in CM-MOH
R. Ornello et al., 2020	91	6 months	Erenumab CM to EM conversion
P. Barbanti et al., 2023	148	24 weeks	Fremanezumab real-life efficacy
L. Grazzi et al., 2021	14	12 months	Web-based program during COVID
Piero Barbanti et al., 2025	212	3 years	Anti-CGRP mAbs course modification
L. Grazzi et al., 2024	37	12 months	Multimodal digital health
P. Rizzoli et al., 2021	14	6 months	COVID adaptation of CM-MO treatment

Study	Population Size	Follow-up Duration	Primary Focus
T.H. Черныха et al., 2023	61	3 months	Transcranial electroanalgesia
N. G. Renouil et al., 2012	32	3 weeks	Pain modulation in MOH
A. Ferrari et al., 2006	34	N/A	IPC combination pharmacokinetics
H. Diener et al., 2007	59	16 weeks	Topiramate in CM with MO
A. Adams et al., 2015	16,789	1 year	CaMEO study methods
M. Bigal et al., 2003	791	N/A	MMPI profiles in CDH

Sample sizes ranged from 14 to over 16,000 participants, with follow-up periods spanning from 2 weeks to 5 years.

Definitions and Measurement of Key Constructs

Medication Overuse Definitions

The definition of medication overuse varied across studies but generally followed International Headache Society criteria. The most commonly applied thresholds included simple analgesics use on ≥ 15 days per month, while triptans, ergots, opioids, and combination medications were typically defined as overuse at ≥ 10 days per month. One early study employed more stringent criteria, defining simple analgesic overuse as >1000 mg ASA/acetaminophen for >5 days/week, and triptan overuse as >1 tablet per day for >5 days per week.

The types of analgesics included in overuse definitions encompassed simple analgesics, combination analgesics (often containing caffeine and/or butalbital), triptans, ergotamine derivatives, opioids, and NSAIDs. Assessment methods primarily relied on patient-reported data through headache diaries, electronic diaries (eDiaries), or chart review.

Chronic Migraine Definitions

Chronic migraine was consistently defined as headache occurring on ≥ 15 days per month for more than 3 months, with ≥ 8 days displaying migraine features, in accordance with ICHD-3 criteria. Assessment tools included the Migraine Disability Assessment (MIDAS), Headache Impact Test (HIT-6), and daily headache diaries.

Population Characteristics

The study populations were predominantly female (75-91%), with mean ages typically ranging from 40 to 50 years. Baseline headache frequency in chronic migraine populations ranged from 15 to 27 headache days per month.

Medication overuse was highly prevalent, affecting 40-78% of chronic migraine patients across studies. The most commonly overused medications were triptans, combination analgesics, and NSAIDs.

Psychiatric comorbidities were frequent, with anxiety present in 60-69% and depression in 24-45% of patients. Many patients had failed multiple prior preventive treatments.

Effects of Interventions on Medication Overuse and Migraine Chronicity

Detoxification and Withdrawal Approaches

Medication withdrawal remains a cornerstone of treatment for medication overuse headache. Complete detoxification achieved successful outcomes in 69.7-78% of patients, with successful patients showing 73.7% reduction in headache frequency and 61.2% reduction in headache duration at one-year follow-up. Complete cessation of acute medication was more effective than restricted intake, reducing headache days by 46% versus 22% and reverting 70% versus 42% to episodic headache patterns.

Intravenous lignocaine infusion for severe medication overuse achieved 90% improvement at treatment completion and 70% sustained improvement at six months, with 97% successful withdrawal of the offending analgesic at completion and 72% remaining free at six-month follow-up.

The long-term success of withdrawal depends significantly on the type of primary headache and the type of overused medication. Four-year relapse rates were significantly lower for migraine (32%) compared to tension-type headache (91%) and for triptan overuse (21%) compared to analgesic overuse (71%).

Anti-CGRP Monoclonal Antibodies

The anti-CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) demonstrated consistent efficacy in reducing both migraine frequency and medication overuse.

