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보건의료전문가용

공동판매원 환인제약

수입판매원 GSK

두통 쉼표 나라믹.[1]

긴 지속시간으로
내 삶에 편안한 휴식을 선사하는[2,3]

References 1. Naramig Prescribing Information. **2.** Ong JJY.Neurotherapeutics:2017;15:274–290. **3.** Ashcroft DM, Millson D. Pharmacoepidemiology and Drug Safey. 2004 Feb;13(2):73–82.

Integrated safety information[1]

1. 다음 환자에는 투여하지 말 것. 1) 이 약에 과민반응의 병력이 있는 환자 2) 허혈심장병 환자 3) 심근경색증 병력이 있는 환자 4) 프린즈메탈협심증/관상혈관경련 환자 5) 말초혈관병 또는 허혈심장병과 일치하는 증상/증후를 보이는 환자 6) 뇌혈관사고(CVA) 또는 일과성허혈발작(TIA)의 병력이 있는 환자 7) 조절되지 않는 고혈압 환자 8) 중증의 신장애(크레아티닌 청소율 <15 mL/분)또는 간장애(Child-Pugh grade C)환자 9) 다른 5-HT1 효능제 투여 후 24시간 이내인 환자 10) 편마비, 뇌기저 또는 안근마비 편두통 환자 11) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. 2. 다음 환자에는 신중히 투여할 것. 설폰아미드에 과민반응을 나타내는 환자(이 약은 설폰아미드 성분을 함유하고 있다.) 3. 이상반응 이상반응은 기관 및 빈도별로 정리하였다. 발현빈도에 따라 매우 자주(≥ 1/10), 자주(≥ 1/100, <1/10), 때때로 (≥ 1/1,000, <1/100), 드물게(≥1/10,000, <1/1,000), 매우 드물게(<1/10,000)로 구분하여 아래와 같이 나타내었다. 1) 임상시험에서 보고된 이상반응 이 약의 치료용량 임상시험에서 보고된 이상반응 빈도는 위약과 유사했다. (1) 신경계 : 통상 일시적인 자통이 자주 보고되었는데, 간혹 심한 경우도 있고 흉부 또는 인후부 등을 포함한 신체 일부분에 영향을 미칠 수 있다. 시각장애가 드물게 보고되었다. (2) 소화기계 : 구역과 구토가 자주 발생하였으나, 발생 빈도가 위약과 유사하거나 높았기 때문에 이 약과의 관련성은 명확하지 않다. (3)근골격계 : 때때로 일시적인 증상강의 보고되었는데, 간혹 심한 경우도 있고 흉부 또는 인후부 등을 포함한 신체 일부분에 영향을 미칠 수 있다. (4) 순환기계 : 서맥, 빈맥, 심계항진이 드물게 보고되었다. (5) 전신 및 투여부위 : 자주 피로, 권태, 어지럼, 홍조, 통증, 저림 및 열감, 때때로 압박감 또는 죄이는 듯한 느낌이 보고되었는데, 통상 일시적인 것으로 간혹 심한 경우도 있고 흉부 또는 인후부등을 포함한 신체 일부분에 영향을 미칠 수 있다.

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References 1. Sacco S *et al*., European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain*. 2022 Jun 11;23(1):67

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Headache and Pain Research

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Aims and scope

Headache and Pain Research (Headache Pain Res; pISSN: 3022-9057, eISSN: 3022-4764) publishes original articles, review articles, and short letters on all aspects of Headache and Pain Research. The main topics include migraine, cluster headache, tension-type headache, intracranial hypotension, intracranial hypertension, reversible cerebral vasoconstriction syndrome, other primary or secondary headache disorders, pediatric headache, and issues related headache and pain such as dizziness, psychological, and cognitive problems, and *Temporomadibular disorder and orofaical pain*. *Headache and Pain Research*, the official journal of Korean Headache Society, aims to rapidly spread updated advances in the headache and pain field to readers and patients, while fostering a scientifically fair and progressive relationship with researchers and reviewers. It aims to be an international journal and welcomes outstanding editorial board members and submissions from all over the world.

Headache and Pain Research is published 3 times (the last day of February, June, and October) a year.

This journal was first published in 2000 under the title '*Korean Journal of Headache*' (ISSN 1598-009X) and its title has been changed to '*Headache and Pain Research*' since 2024.

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Headache and Pain Research

Beyond the Pain: Rethinking Migraine Care with the RELIEF PLAN Approach

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Recent articles in this issue of *Headache and Pain Research* have shed light on the complex nature of migraine, highlighting the need for a multifaceted approach to its understanding and management.[1] Migraine affects approximately 1.1 billion people worldwide and continues to be one of the most disabling neurological conditions. The Global Burden of Disease studies have highlighted its substantial impact, ranking it as the second highest contributor to years lived with disability, with a particularly significant effect on women in their prime working years.[2]

Despite its significant contribution to disability-adjusted life years, especially among women and young adults, migraine frequently fails to receive the recognition given to other chronic conditions. This leads to its widespread trivialization and misunderstanding. The lack of awareness highlights the urgent need for improved public health initiatives aimed at enhancing understanding and recognition of the true impact of migraine.

The articles explore several dimensions of migraine pathology, treatment, and public perceptions. One study discusses the genetic, biological, and environmental factors contributing to migraine, supporting the view that migraine is not merely a headache but a complex disorder requiring a biopsychosocial approach for effective management. This aligns with the growing body of evidence linking potentially traumatic experiences occurring before the age of 18, including abuse, neglect, or household dysfunction, with the development of chronic migraines.[3]

Another contribution examines the evolution of migraine treatment, moving from the vascular theory to recognizing neural circuit dysfunction as the primary factor. The discovery of key players, such as calcitonin gene-related peptide, in migraine mechanisms has transformed therapeutic strategies, emphasizing the need for early detection and intervention to prevent progression to chronic or medication-overuse headaches.

In Korea, cultural and linguistic barriers complicate the recognition of migraines. An article addresses the term "편두통" (one-sided headache), which contributes to widespread misunderstandings about the nature of migraines. It cites a survey that shows a significant portion of the population harbors misconceptions about the characteristics and treatment of migraines, underscoring the need for improved public education.[4]

To address these issues, I propose the "RELIEF PLAN" approach to migraine management:

- R – Recognize adverse childhood events: Acknowledge the role of early trauma.[3]
- E – Educate the family: To change perceptions and provide support.[4]
- L – Lifestyle modifications: Incorporate non-pharmacological interventions.[4]

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- I – Identify triggers: Tailor trigger management to the individual.[4]
- E – Early detection and intervention: Prevent chronicity through timely action.[4]
- F – Foster regular visits: Ensure ongoing care and research participation.[4]
- P – Plan for the future: Develop strategies to reduce societal burden.[4]

This editorial advocates for a future in which migraines are treated with the complexity and attention they deserve. It is informed by the latest research published in this issue, which calls for a holistic approach to care, education, and policy.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: SR; Writing–review & editing: SR.

CONFLICT OF INTEREST

Sanghyo Ryu is the English Editor of *Headache and Pain Research* and was not involved in the review process of this article. Author has no other conflicts of interest to declare.

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Editorial

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Headache and Pain Research

Exploring Secondary Headaches: Insights from Glaucoma and COVID-19 Infection

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Secondary headaches are clinically significant manifestations that often reflect underlying systemic or neurological conditions. Two notable examples include headaches associated with glaucoma and those related to systemic infections, such as COVID-19. This editorial integrates findings from recent studies to explore their clinical implications and pathophysiological mechanisms.

Recent research has identified associations between primary headaches—migraine and tension-type headache (TTH)—and primary glaucoma subtypes, including open-angle glaucoma (OAG) and closed-angle glaucoma (CAG). The study revealed that patients with migraine are at a higher risk of developing OAG due to systemic vasculopathy, while patients with TTH are more likely to experience CAG, which is linked to mechanical and structural factors. These findings underscore the importance of vascular and structural evaluations in managing patients with primary headaches, as they may predispose individuals to secondary complications such as glaucoma.[1]

Similarly, headaches have emerged as a common neurological symptom during and after COVID-19 infections, affecting approximately 25% of infected individuals. These headaches often persist post-recovery, impacting 6%–45% of patients. Key mechanisms include cytokine storms, where elevated inflammatory markers such as interleukin-6 sensitize trigeminal pathways. Additionally, SARS-CoV-2-induced endothelial dysfunction disrupts the blood-brain barrier, and viral entry via ACE2 receptors damages neuronal and glial cells. These mechanisms frequently result in headaches that mimic migraines or TTH, necessitating accurate diagnosis and appropriate intervention.[2]

The overlapping vascular and inflammatory pathways in these conditions highlight the importance of interdisciplinary headache management. Regular neurological evaluations for patients with glaucoma may help identify coexisting headache disorders, while post-COVID-19 patients require persistent headache monitoring with tailored interventions such as nonsteroidal anti-inflammatory drugs, calcitonin gene-related peptide antagonists, or nerve blocks. For high-risk patients with glaucoma or COVID-19-related neurological issues, early screening and targeted neurological testing are essential. This includes assessing anosmia or cognitive changes in COVID-19 patients and conducting vision tests, intraocular pressure measurements, and ophthalmic ultrasound or tonometry to screen for glaucoma. These measures facilitate early identification and intervention, ensuring effective management with tailored treatments and non-pharmacological approaches. Non-pharmacological strategies, such as

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lifestyle modifications, stress management, and dietary adjustments, are particularly critical for patients experiencing prolonged headaches.

These secondary headaches underscore the intricate relationship between systemic and neurological factors. A deeper understanding of their mechanisms supports improved diagnosis and treatment, ultimately alleviating headache symptoms. This approach not only improves patient management but also advances our knowledge of headache-related pathophysiology.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: SKK; Writing–original draft: SKK; Writing–review & editing: SKK.

CONFLICT OF INTEREST

Soo-Kyoung Kim is the Deputy Editor of *Headache and Pain Research* and was not involved in the review process of this article. Author has no other conflicts of interest to declare.

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Evidence-Based Recommendations on Pharmacologic Treatment for Migraine Prevention: A Clinical Practice Guideline from the Korean Headache Society

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Abstract

Purpose: The aim of this clinical practice guideline (CPG) from the Korean Headache Society is to provide evidence-based recommendations on the pharmacologic treatment for migraine prevention in adult migraine patients.

Methods: The present CPG was developed based on the guideline adaptation methodology through a comprehensive systematic search for literature published between January 2012 and July 2020. The overall quality of the CPGs was assessed using the Korean version of the Appraisal of Guidelines for Research and Evaluation II tool. High-quality CPGs were adapted to make key recommendations in terms of strength (strong or weak) and direction (for or against).

Results: The authors selected nine available high-quality guidelines throughout the process of assessment of quality. Regarding oral migraine preventive medications, propranolol, metoprolol, flunarizine, sodium divalproex, and valproic acid are recommended to adult patients with episodic migraines based on high-quality evidence ("strong for"). Topiramate can be recommended for either episodic or chronic migraine ("strong for"). For migraine prevention using calcitonin gene-related peptide monoclonal antibodies, galcanezumab, fremanezumab, erenumab, and eptinezumab are recommended for adult patients with either episodic or chronic migraine on the basis of high-quality evidence ("strong for"). OnabotulinumtoxinA is recommended for adult patients with chronic migraine based on high-quality evidence ("strong for"). Last, frovatriptan, naratriptan, and zolmitriptan are recommended for short-term prevention in women with menstrual migraine ("strong for").

Conclusion: In the present CPG, the authors provide specific, straightforward, and easy-to-implement evidence-based recommendations for pharmacologic migraine prevention. Nevertheless, these recommendations should be applied in real-world clinical practice based on optimal individualization.

Keywords: Appraisal of Guidelines for Research and Evaluation II, Calcitonin gene-related peptide, Guideline, Migraine, Prevention

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INTRODUCTION

Migraine is a common cycling brain disorder that can be characterized of recurrent episodic disabling headache attacks.[1] Migraine affects an estimated more than 12% of the population worldwide, and the prevalence of migraine in Korea was estimated to be 6% (3% in men and 9% in women).[2,3] Since the prevalence of migraine is highest amongst individuals aged 20 to 50, migraine attacks can result in headache-related disability and negative impact on social and occupational function in daily lives, particularly in young and middle-aged population.[4]

For a subset of migraineurs, episodic migraine (EM) attacks may be more frequent over time, which can substantially increase the burden of migraine. In terms of the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs), migraine diagnosis can be conceptualized and subdivided into EM and chronic migraine (CM) as a disease spectrum.[5] CM is defined as having ≥8 MMDs and ≥15 MHDs for at least 3 months, while EM having <15 MHDs. CM and EM patients with frequent headaches generally require preventive therapy to reduce the frequency, duration, or severity of migraine attacks and to reinforce the efficacy of acute (abortive) therapy. Successful preventive therapy reportedly has potential to improve quality of life and reduce migraine-related medical cost.

The purpose of this clinical practice guideline (CPG) is globally to provide evidence-based recommendations on pharmacologic treatment for migraine prevention to guide clinicians treating patients with EM, CM, and menstrual migraine and pregnant women. The CPG committee of the Korean Headache Society (KHS) recommends that migraine prevention based on the recommendations of this CPG should be cooperatively determined by healthcare providers and patients.

MATERIALS AND METHODS

1. Design and participants

The present CPG was based on guideline adaptation methodology and developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[6] The development working group (DWG) in the CPG Committee of the KHS included 16 neurologists who had specialty and interest in headache disorders and one KHS guideline methodologist. The members of DWG developed key question (KQ) that were clinically essential for migraine prevention in patients with EM, CM, and menstrual migraine, using the framework of Patient; Intervention; Comparison and Outcome (PICO) question.[7] The CPG oversight committee approved the composition of the working group and development of evidence-based recommendations with respect to the PICO KQs. All CPG committee members were required to disclose any conflict of interest that may potentially affect their participation and work. The DWG members have regularly communicated using e-mail and online conference during the CPG development period.

2. Patient; Intervention; Comparison and Outcome key questions

First, the DWG set the patient as adult patients with migraine (EM, CM, pregnancy, and menstrual migraine). Next, regarding the intervention and comparison, a systematic review of literature aimed to focus on pharmacologic treatments for migraine prophylaxis. Non-pharmacologic treatments and neuromodulation were not considered for intervention. The migraine prophylactics selected were as follows: beta-blockers (KQ 3), calcium channel blockers (KQ 4), angiotensin receptor blockers (KQ 5), angiotensin-converting enzyme inhibitors (KQ 5), antidepressants (KQ 6), antiseizure medications (KQ 7 and 9), calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) (KQ 8 and 12), botulinum toxin (KQ 11), and triptans (KQ 14). Last, outcome was determined by clinical improvement, in terms of reduction of number of MMDs, MHDs, and menstrual migraine days and proportions of 50% reduction of MMDs and/or MHDs. In this regard, the DWG discussed and settle search terms for each KQ. Consequently, the DWG proposed 16 PICO KQs related to pharmacologic treatment of EM, CM, and menstrual migraine. The CPG oversight committee reviewed the proposed PICO KQs. Then, these were revised according to advice from the CPG oversight committee. Finally, the PICO KQs were approved by the CPG oversight committee.

3. Search and selection of literature

The KHS guideline methodologist conducted comprehensive search for the systematic review of literature to answer the KQs (Figure 1). Based on the fact that the American Headache Society (AHS) and American Academy of Neurology (AAN) jointly published CPGs on migraine prevention in 2012, we searched literature published between January 1, 2012, and July 1, 2020, throughout databases (Guideline international network, Ovid MEDLINE/EMBASE, Cochrane library, and KoreaMed), using the key search terms migraine, prevention, prophylaxis, and treatment. The literature search process was conducted separately for each KQ using a search equation that included the relevant prophylactic agent. We considered only studies involving adult patients (>18 years) with the full article available in English. Two or more DWG members assigned to each KQ independently screened titles and abstracts from the primary literature identification. All disagreements were discussed between the two members or by a third DWG member to reach a consensus. If we could not find an answer to the KQs in the guidelines, we tried to answer the KQs through discover new evidence with recency search of systematic reviews, meta-analyses, and randomized controlled trials (RCTs). Likewise, if we could not find an answer again, we searched and reviewed non-RCT, cohort study, case-control study, case series (single arm before-after study), cross-sectional study, case report, and expert opinion.

Of the guidelines and studies retrieved, the following selection criteria were applied for inclusion in quality assessment of evidence: 1. included PICOs that aligned with the KQs; 2. were peer-reviewed; 3. were published in English; 4. used evidence-based methodology; and 5. were published after 2012. Subsequently, a total of 19 guidelines that met the inclusion criteria were retrieved during the comprehensive literature search.[8-26]

4. Analysis of evidence and recommendations

Regarding assessment of quality of those guidelines, two DWG members were assigned to each guideline, and they independently rated the score of each retrieved guideline using the Appraisal of Guidelines for Research and Evaluation (AGREE) II framework.[27,28] AGREE II consists of 23 items in six domains and two overall assessments. Consequently, of the 19 guidelines, we excluded 10 guidelines that scored less than 60% in the domain 3. Rigour of development (Table 1).

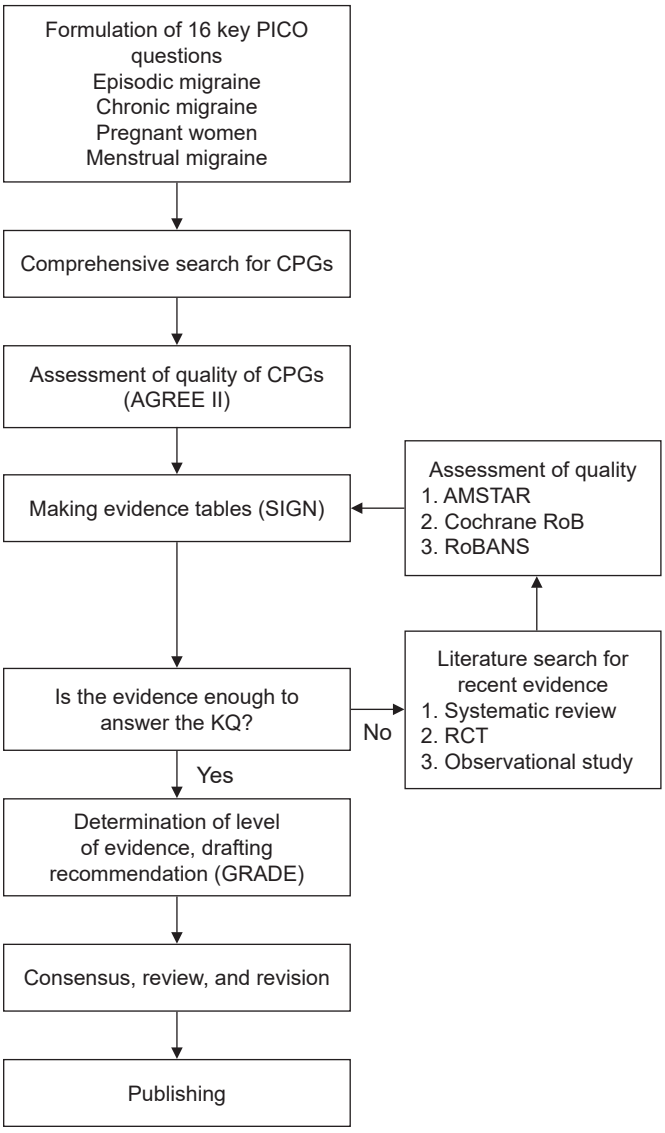

Figure 1. Flowchart of the development of this clinical practice guideline on pharmacologic treatment for migraine prevention.
PICO, Patient; Intervention; Comparison and Outcome; CPG, clinical practice guideline; AGREE II, Appraisal of Guidelines for Research and Evaluation II; SIGN, Scottish Intercollegiate Guidelines Network; KQ, key question; GRADE, Grading of Recommendations Assessment, Development and Evaluation; AMSTAR, A MeaSurement Tool to Assess systematic Reviews; RoB, risk of bias in randomized trials; RoBANS, Risk of Bias Assessment Tool for Nonrandomized Studies; RCT, randomized controlled trial.

Table 1. Quality assessment of clinical practice guidelines on migraine prevention using the AGREE II framework

Clinical practice guideline	Domain 1: Scope and purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence	Overall assessment
2012 AHS/AAN[8]	94.4	77.8	88.5	91.7	79.2	100.0	87.5
2012 Canadian Headache Society[9]	100.0	94.4	96.9	100.0	91.7	100.0	95.8
2012 Croatian Medical Association[10]	52.8	47.2	32.3*	69.4	14.6	0.0	66.7
2012 Danish Headache Society[11]	91.7	66.7	24.0*	75.0	20.8	100.0	58.3
2012 SFEMC[12]	77.8	77.8	76.0	91.7	43.8	87.5	83.3
2012 SISC[13]	63.9	55.6	60.4	88.9	31.3	66.7	75.0
2013 ICSI[14]	94.4	86.1	90.6	86.1	64.6	95.8	95.8
2015 NICE[15]	50.0	50.0	31.3*	72.2	16.7	0.0	41.7
2016 AAN[16]	80.6	44.4	41.7*	50.0	0.0	100.0	70.8
2019 AHS[17]	63.9	63.9	46.9*	69.4	45.8	45.8	54.2
2017 RSSHA[18]	61.1	52.8	34.4*	47.2	50.0	58.3	33.3
2020 EAN[19]	97.2	58.3	74.0	97.2	45.8	83.3	66.7
2019 EHF[20]	97.2	61.1	81.3	94.4	50.0	66.7	75.0
2019 Spanish Society of Neurology[21]	16.7	22.2	7.3*	13.9	16.7	66.7	41.7
2015 Alberta, Canada[22]	66.7	44.4	51.0*	75.0	25.0	87.5	37.5
2018 EHF[23]	77.8	52.8	62.5	72.2	37.5	54.2	79.2
2018 EMA/EHF[24]	61.1	61.1	40.6*	52.8	54.2	79.2	62.5
2013 Latin American and Brazilian Headache Societies[25]	66.7	44.4	35.4*	61.1	16.7	50.0	58.3
2018 SIGN[26]	100.0	77.8	93.8	100.0	58.3	75.0	83.3

Values are average scores independently rated rated by two development working members using the AGREE II framework.
AGREE, Appraisal of Guidelines for Research and Evaluation; AHS, American Headache Society; AAN, American Academy of Neurology; SFEMC, French Society for the Study of Migraine Headache; SISC, Italian Society for the Study of Headaches; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; RSSHA, Russian Society for the Study of Headache; EAN, European Academy of Neurology; EHF, European Headache Federation; EMA, European Medicines Agency; SIGN, Scottish Intercollegiate Guidelines Network.
*Guidelines that scored less than 60% in the domain 3. Rigour of development were excluded.

For each KQ, relevant studies were evaluated in terms of level of evidence (LOE). In this regard, we used the grading of the Agency for Healthcare Research and Quality, with modifications, to define levels of evidence as follows: LOE I, evidence obtained from meta-analysis or at least one RCT; LOE II, evidence obtained from at least one well-designed controlled study without randomization, or at least one other type of well-designed quasi-experimental study; LOE III: evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies; and LOE IV, evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.[29]

Two or more DWG members drafted guidelines for each PICO KQ. In this guideline, evidence-based recommendation was proposed in terms of strength (strong or weak) and direction (for or against) according to the GRADE methodology.[30] This strength of recommendation (SOR) was determined on basis of quality of evidence, balance scale between desirable and undesirable effects, values and preferences, and resources (costs).

All DWG members reviewed the guideline document. They made consensus according to the Delphi method. The guideline was verified by external panels (2 family physicians, 1 urologist, 1 anesthesiologist, 1 nurse, and 1 pharmacist).

RESULTS

1. Key question 1. What factors should be considered for migraine prevention in adult patients with episodic migraine?

1) Analysis of evidence

The recommendations related to this KQ in existing guidelines are all based on expert consensus, which means that the LOE is low and clinical studies are difficult to conduct.[9,12-14,17,26]

Existing guidelines summarize the important associated factors to consider when initiating migraine prevention for adult patients with EM: (1) headache frequency, (2) headache intensity, (3) effectiveness of acute migraine treatment. In addition, (4) the patient's personal preferences and (5) the physician's individual judgment may also play a role in the decision to initiate migraine prevention. In particular, migraine prevention should be initiated when there is a high risk of migraine chronification, (6) when they experience frequent or incremental frequency of migraine attacks, and (7) when they have comorbid medication overuse headache (MOH). Migraine prevention may also be considered even if the frequency of migraine attacks is low, (8) the effectiveness of migraine acute treatment is insufficient, or (9) migraine patients have contraindications to acute migraine treatment that preclude the use of acute migraine treatment. Lastly, migraine prevention may also be considered in (10) some patients whose migraines are accompanied by neurologic disorders, such as migraine with brainstem aura or hemiplegic migraine.

2) Recommendation

- Migraine prevention is recommended for patients with migraine who experience meaningful disability from migraine despite adequate attempts at lifestyle modification and acute migraine treatment (LOE: IV, SOR: Strong for).
- Migraine prevention is recommended for migraine patient (1) if acute migraine treatment does not effectively treat migraine or if they experience migraine-related disability, even if the headache frequency is low, or (2) if acute migraine treatment is effective but the headache frequency is frequent (LOE: IV, SOR: Strong for).
- If migraine patient uses acute migraine medications more than 10 to 15 days per month, migraine prevention is recommended due to the risk of development of MOH (LOE: IV, SOR: Strong for).
- Migraine prevention may be considered if the migraine patient prefers it, regardless of headache frequency, or if the physician determines that migraine prevention is clinically indicated (LOE: IV, SOR: Weak for).
- Migraine prevention may be considered if migraine patient has a medical contraindication to acute migraine treatment (LOE: IV, SOR: Weak for).

2. Key question 2. How should discontinuation of migraine prevention be decided in adult migraine patients?

1) Analysis of evidence

In line with the KQ 1, existing guidelines provide recommendations for discontinuation of migraine prevention based on expert opinion and are similarly worded.[9,12,14,17,26] To determine the efficacy of migraine prevention of specific medication, guidelines recommend trying the optimal or maximum tolerated dose for at least 2–3 months or 8 weeks.

The effectiveness of migraine prevention is considered significant if it reduces the frequency of migraine episodes by 50% or more. Even if migraine prevention does not significantly reduce the frequency of migraine episodes, it may be continued for a period of time and then slowly tapered and discontinued if there are clinical findings of reduced migraine-related disability, reduced pain intensity or duration, or improved response to acute migraine treatment. Guidelines recommend that migraine preventive medications be maintained for 6 months to 1 year. In addition, it is consistently recommended that the effectiveness of migraine preventive medications should be determined solely by patient. In this regard, guidelines also emphasize the significance of keeping a headache diary during migraine prevention.

2) Recommendation

- The efficacy of migraine prevention in adult patients with migraine can only be determined after at least 2 months of use at the optimal or maximal tolerable dose (LOE: IV, SOR: Weak for).
- If migraine prevention is effective, it may be continued for at least 3 months before a dose reduction or discon-

tinuation is attempted. The duration of migraine prevention is individualized for each patient, depending on the frequency and intensity of headaches and the impact of migraine on daily life (LOE: IV, SOR: Weak for).
- If migraine frequency increases after tapering or discontinuation of migraine preventive medication, consider increasing or restarting medication dose (LOE: IV, SOR: Weak for).
- Keeping a headache diary is recommended to assess efficacy, side effects, and adherence to migraine prevention and to determine the duration of maintenance (LOE: IV, SOR: Strong for).

3. Key question 3. Are beta-blockers effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Propranolol has been recommended as effective for migraine prevention in all guidelines to date.[8,9,12-14,26] In particular, propranolol and metoprolol are strongly recommended in most guidelines for migraine prophylaxis based on the highest LOE. Atenolol and nadolol, on the other hand, are rated as weakly recommended in most guidelines with moderate quality evidence. In a recent meta-analysis, propranolol was reported to reduce the number of headache days per month by 1.5 days at 8 weeks (95% confidence interval [95% CI], –2.3 to –0.65), and to reduce headache frequency by 50% at 12 weeks (relative risk, 1.4; 95% CI, 1.1– 1.7).[31]

2) Recommendation

- Propranolol is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Metoprolol is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Atenolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Nadolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Nebivolol may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).

4. Key question 4. Are calcium channel-blockers effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Flunarizine is not marketed in the United States and was not evaluated in the 2012 AHS/AAN guideline, but is recommended for use in migraine prevention guidelines in many other countries.[9,11-13,26] The recommendation for flunarizine for migraine prevention is strongly recommended in Italy and Scotland, and weakly recommended in Canada. Calcium channel blockers other than flunarizine were not included in many guidelines, with cinnarizine, nicardipine, and verapamil each receiving a recommendation rating in one or two guidelines. Nimodipine and nifedipine were only reviewed by the AHS and rated as insufficient evidence. In a 2015 meta-analysis, flunarizine's effectiveness versus placebo in episodic migraine prevention was demonstrated at 8 and 12 weeks (standardized mean difference: –0.60 [95% CI, –1.20 to 0.00]; –0.84 [–1.34 to –0.34]), but not at 4 weeks (standardized mean difference: –0.27 [–0.76 to 0.23]).[32] However, a recently published meta-analysis demonstrated the effectiveness of migraine prevention of flunarizine even at 4 weeks.[33] In an analysis of 5 placebo-controlled studies out of a total of 25 clinical studies, flunarizine reduced migraine attacks by 0.4 migraine attacks per week more than placebo when taken for 4 weeks (mean difference: 95% CI, –0.61 to –0.26), with a response rate 8.86 times higher than placebo (95% CI, 3.57–22.0).

2) Recommendation

- Flunarizine is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Cinnarizine may be considered for use as migraine prevention in adult patients with EM (LOE: IV, SOR: Weak for).
- Verapamil, nicardipine, nifedipine, and nimodipine are not recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong against).

5. Key question 5. Are angiotensin receptor blockers or angiotensin-converting enzyme inhibitors effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Candesartan and lisinopril are recommended in existing migraine prevention guidelines based on weak evidence.[8,9,12,13,17,26] Telmisartan is not recommended for use (the 2012 AHS/AAN guideline) or is not included as a recommended agent in most guidelines.

2) Recommendation

- Candesartan may be considered for use as migraine prevention in adult patients with EM (LOE: I, SOR: Weak for).
- Lisinopril may be considered for use as migraine prevention in adult patients with EM (LOE: IV, SOR: Weak for).
- Telmisartan is not recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong against).

6. Key question 6. Are antidepressants effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Previous guidelines suggested various antidepressants with varying levels of recommendation.[8,9,12-14,17,26] In particular, amitriptyline is highly recommended in most guidelines for migraine prevention. Venlafaxine is recommended as a low-grade recommendation due to its relatively low quality of evidence. Nortriptyline was only recommended with a low recommendation in the 2013 Institute for Clinical Systems Improvement guideline. Fluoxetine is not recommended or included as a recommended agent due to conflicting studies.

2) Recommendation

- Amitriptyline is recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Strong for).
- Nortriptyline may be considered for use as migraine prevention in adult patients with EM (LOE: III, SOR: Weak for).
- Venlafaxine may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Fluoxetine may not be recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak against).

7. Key question 7. Are antiseizure medications effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Topiramate was highly recommended in all migraine prevention guidelines based on a strong LOE.[8,9,12-14,17,26] Valproic acid was also recommended in most guidelines based on higher levels of evidence. Gabapentin has a low LOE and conflicting recommendations in the guidelines. Levetiracetam and zonisamide have somewhat lower levels of evidence or were not mentioned in most guidelines. However, recent systematic reviews and meta-analyses have shown that levetiracetam effectively reduced the frequency of episodic migraine.[34,35] Levetiracetam should be used with caution due to side effects such as drowsiness and psychotic symptoms. Zonisamide was not cited in published guideline recommendations, but RCTs have shown it to be effective in preventing migraine.[36] No studies have compared zonisamide to placebo, but studies have compared it to topiramate and valproic acid.[37]

2) Recommendation

- Topiramate is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Sodium divalproex and valproic acid are recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Levetiracetam may be considered for use as migraine prevention in adult patients with EM (LOE: I, SOR: Weak for).
- Zonisamide may be considered for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak for).
- Gabapentin may not be recommended for use as migraine prevention in adult patients with EM (LOE: II, SOR: Weak against).

3) Additional consideration

Divalproex sodium and valproic acid should be used with caution in women of childbearing potential due to the risk of teratogenicity, including neural tube defects, and are contraindicated in pregnant patients. In addition, divalproex sodium and valproic acid may be restricted in women due to side effects such as weight gain and polycystic ovary syndrome.

8. Key question 8. Are calcitonin gene-related peptide monoclonal antibodies effective in relieving headache compared to other drugs, placebo, or no treatment in adults with episodic migraine?

1) Analysis of evidence

Despite the fact that activation of the trigeminal neurovascular system is an important mechanism in the pathophysiology of migraine pain and that CGRP is the most important neurotransmitter involved in this activation, no specific drugs had been developed to prevent migraine.[17] Since late 2018, four mAbs targeting CGRP itself or its receptor have been approved by the U.S. Food and Drug Administration. These are erenumab, a mAb against the CGRP receptor, and fremanezumab, galcanezumab, and eptinezumab, mAbs against the CGRP ligand, and are the first preventive medications to be developed based on the specific mechanism of migraine. These agents have been shown to be effective, safe, and well-tolerated in well-designed clinical studies and are highly anticipated as preventive medications for CM as well as EM.[1] CGRP mAbs are a recently established class of agents that are not included in the majority of previously published guidelines and are only included in guidelines published after 2019. The European Headache Federation (EHF) guideline suggested that galcanezumab, fremanezumab, and erenumab were strongly recommended based on moderate to high quality evidence, while eptinezumab was moderately recommended based on low quality evidence.[20] After the publication of the EHF guideline, the results of an RCT of eptinezumab were published, confirming the efficacy and safety of this prophylactic treatment for EM.[38] Subsequently published meta-analyses confirmed the effectiveness and safety of CGRP mAbs compared to placebo, particularly for the only intravenously administered agent, eptinezumab.[39-43]

2) Recommendation

- Galcanezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Fremanezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Erenumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).
- Eptinezumab is recommended for use as migraine prevention in adult patients with EM (LOE: I, SOR: Strong for).

9. Key question 9. Are antiseizure medications effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

Topiramate has the highest LOE for oral migraine preventive medication of CM, with proven effectiveness in the CM patients with or without comorbid MOH.[13,19,26] Other antiseizure medications of choice for the prevention of CM include sodium valproate and gabapentin, but the quality of evidence is low. Antiseizure medications used to prevent migraines are generally effective at lower doses than those used for anticonvulsants. Topiramate has been shown to be an effective prophylactic agent in the prophylaxis of CM in two RCTs in patients with CM and has been accepted as an effective prophylactic agent in CM with MOH. Valproic acid has relatively limited research in CM. In an RCT of patients with chronic daily headache, including CM, sodium valproate 500 mg twice daily improved headache frequency and intensity, with more improvement in the CM group than in the chronic tension-type headache group.

2) Recommendation

- Topiramate is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Sodium divalproex and valproic acid may be considered for use as migraine prevention in adult patients with CM (LOE: II, SOR: Weak for).

3) Additional consideration

Divalproex sodium and valproic acid should be used with

caution in women of childbearing potential due to the risk of teratogenicity, including neural tube defects, and are contraindicated in pregnant patients. In addition, divalproex sodium and valproic acid may be restricted in women due to side effects such as weight gain and polycystic ovary syndrome.

10. Key question 10. Are beta-blockers, calcium channel-blockers, angiotensin receptor blockers, or antidepressants effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

There is very limited research on preventive medications in CM patients. Furthermore, even when studies include patients with CM, chronic daily migraine, and mixed (chronic+episodic) migraine, the only medications studied are beta-blockers and antidepressants. However, even for these agents, the evidence is lacking, as there are no well-designed RCTs.

2) Recommendation

- Because EM and CM are on the same spectrum, clinicians may consider selecting agents based on the level of recommendation for EM, assuming that preventive agents that are effective in EM will also be effective in CM. (LOE: IV, SOR: Weak for).