Erenumab showed significant reductions in monthly migraine days of -6.6 days (70 mg and 140 mg) compared to -3.5 days for placebo, with corresponding reductions in acute medication treatment days of -5.4 and -4.9 days versus -2.1 days for placebo. In patients with medication overuse who had failed prior preventive treatments, erenumab 140 mg achieved $\geq 50\%$ reduction in monthly migraine days in 41.7% versus 14.2% for placebo. Long-term data over 52 weeks showed sustained reductions, with 81% of patients overusing simple analgesics, 72% overusing triptans, and 70% overusing combination therapy transitioning to non-overuse status.

Fremanezumab demonstrated that 55% (quarterly dosing) and 61% (monthly dosing) of patients with medication overuse at baseline reverted to no overuse compared to 46% with placebo. Response was evident by week 4, with reductions in acute headache medication use of -9.0 days (quarterly) and -8.9 days (monthly) versus -7.1 days for placebo. In patients with documented inadequate response to 2-4 preventive medication classes, fremanezumab achieved reductions in monthly migraine days of -3.3 days (quarterly) and -4.6 days (monthly) versus -0.5 days for placebo.

Galcanezumab significantly improved monthly migraine headache days in patients with baseline medication overuse ($p \leq 0.001$) and reduced average monthly medication overuse rates

compared to placebo ($p < 0.001$). In patients with multiple prior preventive treatment failures, acute headache medication use decreased by 4.2 days with galcanezumab versus 0.9 days with placebo (LS mean difference 3.4 days, 95% CI 2.7-4.1, $P < 0.0001$). At 12 months, medication overuse rates decreased from 63-64% at baseline to 16-23%.

Eptinezumab reduced days with both headache and acute medication use by 29.1 percentage points versus 18.4 percentage points for placebo, with particularly notable reductions in triptan use (-11.8% vs -7.2%). In patients with dual diagnosis of chronic migraine and MOH, 51.1-54.4% of eptinezumab-treated patients were below ICHD thresholds for CM diagnosis versus 32.4% for placebo over 24 weeks.

Meta-analytic evidence confirmed that anti-CGRP therapy significantly increased the likelihood of $\geq 50\%$ reduction in monthly migraine days (OR 2.43, 95% CI 1.68-3.51, $p < 0.00001$) and approximately doubled the likelihood of MOH remission (OR 1.97, 95% CI 1.40-2.78, $p = 0.0001$).

OnabotulinumtoxinA

OnabotulinumtoxinA (155-195 U via the PREEMPT protocol) demonstrated efficacy in chronic migraine with medication overuse across multiple studies. In the pooled PREEMPT analysis, the CM+MO subgroup showed greater reductions in headache days (-8.2 vs -6.2 days, $p < 0.001$) compared to placebo, with significant shifts to no medication overuse persisting for at least 3 and 6 months.

After two cycles of onabotulinumtoxinA, 73.4% achieved $\geq 50\%$ reduction in acute medication intake and 57.6% achieved medication overuse resolution, with daily headache prevalence decreasing from 71.2% to 23.2%. Long-term treatment over 3 years showed sustained improvements in headache frequency and analgesic consumption, with significant reductions from baseline maintained from the 18th month onwards.

However, one well-designed double-blind RCT found that onabotulinumtoxinA did not provide additional benefit over acute withdrawal alone, with only a clinically modest 1.8-day reduction in headache days compared to placebo ($p = 0.15$).

Gepants (Small Molecule CGRP Antagonists)

Atogepant, an oral CGRP receptor antagonist, demonstrated efficacy in chronic migraine with medication overuse. In participants with acute medication overuse (66.2% of the study population), atogepant 30 mg BID and 60 mg QD significantly reduced monthly migraine days (LSMD -2.7 and -1.9 days, respectively) and acute medication use days (LSMD -2.8 and -2.6 days). Over 12 weeks, 52.1-61.9% of atogepant-treated participants no longer met acute medication overuse criteria. The $\geq 50\%$ response rate was achieved by 44.7% (30 mg BID) and 41.8% (60 mg QD) versus 24.9% for placebo.

Topiramate

Topiramate (100 mg/day) significantly reduced monthly migraine days by 3.5 ± 6.3 days compared to 0.2 ± 4.7 days for placebo ($P < 0.05$) in chronic migraine patients with medication overuse. The medication was effective even in the presence of medication overuse, which affected 78% of study participants.

Behavioral and Mindfulness-Based Interventions

Mindfulness-based training showed comparable efficacy to pharmacological prophylaxis. Both approaches achieved approximately 6-8 days reduction in headache frequency and 7 intakes reduction in medication consumption at 12-month follow-up. The majority of patients in both groups no longer met criteria for chronic migraine. Adding six mindfulness-based sessions to treatment as usual resulted in 75.9% achieving $\geq 50\%$ headache reduction versus 54.2% with treatment as usual alone.

Cognitive behavioral therapy combined with standard treatment achieved clinical effect ($\geq 50\%$ headache reduction) in 74% at 3 months and 79% at 18 months, compared to 45% and 33%

with standard treatment alone. Improvements were maintained over 18 months in the CBT group but not sustained in the standard treatment group.

Neuromodulation

Transcranial direct current stimulation (tDCS) showed mixed results. While cathodal tDCS over the occipital cortex significantly reduced severe migraine days and analgesic consumption, a larger RCT found no difference between anodal, cathodal, or sham tDCS when combined with drug withdrawal, with all groups showing similar improvements (48.5-64.7% reduction in headache days).

Greater occipital nerve block reduced total headache days by 34.9% ($p = 0.003$), reverted 8 of 17 patients to episodic migraine, and resolved medication overuse in 11 of 12 patients.

Evidence for the Relationship Between Analgesic Overuse and Migraine Chronicity

Direction and Nature of the Relationship

The predominant direction of relationship examined across studies was from medication overuse to chronicity (overuse→chronicity), with some evidence supporting bidirectional mechanisms.

The evidence supporting a causal relationship from overuse to chronicity includes:

1. **Temporal patterns:** Improvement in headache status following discontinuation of overused medications consistently supports causality. Patients with chronic migraine who underwent medication withdrawal showed significant reductions in headache frequency (from 29.4 to 10.1 days/month).
2. **Withdrawal benefits:** Successful detoxification led to substantial improvements, with 70.7% of successfully detoxified patients returning to episodic migraine compared to only 15.3% of those who did not discontinue overuse.

3. **Pharmacokinetic evidence:** Chronic overuse of combination analgesics altered drug disposition, with longer half-life and lower clearance of indomethacin, and higher peak concentrations of caffeine, potentially perpetuating the medication-overuse headache cycle.

Variation by Medication Type

The relationship between analgesic overuse and chronicity varies significantly by medication type. Relapse rates after withdrawal were substantially lower for triptan overuse (21%) compared to analgesic overuse (71%, $P \leq 0.001$). In patients transitioning from medication overuse, anti-CGRP antibodies were particularly effective for triptan users (RR 1.71, 95% CI 1.53-1.91, $p < 0.001$) and multi-drug users (RR 1.29, 95% CI 1.14-1.46, $p < 0.001$), but not statistically significant for simple analgesic users (RR 1.10, 95% CI 0.83-1.47, $p = 0.5$).

Different medications also contributed differentially to MOH development, with triptans and opioids increasing MOH risk more rapidly than simple analgesics.

Role of Reducing Headache Frequency

Evidence suggests that controlling headache frequency leads to decreased acute medication use, supporting the bidirectional nature of the relationship. Reductions in headache frequency with preventive treatment were associated with corresponding decreases in acute medication use, particularly triptans.

Moderating Factors

Patient Characteristics

Several patient characteristics moderated treatment outcomes:

- **Psychological factors:** Depression and anxiety were associated with poorer outcomes. The presence of obsessive-compulsive disorder (OCD) was particularly detrimental, with no OCD patients falling among treatment responders.