11. Key question 11. Is onabotulinumtoxinA effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

OnabotulinumtoxinA has been shown to be effective in the preventive treatment of CM.[17,23,26] In an RCT (PREEMPT I), there was no significant difference in headache frequency between the onabotulinumtoxinA and placebo groups, but there was a significant reduction in headache days and migraine days. In another RCT (PREEMPT II), onabotulinumtoxinA reduced the total number of headache days compared to placebo, and also significantly reduced the number of migraine days, severe headache days, and the total number of hours of headache per month, the proportion of patients with severe Headache impact test-6 scores, and the frequency of headache attacks. OnabotulinumtoxinA also significantly reduced disability and significantly improved quality of life compared to placebo. OnabotulinumtoxinA has the disadvantage of having to be injected in multiple areas, and the side effects of having some injections in the facial area. However, it is an effective preventive treatment that can be used when oral migraine preventive medications are not tolerated due to side effects or when oral migraine preventive medications are insufficiently effective.

2) Recommendation

- OnabotulinumtoxinA is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

12. Key question 12. Are calcitonin gene-related peptide monoclonal antibodies effective in relieving headache compared to other drugs, placebo, or no treatment in adults with chronic migraine?

1) Analysis of evidence

The use of CGRP mAbs in patients with CM was recommended by the AHS statement and recommended in the 2019 EHF guideline.[17,20] The EHF guideline states that CGRP mAbs for the prophylaxis of CM is effective and safe based on the results of four RCTs of galcanezumab, fremanezumab, and erenumab. Subsequently published meta-analyses have also shown supportive results for preventive effectiveness in CM.[44] Following the publication of the EHF guideline, the results of an RCT of the remaining CGRP monoclonal antibody, eptinezumab, were published, confirming the efficacy and safety of prophylactic treatment for CM.[45]

2) Recommendation

- Galcanezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Fremanezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).
- Erenumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

- Eptinezumab is recommended for use as migraine prevention in adult patients with CM (LOE: I, SOR: Strong for).

13. Key question 13. Is pharmacological treatment effective in relieving headache compared to other drugs, placebo, or no treatment in pregnant women with migraine?

1) Analysis of evidence

Preventive migraine medications should be avoided in pregnant women due to the potential teratogenic effects on the fetus.[9,12,13,46,47] Particular care should be taken during the first trimester of pregnancy, as the risk of malformations is higher. Migraines often resolve spontaneously in the second and third trimesters, so starting migraine preventive medications in the first trimester should be avoided except in exceptional circumstances. It is important to educate and reassure patients that pregnancy has a positive effect on migraine relief. Avoiding migraine triggers and making lifestyle modifications that help prevent migraines, such as drinking plenty of fluids, eating regularly, and getting regular sleep, should be prioritized. In addition, migraine abortive medications that are relatively safe and only used during migraine attacks or non-pharmacologic migraine prevention should be prioritized over long-term use of migraine preventive medications.[46,47]

There are no RCTs to guide the choice of migraine prevention in pregnant women, and the authors of the various articles are often inconsistent in their recommendations. If it is necessary to start migraine prevention in a pregnant woman, the risks of the medication should be discussed with her. The medication should be used in minimal doses and for as short a period of time as possible. If the use of migraine preventive medications is essential in pregnant women, oral magnesium, propranolol, metoprolol, and tricyclic antidepressants may be considered.[9,12,13]

All antiseizure medications used for migraine prevention are not recommended due to the risk of fetal malformations.[9,13,46] Divalproex sodium and valproic acid are classified as pregnancy drug safety class X and should be avoided in pregnant women due to their teratogenicity for neural tube defects. Valproic acid should also be avoided in all women of childbearing potential who may become pregnant, even if the pregnancy is not planned. If an unplanned pregnancy occurs while taking valproic acid/divalproex sodium, it should be discontinued as soon as possible. Topiramate increases the risk of cleft palate to the fetus when taken in the first trimester of pregnancy. When used in combination with valproic acid, there is a risk of encephalopathic malformations. Therefore, topiramate should be avoided or used with caution in pregnant women or women who may become pregnant.

2) Recommendation

- Pharmacologic treatment is not recommended for use as migraine prevention in pregnant women with migraine (LOE: IV, SOR: Strong for).
- Pharmacologic treatment for migraine prevention may be considered if the risk to the mother and fetus from migraine symptoms is determined to be significantly higher than the risk from the pharmacologic treatment (LOE: IV, SOR: Weak for).
- Sodium divalproex and valproic acid are not recommended for use as migraine prevention in pregnant women with migraine (LOE: III, SOR: Strong against).
- Topiramate is not recommended for use as migraine prevention in pregnant women with migraine (LOE: III, SOR: Strong against).

14. Key question 14. Are triptans effective as short-term prevention in relieving headache compared to other drugs, placebo, or no treatment in women with menstrual migraine?

1) Analysis of evidence

Patients with menstrual migraine can be categorized into pure menstrual migraine, in which migraine attacks occur only during menstruation but not on other days, and menstrual-related migraine, in which migraine attacks occur both during menstruation and on other days. These patients may be considered for short-term prevention focused on the menstrual cycle rather than the usual ongoing migraine prevention.

To date, frovatriptan, naratriptan, and zolmitriptan are the drugs that have been reported in RCTs for the short-term prevention of menstrual migraine. In several guidelines, frovatriptan is strongly recommended as a high LOE for the short-term prevention of menstrual migraine, and naratriptan and zolmitriptan are also recommended for

		Episodic migraine	Chronic migraine	Menstrual migraine
Beta-blockers	Propranolol	KQ 3	KQ 10	
	Metoprolol	KQ 3	KQ 10	
	Atenolol	KQ 3	KQ 10	
	Nadolol	KQ 3	KQ 10	
	Nebivolol	KQ 3	KQ 10	
CCBs	Flunarizine	KQ 4	KQ 10	
	Cinnarizine	KQ 4	KQ 10	
	Verapamil	KQ 4		
	Nicardipine	KQ 4		
	Nifedipine	KQ 4		
	Nimodipine	KQ 4		
ARBs/ACEi	Candesartan	KQ 5	KQ 10	
	Telmisartan	KQ 5		
	Lisinopril	KQ 5	KQ 10	
Antidepressants	Amitriptyline	KQ 6	KQ 10	
	Nortriptyline	KQ 6	KQ 10	
	Venlafaxine	KQ 6	KQ 10	
	Fluoxetine	KQ 6		
ASMs	Topiramate	KQ 7	KQ 9	
	Sodium divalproex	KQ 7	KQ 9	
	Valproic acid	KQ 7	KQ 9	
	Levetiracetam	KQ 7	KQ 9	
	Zonisamide	KQ 7	KQ 9	
	Gabapentin	KQ 7		
CGRP mAbs	Galcanezumab	KQ 8	KQ 12	
	Fremanezumab	KQ 8	KQ 12	
	Erenumab	KQ 8	KQ 12	
	Eptinezumab	KQ 8	KQ 12	
Botulinum toxin	OnabotulinumtoxinA		KQ 11	
Triptans	Frovatriptan			KQ 14
	Naratriptan			KQ 14
	Zolmitriptan			KQ 14

Strength of recommendations

Strong for	Weak for	Weak for	Weak against	Strong against
LOE: I	LOE: I, II, III	LOE: IV	LOE: II, III	LOE: I

Figure 2. Heat map summarizing the evidence-based recommendations on pharmacologic treatment for migraine prevention.
CCB, calcium channel-blocker; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; ASMs, antiseizure medications; CGRP mAb, calcitonin gene-related peptide monoclonal antibody; KQ, key question; LOE, level of evidence.

Table 2. Range of the daily administration dose or single injection dose and common adverse events of migraine preventive medications

Medication	Range of daily dose or single injection dose (mg)	Adverse events
Beta-blockers		
Propranolol	20–160	Fatigue, dizziness, depression, and vivid dreams
Metoprolol	50–200	Fatigue, dizziness, depression, and vivid dreams
Atenolol	50–200	Fatigue, dizziness, depression, vivid dreams, dyspnea, bradycardia, palpitation, and vomiting
Nadolol	40–160	Fatigue, dizziness, depression, vivid dreams, dyspnea, bradycardia, palpitation, and vomiting
Nebivolol	2.5–5.0	Headache, dizziness, dysesthesia, nightmare, gastrointestinal disorder, dyspnea, itching, and edema
Calcium channel-blocker		
Flunarizine	5–10	Weight gain, somnolence, dry mouth, dizziness, hypotension, and depression
Cinnarizine	25–50	Weight gain, somnolence, dry mouth, dizziness, hypotension, and depression
Verapamil	120–480	Palpitation, edema, arrythmia, and rash
Nicardipine	40–80	Constipation, facial flushing, helplessness, headache, myalgia, tremor, and dizziness
Nifedipine	15–60	Constipation, facial flushing, helplessness, headache, myalgia, tremor, and dizziness
Nimodipine	90	Gastrointestinal disorder, headache, dizziness, somnolence, and tremor
Angiotensin receptor blockers and angiotensin-converting enzyme inhibitor		
Candesartan	4–16	Hypotension and aggravation of congestive heart failure
Telmisartan	40–80	Hyperkalemia, dizziness, hypotension, rash, and myalgia
Lisinopril	10–20	Dizziness, headache, cough, fatigue, muscle cramps, diarrhea, and hypotension
Antidepressants		
Amitriptyline	2.5–50.0	Weight gain, dry mouth, somnolence, fatigue, helplessness, dizziness, blurred vision, and constipation
Nortriptyline	25–150	Weight gain, dry mouth, somnolence, fatigue, helplessness, dizziness, blurred vision, and constipation
Venlafaxine	37.5–150.0	Somnolence, insomnia, dizziness, headache, vomiting, dry mouth, anxiety, and sexual dysfunction
Fluoxetine	10–80	Fatigue, vomiting, diarrhea, insomnia, loss of appetite, impotence, tremor, anxiety, and restlessness
Antiseizure medications		
Topiramate	12.5–150.0	Paresthesia, fatigue, anorexia, diarrhea, weight loss, and difficulty with memory
Sodium divalproex	250–1,500	Nausea, vomiting, weight gain, tremor, hair loss, somnolence, and dizziness
Valproic acid	600–2,000	Nausea, vomiting, weight gain, tremor, hair loss, somnolence, and dizziness
Levetiracetam	500–2,000	Fatigue, helplessness, somnolence, myalgia, dizziness, diplopia, rash, and cough
Zonisamide	100–600	Weight loss, diplopia, visual disturbance, somnolence, ataxia, and abnormal thinking
Gabapentin	300–1,800	Peripheral edema, dizziness, somnolence, ataxia, and weight gain
Calcitonin gene-related peptide monoclonal antibody		
Galcanezumab	120 or 240 mg SC (monthly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation
Fremanezumab	225 mg SC (monthly) 675 mg SC (quarterly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation
Erenumab	70 or 140 mg SC (monthly)	Injection site pain, injection site reaction, injection site erythema/pruritis, upper respiratory tract infection, and constipation

(Continued to the next page)

Table 2. Continued

Medication	Range of daily dose or single injection dose (mg)	Adverse events
Eptinezumab	100 or 300 mg IV (quarterly)	Hypersensitivity, infusion site extravasation, upper respiratory tract infection, and constipation
Botulinum toxin		
OnabotulinumtoxinA	155–195 units IM (12-wk interval)	Neck pain, muscular weakness, myalgia, injection site pain, and ptosis
Triptans		
Frovatriptan	2.5–5.0	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting
Naratriptan	1–2.0	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting
Zolmitriptan	2.5–7.5	Triptan sensation, dizziness, somnolence, fatigue, lethargy, headache, and vomiting

SC, subcutaneous; IV, intravenous; IM, intramuscular.

the short-term prevention of menstrual migraine based on high LOE.[8,12,17,26] The meta-analysis confirmed the efficacy of frovatriptan, naratriptan, and zolmitriptan compared to placebo, supporting the recommendations of these agents in previously published guidelines.[48,49]

2) Recommendation

- Frovatriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).
- Naratriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).
- Zolmitriptan is recommended for use as short-term prevention in women with menstrual migraine (LOE: I, SOR: Strong for).

Conclusions

The CPG committee of the KHS compiled and analyzed the evidence to provide specific, straightforward, and easy-to-implement recommendations for pharmacologic treatment of migraine prevention (Figure 2). Range of daily dose of oral migraine preventives and single injection dose of injectable therapies were summarized in Table 2. The authors hope that this guideline will be widely used in a variety of settings, including real-world clinical practice and research, and that it will provide real benefit to migraine patients. The specific recommendation for menstrual migraine would be useful to satisfy unmet clinical need of women with menstrual migraine.[50]

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AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Headache and Pain Research

Does Atogepant Offer a Safe and Efficacious Option for Episodic Migraine Prophylaxis? A Systematic Review and Meta-analysis

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Abstract

Migraine, a chronic neurological disorder, imposes a significant burden on individuals and healthcare systems globally. This systematic review and meta-analysis evaluated the efficacy and safety of atogepant in preventing episodic migraine (EM) in adults. A systematic search was conducted in four major databases (PubMed, Scopus, Web of Science, and Cochrane CENTRAL) up to June 2024. The inclusion criteria targeted randomized controlled trials (RCTs) comparing atogepant to placebo or standard care in patients with EM. Statistical analyses were performed using Review Manager (RevMan) software. Four RCTs with 2,018 patients receiving atogepant and 761 patients receiving placebo or standard care were included. Atogepant significantly reduced monthly migraine days compared to placebo at 10 mg daily (mean difference [MD], −1.16 days; 95% confidence interval [95% CI], −1.60 to −0.73), 30 mg daily (MD, −1.15 days; 95% CI, −1.64 to −0.66), 60 mg daily (MD, −1.48 days; 95% CI: −2.36 to −0.61 days), 30 mg twice daily (MD, −1.30 days; 95% CI, −2.17 to −0.43), and 60 mg twice daily (MD, −1.20 days; 95% CI, −1.90 to −0.50). A ≥50% reduction in migraine days was frequently significantly achieved with atogepant across all dosages. Atogepant was generally well tolerated, though it was associated with higher incidence rates of constipation and nausea compared to placebo. Atogepant is an effective and well-tolerated option for preventing EM, offering patients a noninvasive oral alternative to injectable therapies. Further research is warranted to explore its long-term safety and efficacy in diverse patient populations and refine its role in this field.

Keywords: Atogepant; Calcitonin gene-related peptide antagonist; Episodic migraine; Headache; Migraine disorders

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INTRODUCTION

Migraine is a prevalent neurological disorder that significantly impacts quality of life. Episodic migraine (EM), characterized by headache attacks occurring fewer than 15 days per month, often imposes a substantial burden on patients, particularly when attacks are frequent and inadequately managed.[1,2] Despite advances in acute treatments, many patients continue to experience recurrent migraines, highlighting the need for effective preventive options.[3,4]

Currently available preventive therapies, such as beta-blockers, anticonvulsants, and calcium channel blockers, often have limitations related to efficacy and tolerability.[5,6] These challenges and the lack of migraine-specific mechanisms in older treatments underscore the necessity for targeted approaches.

Recent advancements in understanding migraine mechanisms have identified calcitonin gene-related peptide (CGRP) as a pivotal target in migraine pathogenesis. Elevated CGRP levels during migraine attacks contribute to vasodilation and neurogenic inflammation, processes central to migraine development.[7,8] Consequently, the development of CGRP antagonists, including both injectable monoclonal antibodies (e.g., fremanezumab, eptinezumab, galcanezumab) and small-molecule CGRP receptor antagonists known as "gepants" (e.g., atogepant), has revolutionized preventive migraine treatment.[9] Among these, atogepant, an orally active CGRP receptor antagonist, represents a novel approach to EM prevention, offering the advantages of targeting specific pathophysiological mechanisms and accommodating patient preferences for oral administration.[10,11] Its oral formulation addresses a key patient preference for non-invasive treatment options, especially in comparison to injectables, which, despite their efficacy, may pose compliance challenges.[11]

Initial clinical studies have shown that atogepant significantly reduces the frequency of migraine attacks in patients with EM.[12-15] However, the conclusions from individual trials are often limited by factors such as small sample sizes, differences in study designs, and variation in outcome measures. Therefore, a comprehensive meta-analysis is warranted to aggregate data across studies, offering a more precise evaluation of atogepant's efficacy and safety profile. This meta-analysis addresses these gaps by systematically evaluating the efficacy and safety of atogepant, offering robust evidence to support its role in EM prevention.

By systematically assessing atogepant's therapeutic potential, this review seeks to contribute to clinical decision-making and optimize the management of migraine, particularly for patients inadequately served by existing preventive treatments. Furthermore, it aims to highlight the limitations of previous analyses and clarify atogepants' efficacy and safety across diverse patient populations, guiding their future role in personalized migraine care.

METHODS

This systematic review and meta-analysis followed rigorous methodology as outlined in the 'Cochrane Handbook for Systematic Reviews of Interventions'[16] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] to ensure transparency and reproducibility.

1. Search strategy and screening

A comprehensive search of four databases (PubMed, Scopus, Web of Science, and Cochrane CENTRAL) was performed up to June 5, 2024, using the search query: [("atogepant" OR "calcitonin gene-related peptide antagonists" OR "CGRP antagonists") AND ("migraine disorder" OR "chronic migraine" OR "episodic migraine" OR "headache disorders")]. No filters were applied to ensure a broad capture of relevant studies. The search strategy was designed to identify randomized controlled trials (RCTs) comparing atogepant with placebo or standard care in patients diagnosed with EM. We aimed to include all RCTs, whether open-label or double-blinded, to provide a comprehensive evaluation of atogepant's efficacy and safety profile in EM prevention. The inclusion of an open-label study was justified explicitly by its relevance to safety data and long-term outcomes, which complemented the controlled trial data and addressed existing gaps in the literature. This approach ensured a holistic and comprehensive review of all available evidence regarding atogepant.

Two independent reviewers (A.M. and M.E.M.) screened titles and abstracts using Rayyan software,[18] with discrepancies resolved by consensus and arbitration from a third reviewer (A.M.A.). Studies that met the inclusion criteria

progressed to full-text screening, and any conflicts were further discussed to reach a final decision.

2. Data extraction

Two reviewers used Microsoft Excel 2021 (Microsoft) to extract data independently, ensuring accuracy and completeness. Extracted data included:

- Study characteristics: study design, sample size, country, duration, inclusion criteria, and key findings.
- Patient characteristics: demographics such as age, sex, body mass index, and migraine duration.
- Risk of bias domains as outlined by the revised Cochrane risk-of-bias tool (RoB-2).
- Efficacy outcomes: changes in monthly migraine days, headache days, and acute medication use days, along with the proportion of patients achieving a ≥50% reduction in monthly migraine days.
- Safety outcomes: adverse events (AEs) such as upper respiratory tract infections (URTIs), nausea, constipation, nasopharyngitis, urinary tract infections (UTIs), and fatigue, as well as serious adverse events (SAEs), treatment-related AEs, and discontinuations due to AEs. Discrepancies in data extraction were resolved through discussion or consultation with a third reviewer.

3. Risk of bias assessment

Two authors independently assessed the risk of bias in the included studies using the RoB-2.[19] This tool evaluates bias across five domains: randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and reporting bias. Each domain was rated as low risk, some concerns, or high risk. If any domain showed a high risk or multiple domains showed concerns, the study was considered at high risk of bias.

4. Statistical analysis

Data were analyzed using Review Manager (RevMan) software.[20] Continuous outcomes (e.g., monthly migraine days, headache days, and acute medication use days) were summarized as mean differences (MD) with 95% confidence intervals (CIs). For dichotomous outcomes (e.g., ≥50% reduction in migraine days and AEs), risk ratios (RR) or risk differences (RD) were calculated with 95% CI.

Heterogeneity was assessed using the chi-square test, with the extent of heterogeneity measured using the I-squared (I^2) statistic. A chi-square p-value less than 0.1 or an I^2 greater than 50% indicated significant heterogeneity. In cases of significant heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was applied.[18]

Subgroup analyses were conducted to handle significant heterogeneity and evaluate the efficacy of different atogepant dosage levels (10 mg once-daily [QD], 30 mg QD, 60 mg QD, 30 mg twice-daily [BID], and 60 mg BID) on primary outcomes. Additionally, an overall analysis combining all dosage groups was performed, following the Cochrane Handbook's recommended formula.[21] Given the limited number of included studies (fewer than 10), publication bias could not be formally assessed using funnel plots.[22]

RESULTS

1. Search and screening

The systematic search across four databases yielded 1,598 articles. After removing duplicates, 951 unique records were identified. Title and abstract screening narrowed these to 28 studies, and after full-text evaluation, four RCTs[13-15,23] met the inclusion criteria for this meta-analysis (Figure 1).

2. Baseline characteristics

The included trials involved a total of 2,018 patients treated with atogepant and 761 patients in placebo or standard care groups. The mean age across the studies was 41.3 years, with 312 males among the participants. Three of the four trials were double-blinded and multicenter in design, except for Ashina et al.,[14] which was not double-blinded and compared atogepant to standard care. The latter one was included in this systematic review, not the analysis to allow for consistent analysis of atogepant versus placebo. All studies followed the diagnostic criteria for EM as defined by the International Classification of Headache Disorders, 3rd edition.[24] Study details are provided in Table 1.

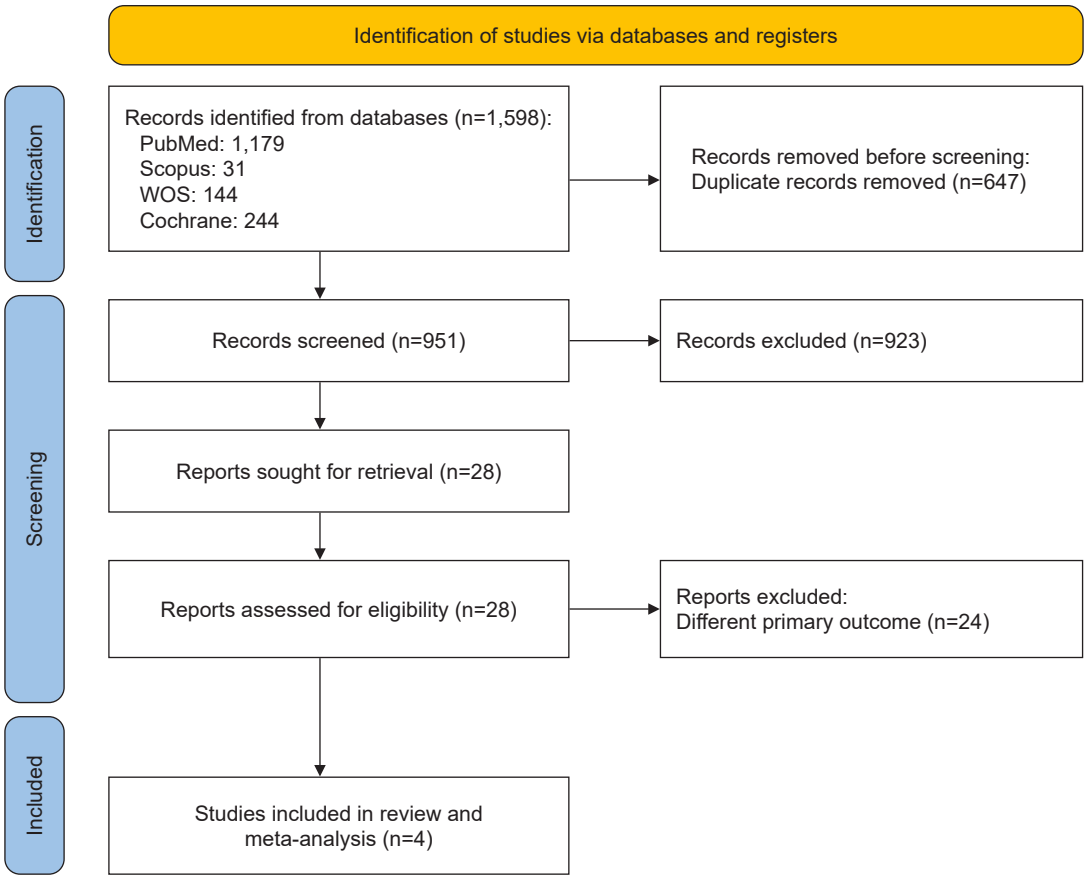

Figure 1. PRISMA flow diagram of study selection process.
WOS, Web of Science.

3. Risk of bias assessment

The ROB-2 tool was used to assess the risk of bias, and all studies demonstrated a low risk. Each trial adequately implemented randomization procedures, and no significant deviations from the intended interventions were observed. Details of the risk-of-bias assessment are included in Supplementary Figure 1 (available online).

4. Mean difference in monthly migraine days

Three studies[13,15,23] reported data on monthly migraine days across varying atogepant doses (10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID).

- At 10 mg QD and 30 mg QD dosages: In two studies, atogepant at 10 mg QD significantly reduced monthly migraine days compared to placebo (MD: –1.16 days, 95% CI: –1.60 to –0.73, p<0.00001), with no significant heterogeneity (p=0.83, I^2=0%). Similarly, at 30 mg QD, there was a significant reduction in migraine days (MD: –1.15 days, 95% CI: –1.64 to –0.66, p<0.00001), with low heterogeneity (p=0.21, I^2=36%) (Figure 2).
- At 60 mg QD dosage: Three studies involving 553 patients in the atogepant group and 547 in the placebo group reported a significant reduction in migraine days for the 60 mg QD dosage (MD: –1.48 days, 95% CI: –2.36 to –0.61, p=0.0009), though with moderate heterogeneity (p=0.008, I^2=79%) (Figure 2).
- At 30 mg BID and 60 mg BID dosages: In one study, atogepant significantly reduced monthly migraine days at both 30 mg BID (MD: –1.30 days, 95% CI: –2.17 to –0.43, p=0.004) and 60 mg BID (MD: –1.20 days, 95% CI: –1.90 to –0.50, p=0.0008) (Figure 2).
- Combined doses vs. placebo: The pooled analysis of the four doses (10 mg QD, 30 mg QD, 60 mg QD, and 30 mg BID) across three studies (n=1,430 atogepant, n=547 pla-

Table 1. Baseline characteristics of the included studies

Study (yr)	Group	Country	Centers	Study duration (wk)	Sample size, n	Age (yr), mean±SD	Male sex, n (%)	BMI (kg/m^2), mean±SD	Key findings
Ailani et al.[15] (2021)	Atogepant 10 mg	USA	Multi-center	12	221	41.4±12.0	21 (9.5)	30.3±7.6	A total of 659 patients with migraine were enrolled in the control or treatment groups (10 mg QD/30 mg QD/60 mg QD). Atogepant showed improvement in migraine in all outcomes measured, including migraine and headache days, MSQ RFR, PDA, and AIM-D, acute medication use days, and a >50% reduction of mean number of migraine; however, 60 mg of Atgopent led to more improvement than other doses.
	Atogepant 30 mg				228	42.1±11.7	24 (10.5)	31.1±7.6	
	Atogepant 60 mg				231	42.5±12.4	32 (13.9)	29.9±7.3	
	Placebo				222	40.3±12.8	24 (10.8)	30.8±8.7	
Ashina et al.[14] (2023)	Atogepant 60 mg	USA	Multi-center	52	543	42.5±12.0	64 (11.8)	30.6±8.0	A total of 543 patients with migraine were enrolled in the control group or received 60 mg (QD) of atogepant. Atogepant led to improvements in migraine outcomes, such as migraine days, and a >50% reduction in the mean number of migraine and medication use days.
	Standard care				196	41.1±12.1	24 (12.2)	30.6±8.0	
Tassorelli et al.[23] (2024)	Atogepant 60 mg	13 countries in Europe and North America	Multi-center	12	156	40.9±10.7	17 (10.9)	25.6±4.9	A total of 156 patients with migraine were enrolled in the control group or received 60 mg (QD) of atogepant. Atogepant showed improvement in migraine outcomes, such as migraine, headache, and acute medication use days, and a >50% reduction in the mean number of migraines.
	Placebo				157	43.4±10.3	16 (10.2)	26.2±5.2	
Goadsby et al.[13] (2020)	Atogepant 10 mg	USA	Multi-center	12	93	39.4±12.4	11 (11.8)	29.9±7.3	A total of 639 patients with migraine were enrolled in the control or treatment groups (10 mg QD/30 mg QD/60 mg QD/30 mg BID/60 mg BID). Atogepant showed improvements in the migraine outcomes measured, such as migraine, headache, and acute medication use days, and a >50% reduction of the mean number of migraines.
	Atogepant 30 mg				183	41.0±13.6	17 (9.3)	30.0±7.1	
	Atogepant 60 mg				186	40.4±11.7	30 (16.1)	30.0±7.8	
	Placebo				186	40.5±11.7	32 (17.2)	30.4±7.6	

SD, standard deviation; BMI, body mass index; QD, once daily; MSQ RFR, Migraine-Specific Quality of Life Questionnaire - Role Function-Restrictive domain; PDA, Performance of Daily Activities; AIM-D, Activity Impairment in Migraine-Diary; BID, twice a day.

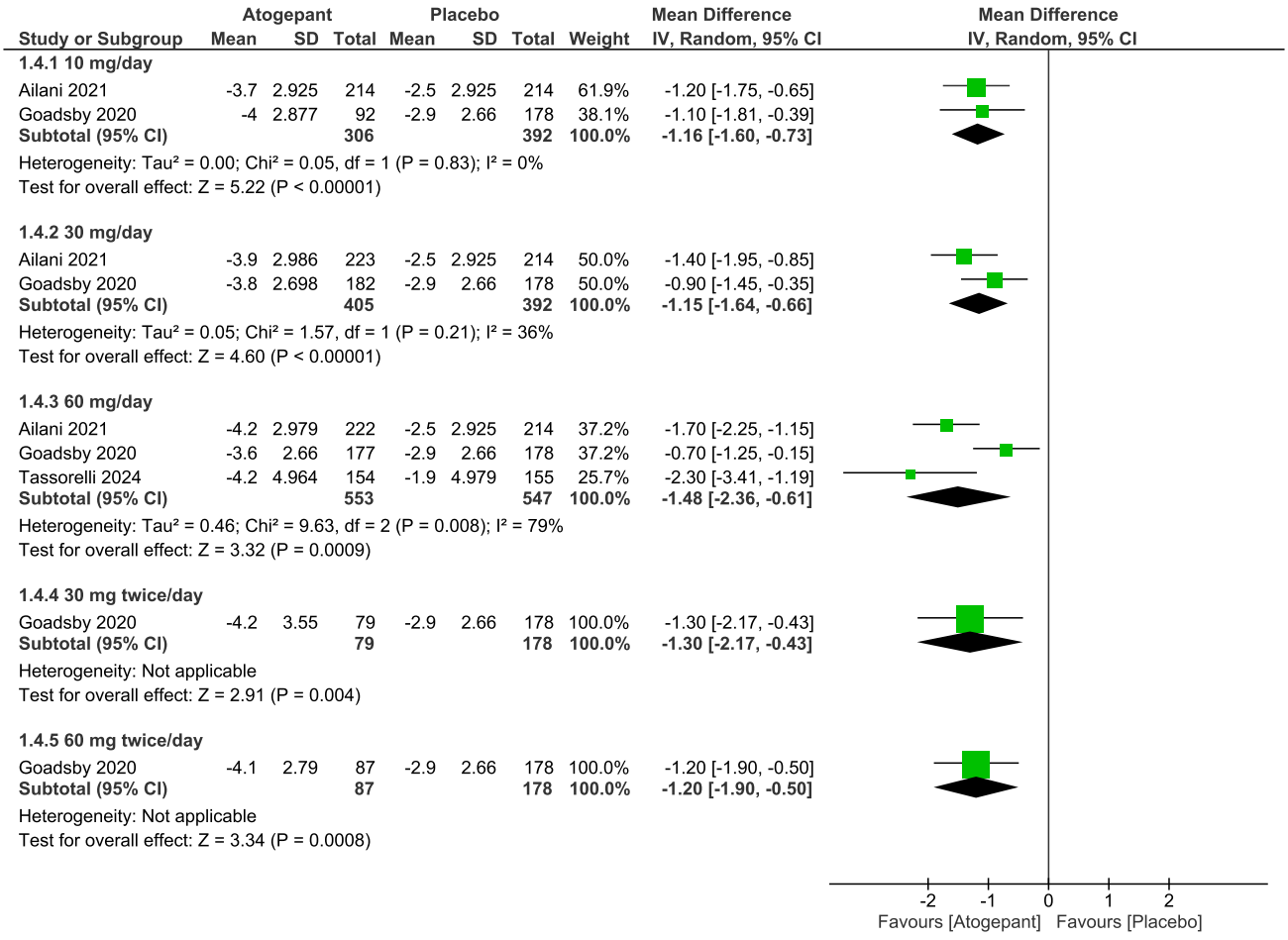

Figure 2. Forest plot of mean differences in monthly migraine days for various dosages of atogepant.
SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree or freedom.

cebo) demonstrated a significant reduction in monthly migraine days compared to placebo (MD: –1.40 days, 95% CI: –1.97 to –0.83, p<0.00001), with moderate heterogeneity (p=0.06, I^2=64%) (Supplementary Figure 2, available online).

5. Analysis of ≥ 50% reduction in monthly migraine days

- At 10 mg QD and 30 mg QD dosages: Two studies[13,15] showed that both 10 mg QD and 30 mg QD dosages resulted in a statistically significant number of patients achieving ≥50% reduction in monthly migraine days compared to placebo (RD: 0.23, 95% CI: 0.14–0.32, p<0.00001 for 10 mg; RD: 0.22, 95% CI: 0.05–0.38, p=0.01 for 30 mg). The number needed to treat (NNT) was approximately 5 for both doses (Figure 3).
- At 60 mg QD dosage: In three studies, the 60 mg QD dose showed a significant effect (RD: 0.25, 95% CI: 0.12–0.39, p=0.0001), with an NNT of 4 (Figure 3).
- At 30 mg BID and 60 mg BID dosages: One study found that both 30 mg BID (RD: 0.18, 95% CI: 0.05–0.31, p=0.008) and 60 mg BID (RD: 0.22, 95% CI: 0.09–0.34, p=0.0007) significantly improved outcomes, with NNTs of 6 and 5, respectively (Figure 3).
- Combined doses vs. placebo: The pooled analysis revealed that atogepant across all doses significantly increased the proportion of patients achieving a ≥50% reduction in migraine days (RD: 0.26, 95% CI: 0.15–0.36, p<0.00001), with moderate heterogeneity (p=0.009, I^2=79%) (Supplementary Figure 3, available online).

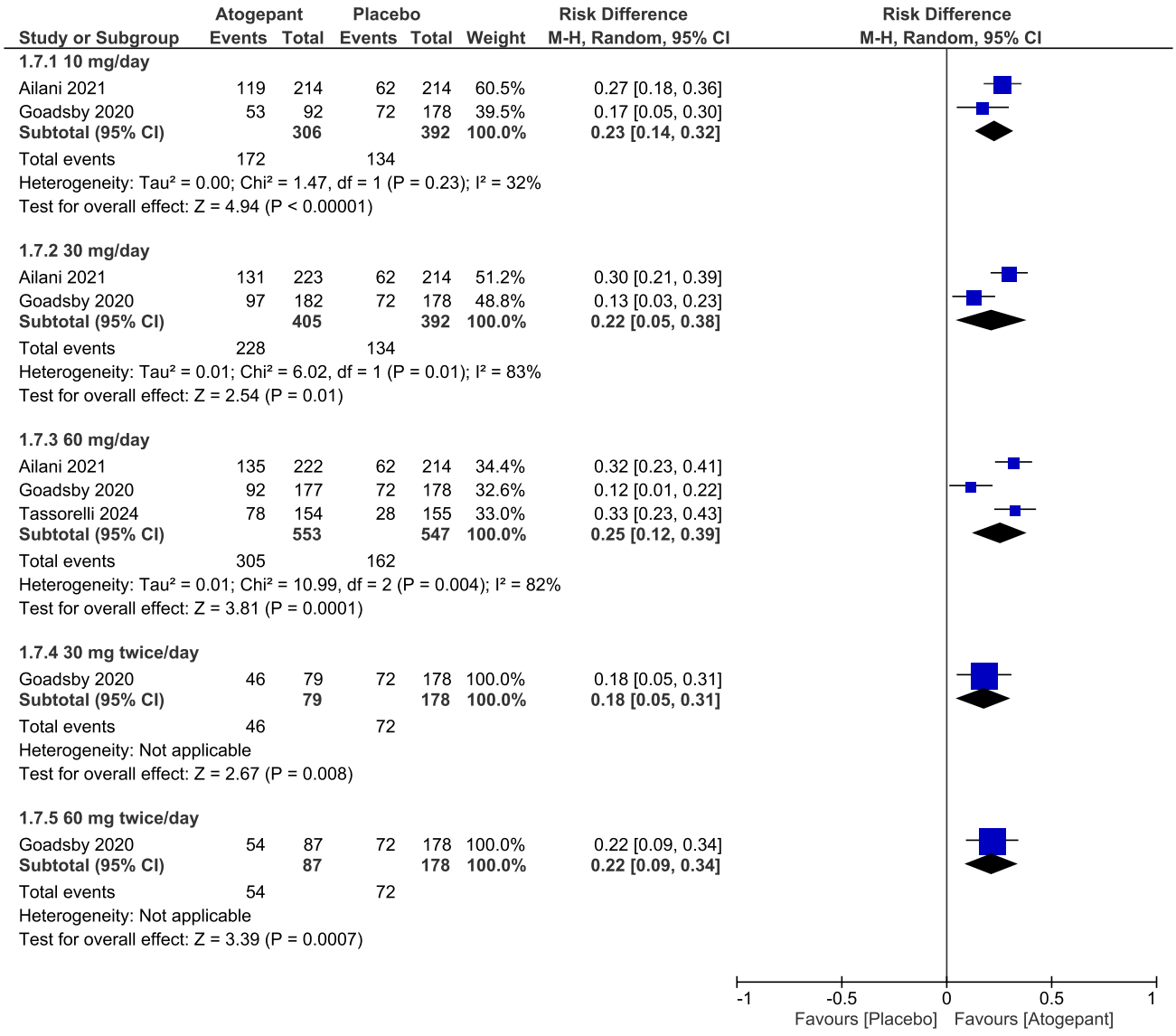

Figure 3. Forest plot of ≥50% reduction in monthly migraine days for various dosages of atogepant.
M-H, Mantel-Haenszel; CI, confidence interval; df, degree or freedom.