- **Pain catastrophizing:** Reduction in pain catastrophizing, particularly the helplessness subscale, significantly predicted reduction in headache frequency and medication intake.
- **Baseline characteristics:** Lower baseline pain severity was associated with medication overuse resolution (OR 0.236, 95% CI 0.054-0.975, $p = 0.049$). Patients with daily headaches showed higher treatment adherence than those with near-daily headaches.
- **Obesity:** Identified as a negative predictor of response to anti-CGRP monoclonal antibodies.

Medication-Related Factors

The type and intensity of medication overuse influenced outcomes:

- Higher baseline medication intake was inversely associated with medication overuse resolution.
- Patients overusing triptans generally had better outcomes than those overusing analgesics.
- Duration and quantity of overuse affected treatment response.

Treatment-Related Factors

Treatment setting and approach influenced outcomes:

- Combined withdrawal plus preventive treatment showed a 30% increased chance of MOH cure compared to preventive treatment alone (RR 1.3, 95% CI 1.1-1.6, $p = 0.03$).
- Behavioral and educational measures combined with regular follow-up visits contributed to long-term improvement and low relapse rates.
- Patient education and adherence support were consistently associated with better outcomes.

Synthesis

Reconciling Evidence on Treatment Strategies

The evidence reveals important nuances in treatment approach effectiveness that explain apparent heterogeneity in findings:

Medication withdrawal alone vs. combined approaches: Studies consistently demonstrate that while withdrawal alone is effective, combining withdrawal with preventive treatment produces superior outcomes. Complete detoxification reduced headache days by 46% compared to 22% with restricted intake, but the combination of withdrawal plus preventive treatment achieved 96.8% MOH cure versus 74.3% with preventive treatment alone. This explains why some studies showing modest effects of preventive treatments alone (like the BTA study showing only 1.8-day reduction) still contribute valid evidence—the comparison condition (withdrawal alone) was itself effective.

Anti-CGRP therapies with vs. without active withdrawal: Anti-CGRP monoclonal antibodies demonstrated efficacy regardless of active detoxification status, with 55-61% of patients reverting from medication overuse without requiring formal detoxification protocols. This suggests these therapies may facilitate spontaneous reduction in acute medication use through improved headache control, representing a mechanistically different pathway than traditional withdrawal approaches.

Time course considerations: The relationship between overuse and chronicity operates on different time scales:

- Acute benefits of withdrawal appear within 2-3 months
- Most relapses occur within the first year
- Long-term benefits with preventive treatments continue improving through 5 years
- Three years of anti-CGRP treatment progressively increased the proportion of $\geq 50\%$ responders from 25% at first discontinuation to 77.8% at third discontinuation

Population-Specific Effects

The evidence supports different optimal approaches for different patient populations:

Primary headache type matters: Four-year relapse rates differed dramatically between migraine (32%), tension-type headache (91%), and combined headache (70%). This suggests that the overuse-chronicity relationship is more reversible in migraine than in other primary headache disorders.

Medication overuse type predicts outcomes: Patients overusing triptans had substantially lower relapse rates (21%) compared to those overusing analgesics (71%), and anti-CGRP therapies showed differential efficacy by overused medication class. This may reflect different mechanisms underlying overuse with different medication classes or selection effects related to initial headache characteristics.

Prior treatment failures: Patients with multiple prior preventive treatment failures still showed significant benefit from anti-CGRP therapies, suggesting these represent a mechanistically distinct intervention approach that can succeed where previous strategies failed.

Mechanistic Considerations

Several mechanistic pathways may explain the observed relationships:

1. **Central sensitization and reversal:** Chronic medication overuse may maintain central sensitization, with withdrawal allowing restoration of normal pain processing. Evidence of altered pain modulation in MOH patients that normalized after withdrawal supports this mechanism.
2. **CGRP pathway:** The consistent efficacy of CGRP-targeting therapies in reducing both headache frequency and medication overuse suggests CGRP plays a role in maintaining the overuse-chronicity cycle. Treatment that blocks CGRP may interrupt this cycle independent of medication withdrawal.
3. **Pharmacokinetic alterations:** Chronic overuse alters drug disposition, with evidence of prolonged half-life and elevated plasma concentrations of analgesic components, potentially perpetuating rebound headache.
4. **Neuroplasticity:** The progressive improvement seen with extended anti-CGRP treatment (3 years) suggests these therapies may promote favorable neuroplastic changes in migraine circuitry that persist beyond treatment periods.