6. Mean difference in monthly headache days

- At 10 mg QD and 30 mg QD dosages: Atogepant at both 10 mg QD (MD: –1.40 days, 95% CI: –1.88 to –0.92, p<0.00001) and 30 mg QD (MD: –1.44 days, 95% CI: –1.90 to –0.98, p<0.00001) significantly reduced monthly headache days compared to placebo, with no significant heterogeneity (p>0.99, I^2=0%) (Figure 4).
- At 60 mg QD dosage: The 60 mg QD dose also significantly reduced headache days (MD: –1.59 days, 95% CI: –2.17 to –1.00, p<0.00001), with low heterogeneity (p=0.20, I^2=38%) (Figure 4).
- At 30 mg BID and 60 mg BID dosages: Atogepant significantly reduced headache days at 30 mg BID (MD: –1.30 days, 95% CI: –2.28 to –0.32, p=0.0009) and 60 mg BID (MD: –1.40 days, 95% CI: –2.37 to –0.43, p=0.005) (Figure 4).
- Combined doses vs. placebo: The pooled analysis confirmed a significant reduction in monthly headache days for atogepant compared to placebo (MD: –1.52 days, 95% CI: –1.89 to –1.15, p<0.00001) with homogeneity of the data (p=0.35, I^2=6%) (Supplementary Figure 2, available online).

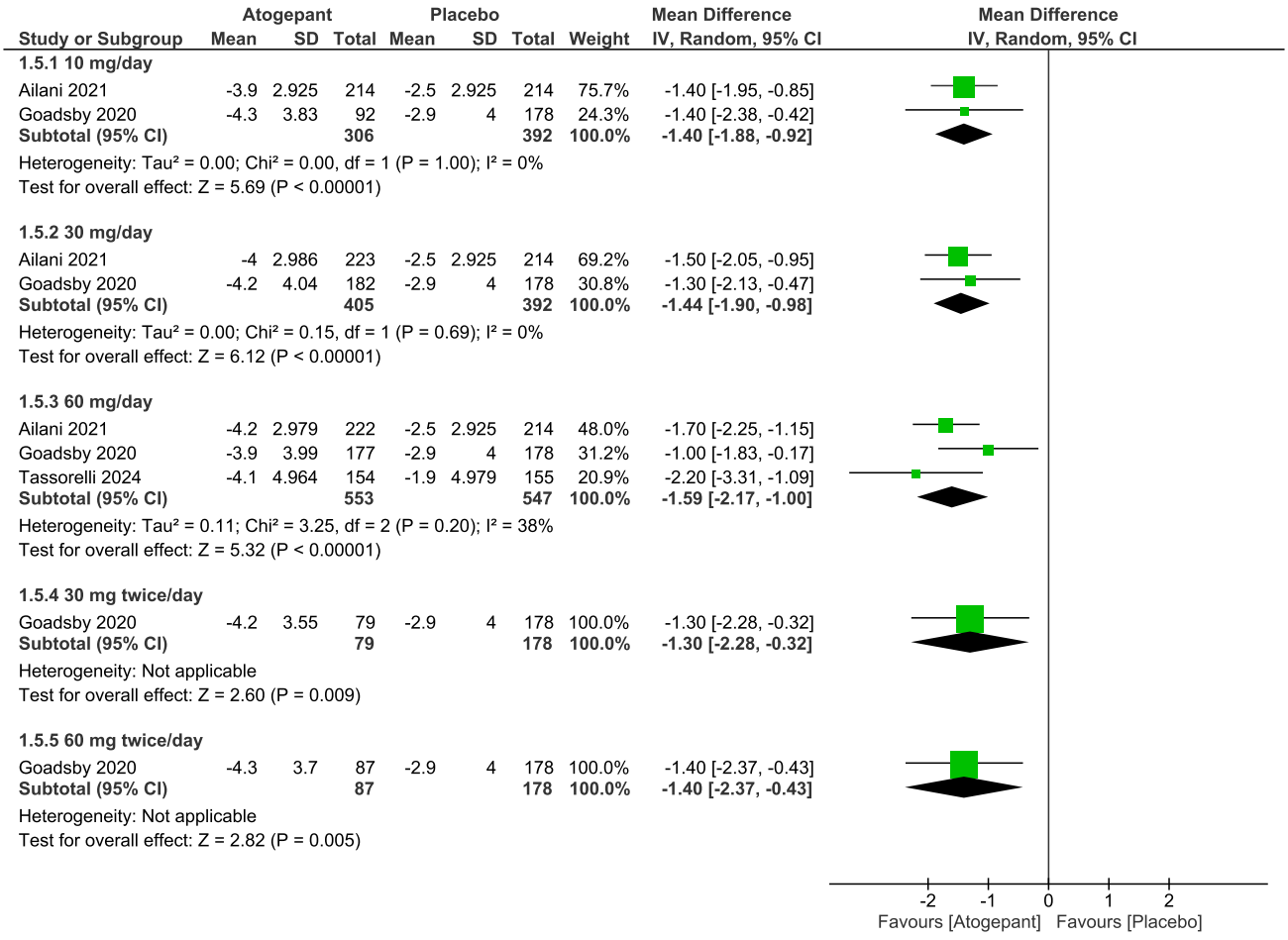

Figure 4. Forest plot of mean differences in monthly headache days for various dosages of atogepant.
SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree or freedom.

7. Mean difference in monthly acute medication use days

Three studies[3,15,23] reported data on acute medication use days.

- At 10 mg QD and 30 mg QD dosages: Both 10 mg QD (MD: –1.30 days, 95% CI: –1.74 to –0.86, p<0.00001) and 30 mg QD (MD: –1.40 days, 95% CI: –1.79 to –1.01, p<0.00001) significantly reduced acute medication use, with no heterogeneity (p>0.99, I^2=0%) (Figure 5).
- At 60 mg QD dosage: The 60 mg QD dose showed a significant reduction (MD: –1.58 days, 95% CI: –2.26 to –0.91, p<0.00001) with moderate heterogeneity (p=0.06, I^2=65%) (Figure 5).
- At 30 mg BID and 60 mg BID dosages: Atogepant significantly reduced acute medication use days at 30 mg BID (MD: –1.40 days, 95% CI: –2.10 to –0.70, p<0.0001) and 60 mg BID (MD: –1.20 days, 95% CI: –1.91 to –0.49, p=0.0009) (Figure 5).
- Combined doses vs. placebo: The combined dose analysis confirmed significant reductions in medication use (MD: –1.54 days, 95% CI: –2.06 to –1.02, p<0.00001) with low heterogeneity (p=0.10, I^2=57%) (Supplementary Figure 2, available online).

8. Dose comparison

Across the studies, there were no statistically significant differences in efficacy between the different dosages of atogepant (10 mg QD vs. 30 mg QD, 60 mg QD, 30 mg BID, or 60 mg BID) for the primary outcomes (p>0.05).

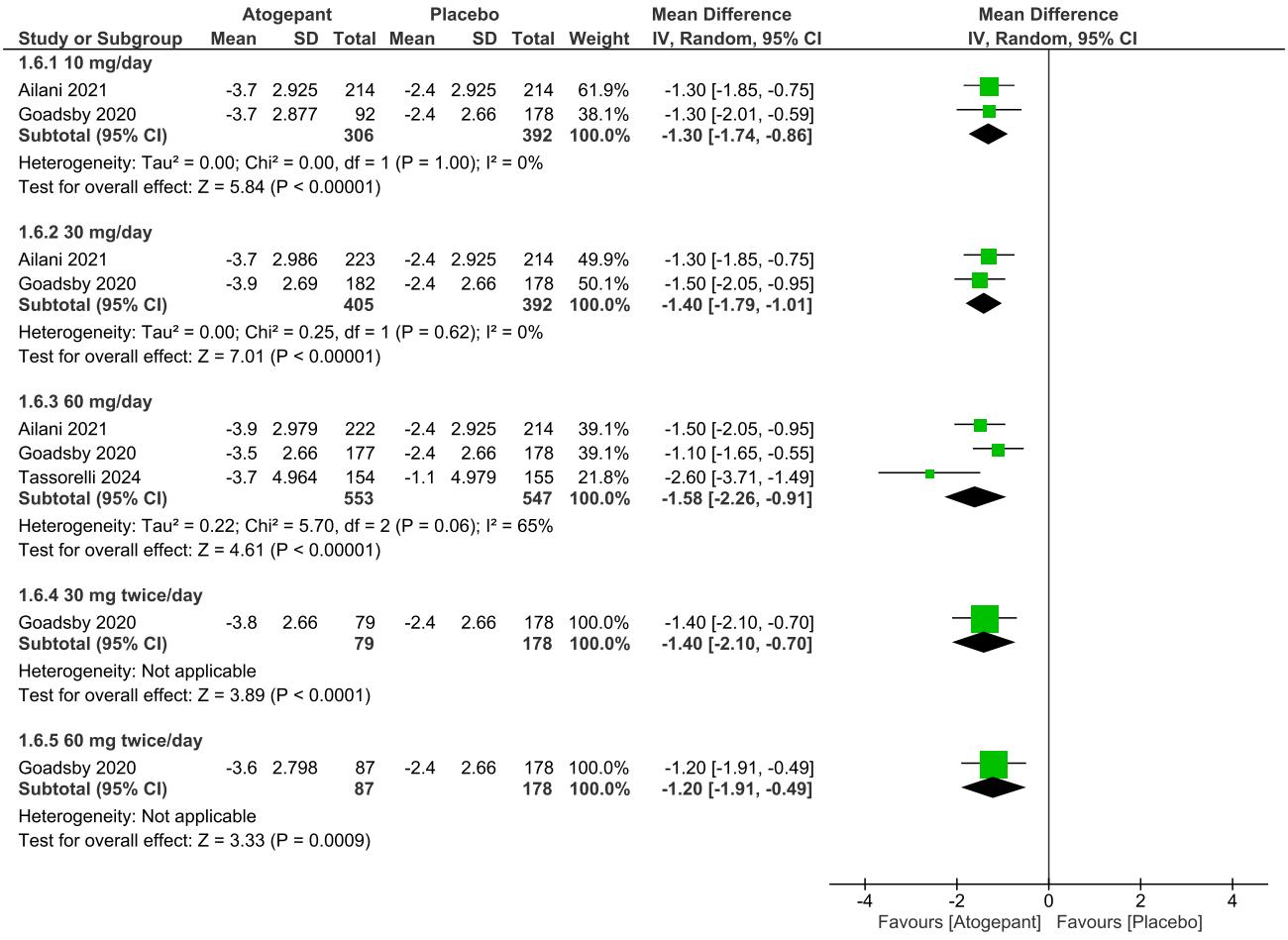

Figure 5. Forest plot of mean differences in monthly acute medication use days for various dosages of atogepant.
SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree or freedom.

9. Adverse events

Atogepant was associated with a higher risk of treatment-related treatment-emergent AEs (TEAEs) (RR: 1.75, 95% CI: 1.36–2.25, p<0.0001), constipation (RR: 4.59, 95% CI: 2.29–9.22, p<0.0001), and nausea (RR: 2.16, 95% CI: 1.31–3.56, p=0.002) compared to placebo. No significant differences were found for other AEs, including SAEs and discontinuations (Figure 6).

10. Adverse events and dose dependence

Given that all dosages of atogepant demonstrated efficacy without significant differences between them, we performed a descriptive analysis focused solely on AEs reported at two or more dose levels. This approach aimed to evaluate potential dose-dependent trends in AEs, providing valuable insights for practitioners to better anticipate and manage AEs in their patients (Supplementary Table 1, available online).

- For 'any TEAEs', the incidence rates were similar across doses, with 56.7% at 10 mg QD, 57% at 30 mg QD, 54.45% at 60 mg QD, 60.4% at 30 mg BID, and 58.24% at 60 mg BID, showing no clear dose-dependent trend.
- 'Treatment-related TEAEs' revealed a potential increase specifically at 60 mg BID (26.4%), compared to lower doses (21.65% at 10 mg QD and 17.76%–20.9% for others), but no clear pattern in QD groups.
- For 'SAEs', incidence rates remained low, ranging from 0%–1.05%, with no apparent dose dependence.
- Similarly, for 'TEAEs leading to treatment discontinuation', rates varied (4.1% at 10 mg QD, 1.8% at 30 mg QD,

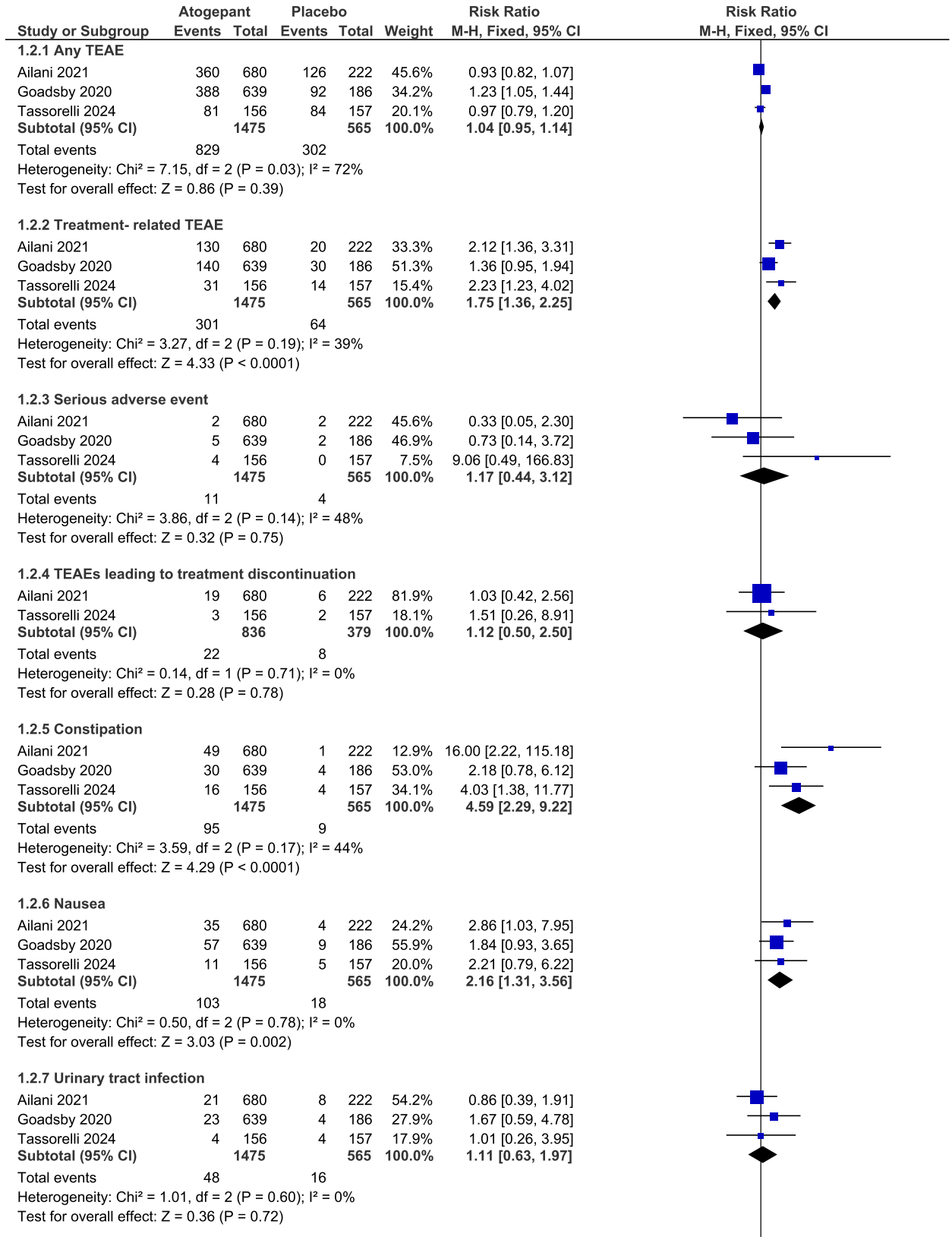

Figure 6. Forest plot of adverse events for atogepant versus placebo.
M-H, Mantel-Haenszel; CI, confidence interval; TEAE, treatment-emergent adverse event; df, degree or freedom.

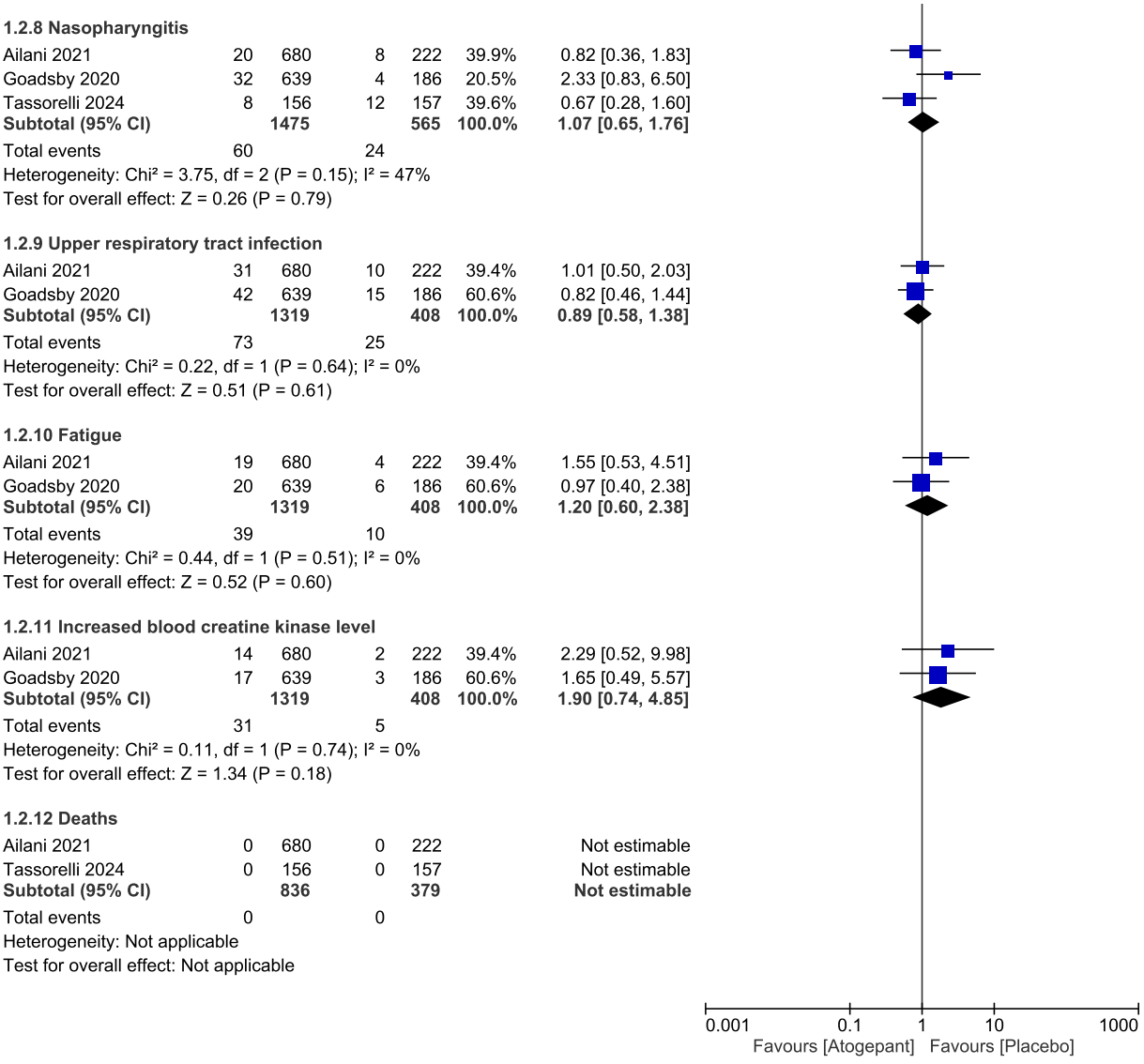

Figure 6. Continued.

and 2.325% at 60 mg QD) without a consistent trend.

- 'Constipation' demonstrated a dose-dependent increase in QD doses, rising from 6.05% at 10 mg QD to 7.15% at 60 mg QD, though BID doses showed a lower incidence (3.49%–4.4%).
- A strong dose-dependent relationship was observed for 'nausea,' increasing consistently from 5.09% at 10 mg QD to 9.9% at 60 mg BID. Similarly, 'fatigue' exhibited a clear increase at higher doses, peaking at 9.9% with 60 mg BID, compared to lower QD doses (1.27%–3.35%).
- For 'UTIs,' a peak incidence of 4.86% was reported at 30 mg QD, without a linear trend.
- 'Nasopharyngitis' showed a slight dose-dependent increase in QD doses, from 2.23% at 10 mg QD to 5.325% at 60 mg QD, while BID dosing rates remained inconsistent.
- 'URTIs' had variable rates (4.8%–6.97%) across doses with no clear trend.
- Other AEs, including 'increased blood creatine kinase levels' (6.97% at 30 mg BID), 'sinusitis' (1.8%–2.2%), 'gastroenteritis' (0.9%–2.2%), 'influenza' (1.4%–2.2%), and 'sinus congestion' (0.5%–1.7%), displayed minimal or inconsistent patterns across doses. Notably, 'anxiety' showed a slight increase at 60 mg QD (2.2%) compared to lower doses (0.4%–0.9%), while 'somnolence' (1.7%–3.2%)

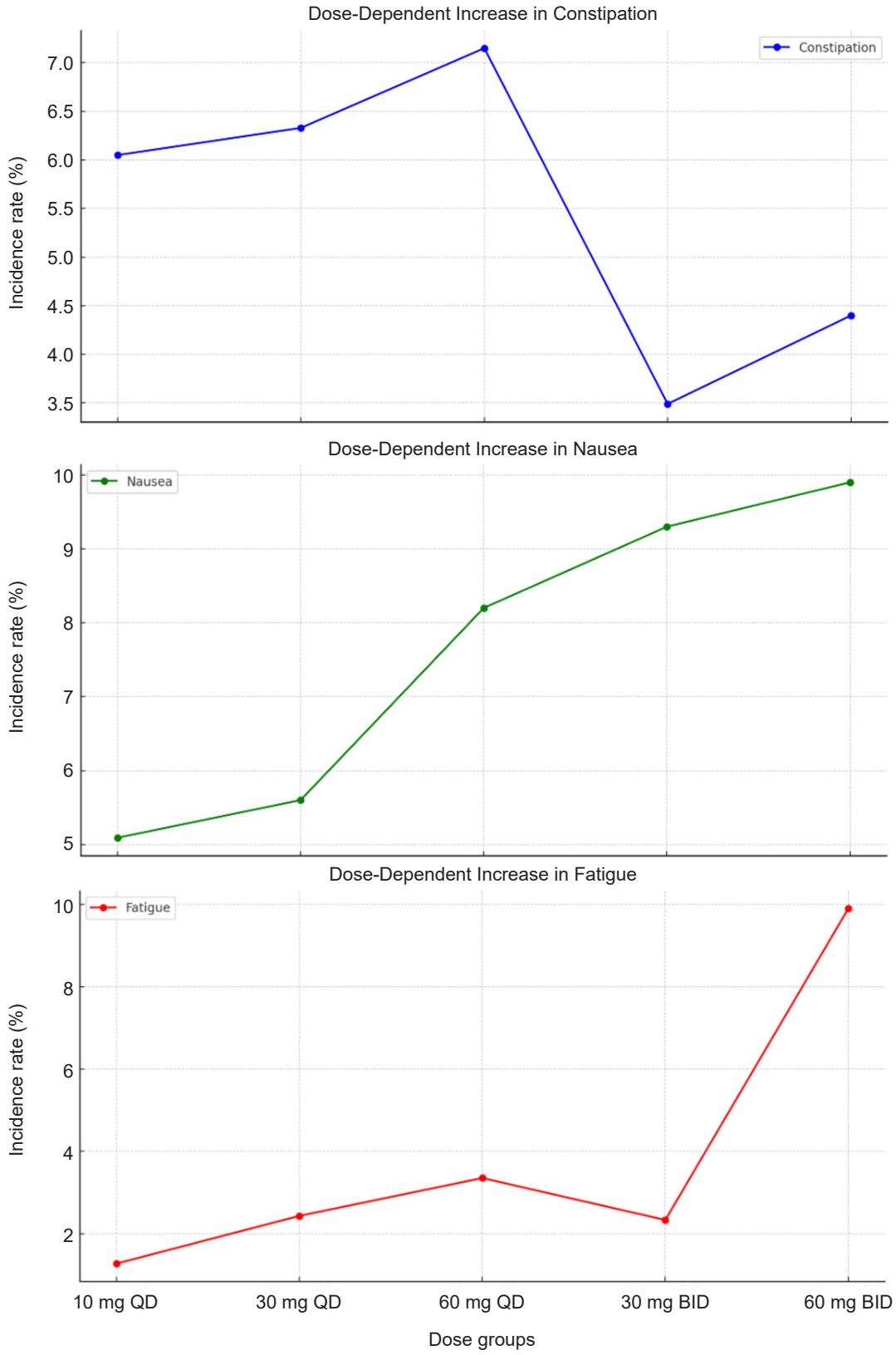

Figure 7. Graph for adverse events that show clear dose-dependence.
QD, once daily; BID, twice a day.

and 'increased alanine aminotransferase levels' exhibited no clear dose relationship.

In conclusion, dose-dependent trends were most apparent for 'nausea', 'fatigue', and 'constipation', particularly in higher doses, while other AEs showed inconsistent or minimal trends across the dose groups. The incidence for these three AEs is visualized in Figure 7.

DISCUSSION

Our meta-analysis demonstrated that atogepant at doses of 10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID significantly reduced the number of monthly migraine days and monthly headache days compared to placebo, highlighting its efficacy in migraine prevention. The dose-dependent reduction in monthly migraine days, ranging from –1.16 to –1.48 days, is consistent with other CGRP receptor antagonists, further validating atogepant as an effective preventive treatment for EM.

Moreover, atogepant was effective in reducing acute medication use days, particularly at higher doses, which is clinically relevant in reducing the reliance on rescue medications during migraine attacks. A ≥50% reduction in monthly migraine days was also observed in a significant proportion of patients, with RD ranging from 0.18 to 0.25 depending on the dosage, underscoring the dose-response relationship and therapeutic potential of atogepant.

The efficacy of atogepant across different dosages provides flexibility in tailoring treatment based on individual patient needs. The choice of dosage (10 mg, 30 mg, or 60 mg QD) should be guided by factors such as the frequency of migraine attacks, the presence of comorbidities, and the potential for drug interactions.[25] Dose reduction or contraindication of atogepant should be considered in specific conditions, such as concurrent use of strong CYP3A4 inhibitors (e.g., ketoconazole) and in patients with severe renal or hepatic impairment.[26] Higher doses, while more effective, may also be associated with a greater incidence of AEs, which must be weighed against the benefits for individual patients.

The safety profile of atogepant is an essential consideration in its clinical use. Our analysis revealed that treatment with atogepant was associated with a higher incidence of treatment-related TEAEs, constipation, and nausea, compared to placebo. However, no significant differences were observed for other AEs, including UTIs, URTIs, fatigue, nasopharyngitis, increased blood creatinine levels, or deaths. Additionally, there was no significant difference in treatment discontinuations due to AEs or in the incidence of SAEs between atogepant and placebo. These findings suggest that atogepant is generally well tolerated but warrants monitoring for gastrointestinal side effects, particularly in patients with pre-existing gastrointestinal conditions.

The introduction of atogepant into clinical practice could substantially improve patients' quality of life by reducing the frequency of migraine attacks, decreasing medication use, and lowering healthcare costs associated with migraine care. This is particularly significant given the high disability burden of EM and the economic impact of migraine on healthcare systems.[27-30]

A unique aspect of our work is the comparative analysis of different atogepant doses to evaluate if there were statistically significant differences in efficacy across dosages. Importantly, when comparing doses directly, no statistically significant differences were observed in efficacy for any primary outcome. This finding suggests that the therapeutic effect of atogepant does not substantially increase with higher doses, indicating a potential plateau in dose-response. Clinically, this supports the use of lower doses, such as 10 mg QD or 30 mg QD, to achieve similar benefits while potentially minimizing the risk of AEs associated with higher dosages. By adhering strictly to Cochrane guidelines, we provided a methodologically sound and clinically relevant assessment of atogepant's efficacy and safety profile in EM prevention.

Schwedt et al.[31] reported that approximately 62% of participants receiving galcanezumab and 61% of participants receiving rimegepant achieved a ≥50% reduction in monthly migraine days, with no statistically significant difference between the two treatments.

In our meta-analysis, atogepant demonstrated a similar response, with 23% to 25% of participants achieving a ≥50% reduction in monthly migraine days depending on the dose, corresponding to an NNT of 4 to 5 across doses. These differences may reflect variations in trial populations, baseline characteristics, and endpoints assessed. The trial by Schwedt et al.[31] primarily compared galcanezumab and rimegepant in a single trial setting, whereas our meta-analysis pooled multiple trials of atogepant,

focusing on dose-response relationships and placebo-controlled outcomes.

Furthermore, Schwedt et al.[31] highlighted that monoclonal antibodies, such as galcanezumab, often require subcutaneous administration, which can pose adherence challenges despite their efficacy. In contrast, atogepant's oral formulation aligns with patient preferences for non-invasive options, offering a convenient alternative without compromising efficacy.

Rimegepant, another CGRP receptor antagonist with a half-life similar to atogepant (approximately 11 hours), supports a QOD dosing schedule as an alternative to daily dosing.[32,33] This option could benefit patients with concerns about daily medication, offering greater flexibility without sacrificing clinical efficacy.

In conclusion, while direct comparisons between atogepant and CGRP monoclonal antibodies like galcanezumab are limited by differences in study design and methodology, our findings support atogepant as a flexible and effective preventive option for EM, particularly for patients seeking oral treatment alternatives. Further head-to-head studies would be valuable to establish the comparative effectiveness of these therapies.

1. Implications for clinical practice

Atogepant offers versatile dosing options that can be tailored to individual patient needs and treatment goals. In our analysis, we conducted a head-to-head comparison of different atogepant doses (10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID) across all efficacy outcomes, including reductions in monthly migraine days, headache days, and acute medication use. The results showed no statistically significant differences in efficacy between the various doses. This finding indicates that clinicians can prioritize dose selection based on individual patient preferences, tolerability, and clinical circumstances rather than relying on higher doses to achieve greater efficacy.

The 60 mg QD dose is the most effective option for patients requiring robust reductions in monthly migraine and headache days. It also minimizes acute medication use, making it particularly suitable for individuals with frequent migraines seeking potent preventive effects.

For patients prioritizing a balance between efficacy and tolerability or those sensitive to side effects, the 30 mg QD dose serves as an excellent starting point. This dosage effectively reduces migraine days and acute medication use while maintaining a favorable safety profile, making it an ideal choice for achieving preventive benefits with fewer AEs. The 10 mg QD dose provides an alternative for patients with milder symptoms or those initiating preventive therapy. While its impact on migraine and headache days is slightly lower than higher doses, it still offers meaningful reductions in attack frequency with minimal side effects. For patients requiring a more intensive approach, the BID dosing options—30 mg or 60 mg BID—offer additional flexibility. These regimens may benefit patients who do not achieve adequate relief with QD dosing or prefer split dosing throughout the day.

In summary, the 60 mg QD dose is optimal for maximum efficacy, while the 30 mg QD dose balances effectiveness and tolerability. Lower doses and BID regimens provide personalized options, making atogepant a flexible and patient-centered choice for migraine prevention.

2. Limitations and recommendations

This meta-analysis has several limitations that may affect the generalizability and reliability of the findings. First, the inclusion of only four RCTs represents a relatively limited evidence base, reducing the statistical power and precision of the estimates. Despite subgroup analyses to address this limitation, significant heterogeneity among studies, particularly regarding dosing regimens, raises concerns about the consistency of results. Variability in study designs, patient populations, and outcome measures further complicates direct comparisons.

Additionally, three of the four RCTs were conducted in the United States, limiting the findings' external validity to non-United States populations. The under-representation of male and non-White patients, as noted by Tassorelli et al.,[23] restricts the applicability of the results to more diverse demographics. Expanding future research to include broader patient populations is essential to enhance generalizability, especially in regions with differing healthcare systems and patient characteristics.

Another notable limitation is the lack of long-term safety and efficacy data, particularly for patients resistant to multiple migraine therapies. The current evidence focuses on

short-term outcomes, leaving uncertainty about atogepant's long-term impact, especially in patients with complex clinical profiles or comorbidities, which may influence its pharmacokinetics and safety.

Furthermore, questions remain about the relative advantages of oral CGRP antagonists like atogepant compared to injectable monoclonal antibodies targeting the CGRP receptor. While oral formulations offer convenience, issues of adherence, patient acceptance, and long-term preference require further investigation. Patient-centered research is crucial to better understand these factors and their influence on clinical outcomes.

Safety concerns, particularly gastrointestinal side effects such as reduced motility and constipation,[15] also warrant attention. These AEs may affect patient quality of life and should be carefully monitored, especially in individuals with pre-existing gastrointestinal conditions.

Future research should prioritize long-term safety and efficacy studies, particularly in EM patients and those with complex treatment histories. Additionally, trials should include more diverse patient populations in terms of gender and ethnicity to improve generalizability. Investigating optimal dosing strategies and comparing atogepant to other CGRP-targeted therapies will also be essential to better define its role in the prevention and management of EM.

CONCLUSION

Atogepant demonstrates significant efficacy in reducing monthly migraine and headache days and decreasing acute medication use, making it a valuable option for EM prevention. Its selective CGRP receptor antagonism underpins its clinical benefits, though side effects such as constipation and nausea require careful monitoring. While evidence supports its short-term safety and efficacy, gaps remain regarding long-term use in EM and in diverse demographic groups. The under-representation of male and non-White patients highlights the need for broader, more inclusive research. Additionally, further studies should investigate optimal dosing strategies to refine atogepant's clinical role and enhance its utility in the prevention of EM. Addressing these gaps will improve outcomes for diverse EM patient populations.

AVAILABILITY OF DATA AND MATERIAL

This systematic review and meta-analysis relied on publicly available data from previously published studies. The original research contributions utilized in this study can be accessed within the main article and supplementary materials.

AUTHOR CONTRIBUTIONS

Conceptualization: AMA, AA; Methodology: AMA, AA; Investigation: AMA, AM, MEM, HS; Data Curation: AMA, AM, MEM, HS; Formal Analysis: AMA, AA; Validation: AMA, AA, HS, AO; Writing–original draft: AA, SAA, HA, MTH, AO; Writing–review & editing: AMA, AA, HS, AO.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

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Review Article

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Headache and Pain Research

Update on Tension-type Headache

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Abstract

Tension-type headache (TTH) is the most common type of headache, characterized by mild to moderate intensity, bilateral, with a pressing or tightening (non-pulsating) quality. Migraine and TTH can occur in the same person, and their risk factors and treatments can overlap. However, TTH receives less attention than migraine. Furthermore, despite the expanding market for migraine treatments targeting calcitonin gene-related peptide (CGRP) mechanisms, the lack of evidence regarding mechanisms related to CGRP-related mechanisms in TTH continues to be neglected. There remains a need to develop effective preventive treatments for chronic TTH, which imposes a very high burden of disease. From this perspective, this review aims to provide the latest evidence on TTH.