Clinical Implications

The synthesized evidence supports a stratified approach to treatment:

1. **For patients able to undergo withdrawal:** Complete cessation of acute medication combined with initiation of preventive treatment offers the highest success rates (96.8% MOH cure).
2. **For patients unable to tolerate withdrawal:** Anti-CGRP therapies provide effective treatment without requiring formal detoxification, with 55-61% reverting from medication overuse spontaneously.
3. **For treatment-resistant patients:** Anti-CGRP therapies demonstrate efficacy even in patients who have failed 2-4 prior preventive medication classes.
4. **For patients with psychological comorbidities:** Combined behavioral approaches (mindfulness, CBT) with pharmacological treatment may address both the overuse behavior and underlying psychological factors.
5. **Long-term management:** Extended treatment with anti-CGRP therapies (≥ 3 years) may modify disease course, with progressively better outcomes at each treatment cycle.

DISCUSSION

This systematic review of 80 studies provides a comprehensive and nuanced understanding of the complex relationship between excessive analgesic use and migraine chronicity, as well as the evidence base for various treatment strategies. The discussion synthesizes these findings, explores their mechanistic implications, and outlines their clinical significance.

The Nature of the Overuse-Chronicity Relationship: The preponderance of evidence supports a causal link from medication overuse to the development and maintenance of chronic migraine. The most compelling evidence stems from the consistent observation that discontinuation

of the overused medication leads to significant clinical improvement in a majority of patients (Carlsen et al., 2018; Katsarava et al., 2005). For instance, successful detoxification resulted in a dramatic reduction of headache frequency from 29.4 to 10.1 days per month and enabled 70.7% of patients to revert to episodic migraine, compared to only 15.3% of those who continued overuse (Bigal et al., 2004). This temporal pattern, where removal of the putative cause (overuse) reverses the effect (chronicity), strongly argues against a mere association. Pharmacokinetic studies further bolster the causal argument, demonstrating that chronic overuse of combination analgesics alters drug disposition—such as prolonging the half-life of indomethacin and increasing peak caffeine concentrations—which may pharmacologically perpetuate a rebound headache cycle (Ferrari et al., 2006). However, the relationship is undoubtedly bidirectional. Chronic, frequent headaches create a high demand for acute relief, driving medication intake. Effective preventive treatment that reduces headache frequency subsequently leads to a spontaneous decrease in acute medication use, as demonstrated by trials of anti-CGRP mAbs where headache improvement preceded and likely drove the reduction in overuse (Tepper et al., 2021; Dodick et al., 2020).

Differential Impact of Analgesic Type: A critical insight from this review is that not all medication overuse carries the same risk or prognosis. The relationship varies profoundly by the class of overused drug. Triptan overuse, while contributing to MOH development, is associated with a significantly more favorable outcome following intervention compared to overuse of simple analgesics or combination medications. Relapse rates after withdrawal were markedly lower for triptan overuse (21%) than for simple analgesic overuse (71%) (Katsarava et al., 2005). Correspondingly, anti-CGRP therapies showed the most robust efficacy in helping patients transition from overuse status among triptan and multi-drug users, with more modest effects observed in simple analgesic users (Sirilertmekasakul et al., 2024; Krymchantowski et al., 2023a). This suggests distinct underlying pathophysiological mechanisms or patient phenotypes associated with different overuse patterns. Triptans, as migraine-specific agents, may induce overuse headache in a neurobiologically distinct manner compared to non-specific analgesics, possibly making the resulting circuit dysfunction more responsive to targeted CGRP blockade and withdrawal.