Keywords: Headache, Tension-type headache, Headache disorders, Primary, Migraine

INTRODUCTION

Tension-type headache (TTH) is the most common headache disorder. It is characterized by mild to moderate intensity, bilateral, pressing, or tightening pain quality in the forehead, occiput, and neck. The term "tension" emphasizes the role of muscle contraction and emotional tension, leading to various treatments that focus on muscle relaxation and stress management.

Despite knowing the nature of how TTH and migraine can co-occur and having similar medical treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) or amitriptyline, TTH remains less researched, poorly diagnosed and treated than migraine.[1] For example, a PubMed search for the word "migraine" yields to almost 50,000 hits, compared to less than 5,000 hits for the word "tension-type headache." It is also interesting to note that while migraine and TTH can become interchangeable over time and share similar risk factors, triggers, and comorbidities in individuals, they have distinctly different headache characteristics.[2] The distinctive features of migraine, as opposed to TTH, appear to be influenced in part by the calcitonin gene-related peptide (CGRP) mechanism, which has recently received a great deal of attention. In contrast, TTH

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has been neglected as a research topic due to the lack of a clear biomarker and the absence of randomized controlled trial-based effective preventive medications for frequent episodic or chronic TTH.

This review aims to provide an overview of recent findings on the epidemiology, pathophysiology, diagnosis, and treatment of TTH.

EPIDEMIOLOGY

The global prevalence of TTH is approximately 26% of adults, with wide variation between studies and ethnicities, but it is generally estimated that 30% to 80% of the adult population will be affected at some point in their lives.[3-6]

The incidence of TTH is higher in women than in men, and this gender difference may be due to hormonal factors, stress, and psychosocial influences. TTH can occur at any age, but the greatest burden in terms of years of life lived with disability is in the between 15 and 49 age group.[7] The incidence of TTH tends to decrease with age, although it remains a significant health problem in the elderly population.[7]

Lower socioeconomic status is often associated with higher levels of stress, poorer access to healthcare, and lower levels of education, all of which may contribute to the prevalence and severity of TTH.[8] Cultural attitudes toward pain and healthcare-seeking behaviors may influence how individuals report and manage their headache symptoms. In some cultures, headache may be underreported due to stigma or misconceptions about headache. In addition, infrequent episodic TTH may be under-reported in epidemiological studies.[9]

CLINICAL PRESENTATION

TTH is characterized by a diffuse, mild to moderate, bilateral headache that is often described as a tightening sensation. Unlike migraine, the headache is not typically pulsating and does not worsen with routine physical activity. Also, TTH is also not usually associated with nausea or vomiting, although mild photophobia or phonophobia may be present in some cases. The clinical presentation of TTH is highly variable between individuals, with some experiencing infrequent episodic headaches and others suffering from chronic daily headaches.[10]

The frequency of TTH episodes can vary widely, ranging from infrequent episodic TTH (occurring less than 1 day per month) to chronic TTH (occurring more than 15 days per month).

Factors that contribute to the chronicity of TTH include high levels of stress, co-existing migraine, fatigue, anxiety, and depression, and an inability to relax after work.[11]

DIAGNOSIS

The diagnosis of TTH is primarily clinical and based on the patient's history and symptoms according to the criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3) (Table 1).[12] However, due to the non-specific nature of TTH symptoms, diagnosis can be challenging because of overlap with other headache disorders and medical conditions. This diagnostic ambiguity can lead to misdiagnosis, inappropriate treatment, and unmet patient needs. Therefore, it is important to rule out other diseases on the basis of the headache history.

Headache diaries are the best assessment tool for diagnosis and classification. However, additional diagnostic tests such as neuroimaging, blood sampling, and lumbar puncture may be necessary if any red flags are present.[13]

Without strict criteria are applied, both migraine and TTH may coexist and sometimes overlap, further complicating the diagnostic process. Migraine and TTH may have some overlap in their clinical features. Photophobia and phonophobia are more common in migraine than in TTH, also nausea and vomiting are more common in migraine than in TTH, although mild nausea may be present in chronic TTH according to the ICHD-3.[14,15] This can lead to clinicians misdiagnosing a patient as having migraine when they are actually have TTH, and vice versa. In children and adolescents, the transition from migraine to TTH or from TTH to migraine occurs within a few years, supporting the continuum theory of headache in this subgroup of individuals. Not only are mixed presentations and diagnostic shifts common at younger ages, but the challenges associated with distinguishing TTH from migraine in clinical practice, clinical research, and epidemiologic studies have been widely recognized.[16,17] TTH with migraine comorbidity is associated with genetic factors.[18] Recently, machine learning models have demonstrated high

Table 1. Diagnostic criteria of tension-type headache according to the International Classification of Headache Disorders, 3rd edition (ICHD-3)[1]

	2.1. Infrequent episodic tension-type headache	2.2. Frequent episodic tension-type headache	2.3. Chronic tension-type headache	2.4. Probable tension-type headache		
				2.4.1. Probable infrequent episodic tension-type headache	2.4.2. Probable frequent episodic tension-type headache	2.4.3. Probable chronic tension-type headache
A	At least 10 episodes of headache occurring on <1 day/mo on average (<12 days/yr) and fulfilling criteria B–D	At least 10 episodes of headache occurring on 1–14 day/mo on average for >3 months (≥12 and <180 day/yr) and fulfilling criteria B–D	Headache occurring on ≥15 day/mo on average for >3 months (≥180 day/yr), fulfilling criteria B–D	One or more episodes of headache fulfilling all but one of criteria A–D for 2.1. Infrequent episodic tension-type headache	Episodes of headache fulfilling all but one of criteria A–D for 2.2. Frequent episodic tension-type headache	Headache fulfilling all but one of criteria A–D for 2.3. Chronic episodic tension-type headache
B	Lasting from 30 minutes to 7 days		Lasting hours to days, or unremitting	Not fulfilling ICHD-3 criteria for any other headache disorder		
C	At least two of the following four characteristics: 1. bilateral location 2. pressing or tightening (non-pulsating) quality 3. mild or moderate intensity 4. not aggravated by routine physical activity such as walking or climbing stairs			Not better accounted for by another ICHD-3 diagnosis		
D	Both of the following: 1. no nausea or vomiting 2. no more than one of photophobia or phonophobia		Both of the following: 1. no more than one of photophobia, phonophobia or mild nausea 2. neither moderate or severe nausea nor vomiting			
E	Not better accounted for by another ICHD-3 diagnosis[1]					

diagnostic accuracy in migraine from electronic health records or questionnaires.[19-21] However, these are not yet sufficient for application to TTH.[21]

Premonitory or prodromal symptoms are characteristic of migraine and include yawning, mood changes, fatigue, and neck pain. These symptoms typically occur within 2–48 hours of the onset of migraine headache.[22] There are no of premonitory symptoms in patients with TTH. Migraine headaches may also be associated with menstrual periods, with the drop in estrogen levels affecting the frequency of migraine headaches. Migraine attacks are common during the perimenstrual period and usually improve during pregnancy.[23]

And the selective 5HT1B/1D agonist is thought to relieve migraine by stimulating the 5HT1B receptor on cranial vascular smooth muscle to reduce the pain-inducing vasodilation that may be responsible for the headache.[24] However, it is not effective for the treatment of TTH, except in people who also have migraine.[25] The healthcare provider caring for patients with headache should be aware of these overlaps and their implications for the management of patients with headache.

PATHOPHYSIOLOGY

The pathophysiology of TTH is complex, multifactorial, and not fully understood, involving both peripheral and central mechanisms. The peripheral mechanisms are primarily related to myofascial tissues and nociception, while the central mechanisms of chronification are related to pain processing in the central nervous system.[26,27] There has been some research into the mechanisms of nitric oxide-induced TTH and drug development is currently underway, but to date there have been no significant results.[20,28,29] The role of CGRP in the progression and remission of chronic TTH is becoming a subject of interest, although treatment response to anti-CGRP monoclonal antibodies is poor.[14,30]

1. Peripheral mechanisms

The peripheral mechanisms of TTH are mainly related to pericranial muscle tenderness during acute headache attacks and myofascial trigger points.[31-33] The most common method used to assess tenderness is manual palpation of the pericranial muscles and calculation of the total tenderness score.[34] And muscle hardness can be measured using the hardness meter, a quantitative method.[35] Pericranial tenderness is exacerbated during the acute headache phase and increases with the severity and frequency of TTH attacks, supporting the presence of more severe tenderness in individuals with chronic TTH than in those with episodic TTH.[36]

Myofascial tissues, which include muscles and connective tissues, can develop localized areas of tenderness called trigger points. These trigger points can cause pain in other areas, such as the neck or shoulder, which may contribute to the headache pain experienced in TTH.[37] Active myofascial trigger points are common in TTH consistent with the hypothesis that peripheral mechanisms are involved in the pathophysiology.[27] However, the relationship between myofascial trigger points and the severity of TTH varies between studies.

Electromyography studies have shown increased muscle activity and tension in individuals with TTH, suggesting that sustained muscle contraction and tension play a role in the development of headache pain.[38]

2. Central mechanisms

Central sensitization of second-order neurons in the spinal cord or the spinal trigeminal nucleus is a key mechanism in the pathophysiology of transformation from episodic to chronic TTH.[39,40] Patients with chronic TTH had higher pain sensitivity and lower tolerance to pressure stimulation of cranial and extracranial structures than patients with episodic TTH patients.[26,41]

Comorbidities, such as back pain, fibromyalgia, and sleep disorders, may alter pain sensitivity in patients with chronic TTH and increase central sensitization compared to patients with transient TTH, suggesting shared central mechanisms between the two groups. Anxiety and depression are in patients with TTH and are associated with worsening symptoms.[42,43]

Functional magnetic resonance imaging studies have provided insight into the central mechanisms of TTH by examining dynamic brain changes between pain and pain-free periods in patients with episodic TTH.[44,45] These studies have shown changes in activation in pain-processing regions of the brain, including the anterior cingulate cortex, insula, and prefrontal cortex. These findings suggest that individuals with TTH have abnormal pain processing and modulation, which may contribute to the perception of headache pain.

In addition, neurotransmitters such as serotonin and norepinephrine have been found to be associated with TTH, although several studies have yielded conflicting results.

TREATMENT

There are significant gaps in the management of TTH, and many patients are not receiving adequate treatment. A multidisciplinary approach tailored to each individual patient. For example, patients with infrequent episodes of TTH can be managed with acute medications and non-pharmacological treatments such as lifestyle modifications, while patients with frequent episodes of TTH or chronic TTH may require preventive pharmacological treatments with behavioral interventions (Figure 1).

1. Acute pharmacological treatments

Acute treatment aims to provide rapid relief of headache attacks quickly and is typically used at the onset of a headache episode. Simple analgesics have evidence-based efficacy and are widely accepted as the first-line treatment for the acute treatment of patients with TTH.[46]

NSAIDs and acetaminophen are commonly used for acute symptom management. Opioids, triptans, and muscle relaxants are not generally recommended for symptomatic TTH.[47,48]

• NSAIDs

NSAIDs inhibit the enzyme cyclooxygenase, which reduces the production of prostaglandins that which mediate inflammation and pain. Initial treatments for acute TTH include ibuprofen, ketoprofen, naproxen, and diclofenac.[49,50] Side effects include gastrointestinal discomfort, ulcers, and cardiovascular risks with long-term use.

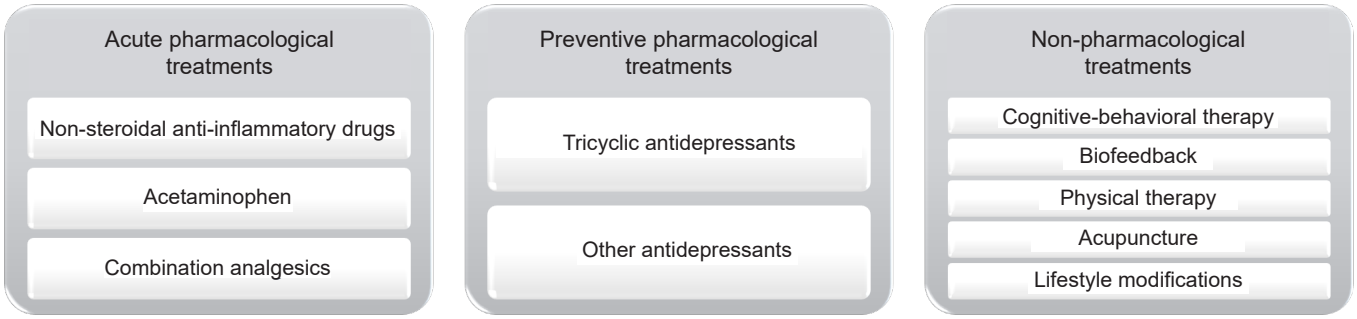

Figure 1. Current treatments for tension-type headache.

• *Acetaminophen*

Acetaminophen is the preferred initial therapy for patients with TTH who are intolerant of or contraindicated for NSAIDs for pregnant patients. Acetaminophen is typically used in a single oral dose of 500 to 1,000 mg. It is generally well tolerated, but overdose may cause liver toxicity.[51]

• *Combination Analgesics*

Combination of caffeine with acetaminophen, aspirin, or ibuprofen improves the efficacy for the acute treatment of TTH.[52] Caffeine may enhance the analgesic effects by promoting their gastric absorption.[53] However, frequent use may increase gastrointestinal discomfort and increase the risk of medication overuse headache.

2. Preventive pharmacological treatments

Preventive treatments have been shown to help reduce headache frequency and severity in patients with frequent episodic TTH (1 to 14 headache days per month) or chronic TTH (≥15 headache days per month). Preventive treatment is also indicated in patients with infrequent TTH when simple analgesics are ineffective, poorly tolerated, or contraindicated.

The goal of treatment is to reduce the frequency, severity, and duration of attacks and to improve the response to treatment of acute attacks. It is important to understand patient expectations and consider patient preferences when deciding which of the various preventive therapies to use. For patients who respond well (over 50% reduction in headache days per month), an adjunctive approach is to discontinue treatment after 3 or 6 months and monitor for headache recurrence, unless there are other comorbidities, such as depression or anxiety disorders.

• *Tricyclic Antidepressants (TCAs)*

TCAs have moderate to high potency for TTH, and amitriptyline controls pain through its inhibitory effects on serotonin and norepinephrine reuptake.

Amitriptyline also reduces pericranial muscle tenderness, resulting in peripheral antinociception and inhibition of central sensitization. It is common for clinicians to start amitriptyline at 2.5–10 mg nightly and increase by 5–10 mg per week to a maximum of 70–80 mg. Common side effects include sedation, weight gain, dry mouth, and constipation.

• *Other Antidepressants*

Mirtazapine (noradrenergic and specific serotonergic antidepressant) is comparable to amitriptyline and has a better tolerability profile than amitriptyline. Evidence for the effectiveness of venlafaxine (serotonin-norepinephrine reuptake inhibitor) in preventing TTH is weak and supports a level B rating by the EFNS-TF.[46]

3. Non-pharmacological treatments

Non-pharmacological treatments such as cognitive behavioral therapy (CBT), biofeedback, and relaxation therapy are often recommended as first-line interventions. In addition, integrative medicine (acupuncture and massage) and lifestyle modifications (sleep management, healthy diet, hydration, and exercise) may be considered to reduce headache triggers. However, the evidence for non-pharmacological approaches in TTH are very limited.[54]

• *CBT*

CBT is a psychological intervention that helps patients identify and modify negative thought patterns and behaviors that cause stress and muscle tension, both of which

are important factors in TTH.[55] CBT techniques for TTH include cognitive restructuring, behavioral activation, and relaxation techniques, among others. Stress management therapy has demonstrated efficacy in randomized and placebo-controlled trials and has been shown to be equivalent to amitriptyline in preventing chronic TTH.[56] Long-term group behavioral therapy has been shown to be effective in reducing headache frequency and intensity, improving coping strategies, and improving overall mental health.[57,58] CBT has been shown to improve quality of life and reduce comorbid symptoms of anxiety and depression.

• *Biofeedback*

Biofeedback is a technique that teaches individuals how to regulate physiological processes such as muscle tension, heart rate, and skin temperature through real-time feedback. Biofeedback helps patients become aware of and voluntarily control these processes, which can help reduce the frequency, duration, and intensity of headaches in patients with TTH.

• *Physical Therapy*

Physical therapy involves the use of massage, cervical spine manipulation, and exercise to improve muscle function, reduce tension, and promote relaxation.[59] It is particularly useful for TTH patients with severe musculoskeletal problems, such as poor posture, muscle imbalances, and trigger points.[60] However, there is no standardized protocol for treating TTH, and a combination of techniques appears to be more effective.[61]

• *Acupuncture*

The exact mechanism by which acupuncture relieves TTH is not fully understood, but it is believed to involve the modulation of pain pathways, release of endogenous opioids, and reduction of muscle tension and inflammation.[62] As the efficacy of greater occipital nerve block in various headache disorders has been confirmed, attempts have been made to use it as a treatment for TTH.[63-65] One systematic meta-analysis found acupuncture to be effective and safe for frequent episodic TTH and chronic TTH.[66]

• *Lifestyle Modifications*

Adopting healthy lifestyle habits can play an important role in the management and prevention of TTH. Important lifestyle changes include regular physical activity, healthy sleep patterns, a balanced diet, and effective stress management.[67,68]

Regular exercise, such as aerobic exercise, yoga, and stretching, has been shown to help reduce stress, improve sleep quality, and relieve muscle tension, all of which can help prevent TTH.

Strategies such as maintaining a consistent sleep schedule, avoiding caffeine and electronic devices before bedtime, and creating a comfortable sleep environment can help prevent headaches caused by sleep deprivation.

Eating a balanced diet that includes a variety of nutrients can help prevent and manage TTH.