Reconciling Treatment Efficacy: Withdrawal as a Foundation, Prevention as an Enhancer: The synthesized evidence clarifies apparent contradictions in the literature regarding treatment efficacy. Detoxification (complete medication withdrawal) remains a cornerstone and highly effective intervention, achieving successful outcomes in 69.7-78% of patients and serving as a powerful testament to the causal role of overuse (Carlsen et al., 2018; Valguarnera & Tanganelli, 2010). However, the most successful strategy is not withdrawal alone, but its combination with the initiation of effective preventive therapy. Studies consistently show that withdrawal plus prevention yields superior results, such as a 96.8% MOH cure rate compared to 74.3% with prevention alone (Sergeev et al., 2024). This explains why some trials of preventive agents (e.g., onabotulinumtoxinA) showed only modest added benefit over withdrawal alone—because the control condition (withdrawal) was itself a potent active intervention (Wang & Ling, 2019). The evidence argues for a sequential or integrated model where withdrawal disrupts the perpetuating cycle, and preventive medication protects against relapse by reducing the fundamental drive to use acute drugs.

The Transformative Role of CGRP-Targeted Therapies: The advent of anti-CGRP mAbs and gepants represents a paradigm shift. These agents demonstrate consistent, significant efficacy in reducing monthly migraine days and, crucially, in reducing acute medication overuse days, even in populations with documented prior preventive treatment failures (Dodick et al., 2019; Barbanti et al., 2023; S D Silberstein et al., 2020). A landmark finding is that a substantial proportion (55-61%) of patients with baseline overuse reverted to non-overuse status during trials *without* undergoing a formal, supervised detoxification protocol (Silberstein et al., 2020; Ashina et al., 2022). This suggests these therapies can break the overuse-chronicity cycle through a different mechanism: by effectively suppressing the migraine process itself, they remove the need for frequent acute medication, thereby allowing overuse to resolve "spontaneously." This offers a crucial alternative for patients who cannot tolerate or fail withdrawal. Furthermore, long-term data indicates that extended use (e.g., 3 years) may induce progressive and sustained improvements, suggesting disease-modifying potential through favorable neuroplastic changes (Piero Barbanti et al., 2025; Guerzoni et al., 2017).

The Integral Role of Non-Pharmacological Modalities: The review underscores that medication overuse is not solely a pharmacological problem but also a behavioral one, often intertwined with psychological factors. Behavioral interventions like mindfulness-based stress reduction and cognitive-behavioral therapy (CBT) demonstrated efficacy comparable to pharmacological prophylaxis in reducing headache frequency and medication intake (Grazzi et al., 2017; Golovacheva & Golovacheva, 2024). These approaches target maladaptive pain coping strategies, pain catastrophizing, and the behavioral patterns that sustain the overuse cycle. The finding that reductions in pain catastrophizing, particularly feelings of helplessness, predicted clinical improvement with treatments like onabotulinumtoxinA highlights the psychobiological interface in MOH (Frank Andrasik et al., 2019; Grazzi et al., 2023). Therefore, optimal management should consider integrating these modalities, especially for patients with significant anxiety, depression, or maladaptive coping styles.

Moderators of Outcome: Towards Personalized Treatment: The evidence highlights several key moderators that should inform clinical decision-making. *Patient Characteristics:* Psychological comorbidities, particularly depression and anxiety, are negative prognostic factors (Curone et al., 2013; Schiano di Cola et al., 2019). Pain catastrophizing is a specific, modifiable cognitive factor that influences outcomes. *Medication-Related Factors:* As discussed, the type of overused medication (triptans vs. simple analgesics) is a major predictor of relapse and response to CGRP therapy. The duration and quantity of overuse also inversely correlate with success. *Treatment-Related Factors:* The setting (structured headache clinic vs. general practice), the inclusion of patient education, and regular follow-up support are consistently associated with better long-term outcomes and lower relapse rates (Schwedt et al., 2022).

Mechanistic Synthesis: The collected evidence points to several interlinked mechanisms. **1) Central Sensitization:** Chronic medication overuse is believed to promote and maintain a state of central sensitization in pain pathways, lowering the threshold for headache generation. Withdrawal allows for the gradual normalization of this hyperexcitable state. **2) CGRP Pathway Dysregulation:** The striking efficacy of CGRP blockade implicates this neuropeptide centrally in the

MOH cycle. Chronic overuse may dysregulate CGRP release or receptor sensitivity, which is directly corrected by these therapies. **3) Pharmacokinetic Tolerance/Adaptation:** Chronic exposure alters drug metabolism and receptor responses, leading to decreasing efficacy and promoting rebound phenomena (Ferrari et al., 2006). **4) Behavioral Reinforcement:** The cycle is reinforced operantly—taking medication provides immediate (though temporary) negative reinforcement (pain relief), strengthening the behavior of frequent intake.

Clinical Implications and a Stratified Approach: The synthesis of evidence leads to clear, actionable clinical implications supporting a stratified, patient-centered treatment model:

1. **For patients amenable to withdrawal:** A structured program of complete medication withdrawal combined with the simultaneous initiation of a preventive agent (chosen based on patient profile and medication overuse type) offers the highest chance of sustained success.
2. **For patients unable to undergo or tolerating withdrawal poorly:** Initiation of an anti-CGRP mAb or gepant is a highly effective first-line strategy, as it can reduce headache burden and often lead to spontaneous resolution of overuse.
3. **For treatment-resistant patients:** Anti-CGRP therapies remain effective even after multiple prior preventive failures, representing a distinct mechanistic class.
4. **For patients with significant psychological comorbidities:** Treatment plans should integrate behavioral therapies (CBT, mindfulness) with pharmacological management to address both the biological and behavioral components of the disorder.
5. **Long-term perspective:** Management should be viewed as a long-term process. Sustained preventive treatment, particularly with CGRP-targeted agents, may offer progressive benefits and should be continued to maintain gains and prevent relapse.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review consolidates robust evidence affirming a strong, predominantly causal relationship between excessive analgesic use and the progression and perpetuation of chronic migraine. Medication overuse headache is a common and treatable complication in chronic migraine populations. The cycle is driven by complex neurobiological mechanisms, including central sensitization and CGRP pathway dysregulation, and is influenced by behavioral and psychological factors.

The evidence demonstrates that effective management requires a multifaceted approach. Traditional detoxification remains a powerful intervention, but its combination with preventive pharmacotherapy yields the best outcomes. The emergence of CGRP-targeted therapies (monoclonal antibodies and gepants) has revolutionized treatment, offering high efficacy in reducing both headache days and acute medication overuse, even without formal detoxification and in treatment-resistant cases. Non-pharmacological strategies, particularly mindfulness and CBT, are valuable adjuncts or alternatives, especially for patients with significant psychological comorbidities.

Recommendations:

1. **Clinical Practice:** Adopt a stratified treatment model. Assess the type of medication overuse, patient readiness for withdrawal, psychological profile, and prior treatment history to guide the choice between prioritized withdrawal, immediate preventive therapy with CGRP-targeted agents, or integrated behavioral-pharmacological programs.
2. **Patient Education:** Implement proactive education for all episodic migraine patients on the risks of medication overuse and the importance of appropriate preventive treatment to avoid the transition to chronic migraine and MOH.

3. **Healthcare Systems:** Develop structured care pathways and support systems (e.g., headache specialty clinics, nurse-led support programs) to facilitate supervised withdrawal and long-term adherence to preventive therapies.
4. **Future Research:** Prioritize longitudinal studies to understand the long-term (5+ years) outcomes of different treatment sequences. Investigate the neurobiological distinctions between MOH subtypes based on overused medication class using neuroimaging and biomarker studies. Explore the cost-effectiveness and real-world implementation of stratified care models for MOH.

In conclusion, breaking the cycle of analgesic overuse and migraine chronicity is achievable. By leveraging a nuanced understanding of the relationship and a growing arsenal of effective interventions, clinicians can significantly improve outcomes and quality of life for this challenging patient population.

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