FUTURE RESEARCH DIRECTIONS

Future research should focus on addressing the diagnostic challenges and improving our understanding and treatment of TTH. The co-occurrence of migraine and TTH may be coincidental, but more research is needed to determine whether there is a causal mechanistic relationship between the two disorders.[69]

One of the major challenges in diagnosing these headaches is the lack of reliable biomarkers, with diagnosis largely based on clinical criteria and patient self-report. More research is needed to improve diagnostic accuracy. While both migraine and TTH are associated with genetic factors, the specific genes responsible for the heritability of TTH remain unknown, in contrast to the multiple risk loci identified for migraine.

Pharmacological provocation studies have provided valuable insights into the pathophysiology of migraine, leading to the discovery of important therapeutic targets. However, similar studies have not been thoroughly performed for TTH. Unfortunately, in the absence of identified therapeutic targets, this approach is not currently feasible for TTH patients.

In addition, the evidence supporting the use of botulinum toxin and anti-CGRP monoclonal antibodies in the treatment of TTH is limited. We believe additional studies are needed to evaluate the utility of botulinum toxin and other emerging therapies for this common and debilitating condition.

CONCLUSION

TTH remains a common and often debilitating headache disorder. Despite its high prevalence, TTH remains under-recognized and under-treated, with significant public health implications. A comprehensive understanding of its epidemiology, pathophysiology, and clinical management is essential to improve patient outcomes. Continued research into the underlying mechanisms and public health efforts are needed to address the diagnostic and treatment gaps and ultimately improve the quality of life for individuals affected by TTH.

AVAILABILITY OF DATA AND MATERIAL

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: HJL, SJC, JGS; Data curation: JGS, HWS; Formal analysis: JGS, HWS; Investigation: SJC; Methodology: HJL, SJC; Project administration: SJC, HWS; Resources: JGS; Software: JGS; Supervision: SJC, HWS; Validation: HJL, SJC, JGS, HWS; Visualization: HJL; Writing–original draft: HJL, SJC; Writing–review & editing: JGS, SJC, HWS.

CONFLICT OF INTEREST

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Headache and Pain Research

The Current Role of Artificial Intelligence in the Field of Headache Disorders, with a Focus on Migraine: A Systemic Review

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Abstract

The application of artificial intelligence (AI) in the field of headache disorders, particularly migraine, is rapidly expanding, and AI has demonstrated significant potential for diagnosis, treatment, and research. This review examines the current role of AI in migraine management, categorizing AI applications into diagnosis and classification, assessment of treatment response, prediction of migraine attacks, and research. A systematic review of literature published between 2000 and 2024 was conducted, following PRISMA guidelines and utilizing the snowball technique. Of the 398 articles identified, along with five additional articles, 61 were finally reviewed. The results highlight promising AI applications, including the use of patient questionnaires, natural language processing, and imaging for migraine diagnosis, as well as predicting treatment responses and forecasting migraine attacks. Nonetheless, challenges remain in improving the accuracy, generalizability, validation, and clinical relevance of AI applications. Despite the substantial promise of AI for improving migraine management, it does not always guarantee better results than traditional methods. Careful consideration of the study design and method selection is crucial. Additionally, the interpretation of AI-generated results, particularly those from generative models, requires caution to avoid potential pitfalls.

Keywords: Computational, Deep learning, Large language models, Machine learning, Neural network

INTRODUCTION

The evolution of artificial intelligence (AI) has been transformative, significantly impacting various aspects of the medicine, including diagnosis, treatment, research, and the development of medical devices. However, the application of AI in the field of headache disorders, including migraine, has been relatively slow. A meta-analysis published in 2020 revealed that only four (<1%) of the 985 selected articles published on Google Scholar between 2010 and 2019 that utilized deep learning (DL) techniques focused on migraine. In contrast, 303 (40%), 161 (21%), and 131 (18%) of these articles addressed Alzheimer's disease, autism, and epilepsy, respectively.[1] Nevertheless, research, tools, and applications related to migraine and headache disorders have expanded considerably since then, leading

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to a significant increase in published studies. According to a systematic review of computerized migraine diagnostic tools, the number of such tools has increased by 4.5 times since 2005, compared to the period before 2005.[2]

The current concept of AI and its application in the field of headache disorders is summarized in Figure 1. Briefly, AI can be categorized into symbolic and statistical methods. The symbolic method is based on logic and rule-based reasoning, using knowledge as inputs to produce knowledge that can be directly interpreted.[3] Statistical methods generally rely on raw, continuous inputs and use statistical techniques to produce associations that need to be interpreted with background knowledge.

Examples of symbolic AI include Deep Blue for chess gameplay and MYCIN in the medical field, a computer-based consultation system designed to assist physicians in the diagnosis and therapy selection for patients with bacterial infections.[4]

The evolution of computer systems has driven the rapid advancement of AI technologies, particularly in the area of statistical AI. Statistical methods can be divided into 'supervised' and 'unsupervised' learning, based on whether they have answers, known as 'labels.' Machine learning (ML) is a type of statistical AI that involves algorithms for data-driven pattern analysis, decision-making, and prediction. Among ML algorithms, neural networks are models inspired by the human neural network. Among artificial neural networks (ANN), convolutional neural networks (CNN) are better suited for image analysis, while recurrent neural networks and long short-term memory networks are more appropriate for linear and wavelet data. DL refers to neural network algorithms with multiple, deep layers.

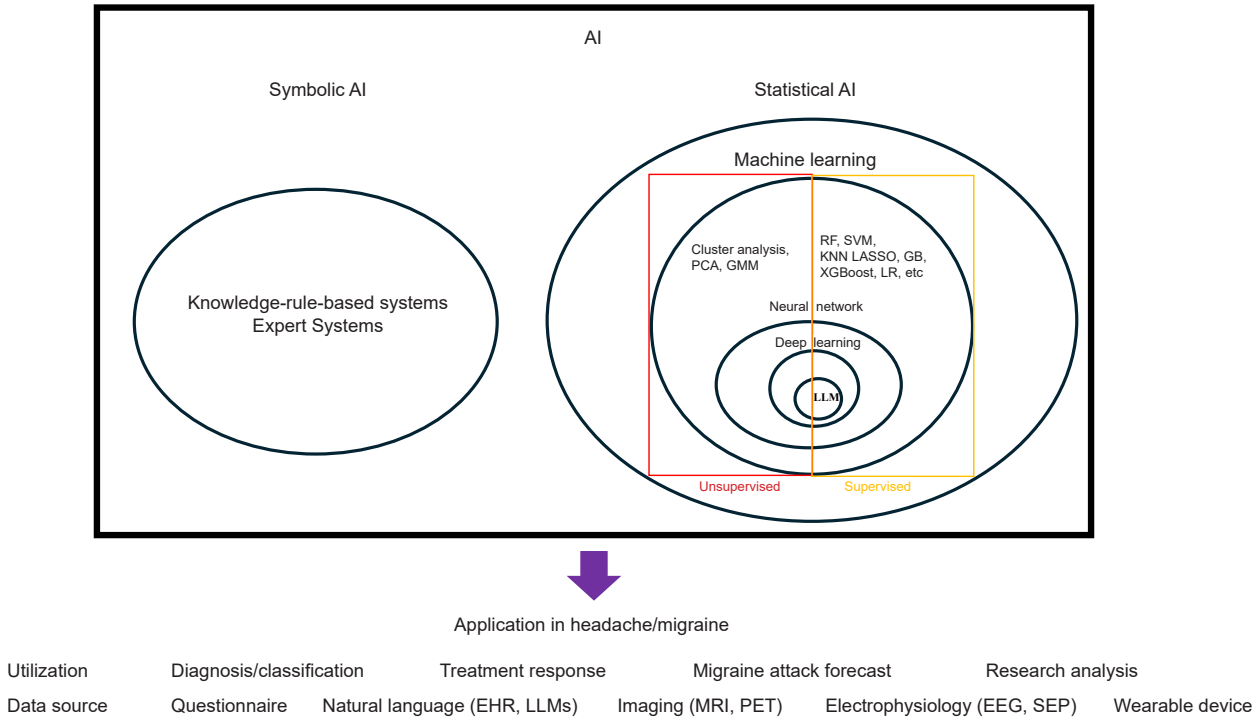

Figure 1. Schematic diagram of AI and its applications in the headache field AI can be divided into symbolic and statistical methods. Machine learning, neural networks, deep learning, and LLMs are examples of statistical methods. These methods can also be categorized as unsupervised or supervised based on their use of labeled data. The applications of AI in headache and migraine can be analyzed in terms of its utilization and the data source.
AI, artificial intelligence; PCA, principal component analysis; GMM, Gaussian mixture models; RF, random forest; SVM, support vector machine; KNN, K-nearest neighbor; LASSO, least absolute shrinkage and selection operator; GB, gradient boosting; XGBoost, extreme gradient boosting; LR, logistic regression; LLM, large language model; EHR, electronic health records; MRI, magnetic resonance imaging; PET, positron emission tomography; EEG, electroencephalography; SEP, somatosensory evoked potentials.

Numerous DL architectures are available, each proven effective for specific type of data.

Utilization of AI in headache medicine can be categorized into several key areas: diagnosis or classification of headache disorders, assessment of treatment response, forecasting of migraine attacks, and as a tool for analysis during research. Regarding data sources and methods, AI applications utilize a range of inputs including questionnaires, language data (e.g., generative language models or electronic health records [EHR]), medical devices or tools such as magnetic resonance imaging (MRI), results from electrophysiology studies (e.g., electroencephalography [EEG], somatic evoked potential [SEP]), and wearable devices, either individually or in combination. This review aims to outline the current use and role of AI in the field of headache disorders, with a focus on migraine, and to discuss future perspectives.

METHODS

1. Search strategies

Although this is not a systematic review, the search process was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] A literature search was performed in PubMed using the following terms: ((migraine*) AND ((artificial*) OR (artificial intelligence*) OR (AI*) OR (deep learning*) OR (machine learning*) OR (artificial intelligence [MeSH Terms]) OR (AI [MeSH Terms]) OR (deep learning [MeSH Terms]) OR (machine learning [MeSH Terms])))

The search was restricted to literature published between 1 January 2000 and 31 July 2024. Only abstracts in the English language were included for review.

2. Inclusion and exclusion criteria

In reviewing abstracts, only studies that explicitly included AI, ML, or DL methods in their analytical processes were considered for inclusion. Studies where the authors used ML or DL methods but did not specify this in the abstract were excluded. Semi-automated approaches that involved computational methods alongside expert-suggested algorithms were included if they were specified as AI-based methods or if they were well-organized for comparative review. Medical tools, including imaging techniques such as MRI and positron emission tomography (PET), electrophysiology methods such as EEG and SEP, magnetoencephalography (MEG), and other devices such as wearable technologies, were included if the analytical methods utilized AI techniques. Review articles, editorials, opinions, and viewpoints were considered for snowballing purposes but were generally excluded from the systematic review. Additionally, studies for which the full text was unavailable or not published in English were excluded. Manuscripts were further excluded if they employed inappropriate methodologies, such as not applying the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria, or if they involved improper headache diagnosis or did not specify headache participants.

RESULTS

1. Search results and article inclusion/exclusion

Of the 398 articles identified, one was a duplicate and 317 were excluded based on abstract review. Of the remaining 80 articles, six were review articles, four were editorials or opinion pieces, two did not utilize AI methodology, one was not related to the headache field, seven did not adhere to ICHD-3 criteria or did not specify headache diagnosis methods, and four had full texts that were unavailable. An additional five articles were identified through the snowball technique. In total, 61 articles published between 2002 and 2024 were included in the review, with the majority published since 2020. The PRISMA flow chart outlining the selection process is shown in Figure 2. The summaries of the included studies are demonstrated in Table 1.

ARTIFICIAL INTELLIGENCE APPLICATIONS IN THE DIAGNOSIS OF HEADACHE DISORDERS

1. Questionnaire/survey

Traditionally, questionnaires have been valuable tools in aiding the diagnosis of headache disorders, given that such diagnoses are typically based on clinical profiles. Furthermore, previously collected data from these questionnaires facilitates the swift and effective application of AI technology.

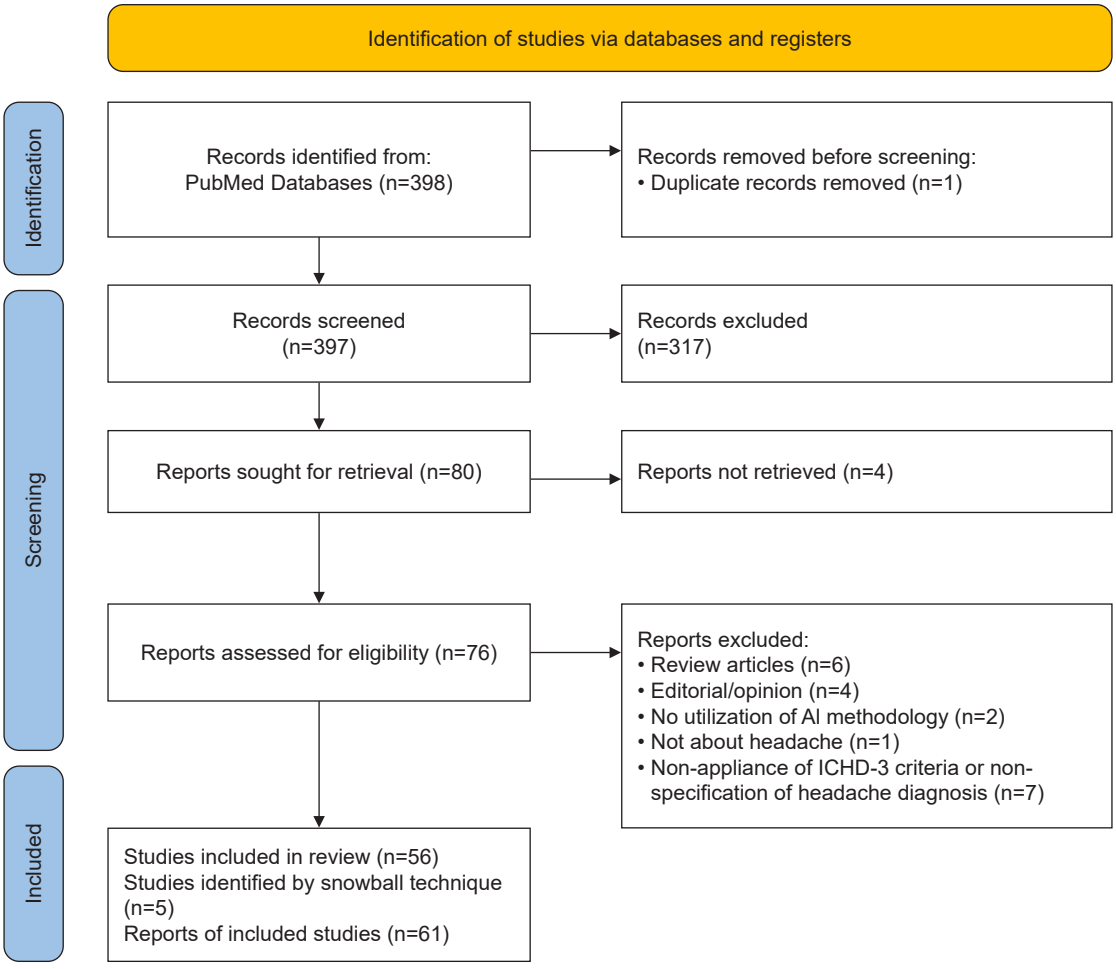

Figure 2. PRISMA 2020 flow diagram.[5]
AI, artificial intelligence; ICHD-3, International Classification of Headache Disorders, 3rd edition.

The number of items in the questionnaires varied from 17–22[6-12] to 75.[13] While the details differed, all questionnaires included demographic data (age, sex), headache characteristics, duration, frequency, and accompanying symptoms.

The number of participants and the number of classifying groups varied across studies. Liu et al.[6] distinguished between 84 migraine and 89 tension-type headache (TTH) participants using a 19-item questionnaire. Simić et al.[7] utilized a 20-item questionnaire to classify 1,022 subjects, identifying 169 with migraine, 224 with TTH, and 186 with other headache types. Kwon et al.[13] employed a 75-item questionnaire from a headache center to classify 2,162 individuals with headache disorders, including migraine, TTH, trigeminal autonomic cephalalgias (TAC), epicranial headaches, and thunderclap headaches.

Most studies utilized supervised ML methods, including decision trees (DTs), random forests (RFs), gradient boosting (GB), logistic regression (LR), and support vector machines (SVMs). The performances were presented with sensitivity, specificity, accuracy, area under the receiver operating characteristic curve (AUROC), and F1 score. The F1 score is the harmonic mean of precision and recall ($2 \times \frac{precision \times recall}{precision + recall}$), where precision is calculated as ($\frac{True\ Positive}{True\ Positive + False\ Positive}$) and recall is calculated as ($\frac{True\ Positive}{True\ Positive + False\ Negative}$). The F1 score is particularly useful for evaluating predictive performance, especially when the dataset is imbalanced.

Kwon et al.[13] used a stacked classifier model with four layers of eXtreme Gradient Boosting (XGBoost) classifiers, each layer classifying migraine, TTH, TAC, epicranial headaches, and thunderclap headaches. Different features

Table 1. Summary of studies involving AI in the headache field

Purpose	Data source	Study	Year	AI method	AI method specification
Diagnosis					
	Questionnaire	Kwon et al.[13]	2020	ML	Stacked classifier model with four layers of XGBoost classifiers, LASSO
	Questionnaire	Liu et al.[6]	2022	ML	RF, GB, LR, SVM
	Questionnaire/NL	Katsuki et al.[14]	2020	DL	NLP, ANN
	Questionnaire	Simić et al.[7]	2021	Hybrid system	Calinski-Harabasz index, Analytical Hierarchy Process, and Weighted Fuzzy C-means Clustering algorithm (ML)
	Questionnaire	Katsuki et al.[10]	2023	ML	GB, LR, Ridge Classifier, RF, Extra Trees Classifier, K Neighbors Classifier, Dummy Classifier, DT, SVM, AdaBoost Classifier, LDA, Naïve Bayes, QDA, best performance: GB
	Questionnaire	Katsuki et al.[8]	2023	ML	Light GB machine, RF, LDA, Ridge Classifier, Extra Trees, GB Classifier, LR, AdaBoost Classifier, DT, K Neighbors, Naïve Bayes, Dummy Classifier, SVM, QDA, best performance: light GB machine classifier
	Questionnaire	Sasaki et al.[12]	2023	ML	Light GB machine, RF, LDA, Ridge Classifier, Extra Trees, GB Classifier, LR, Ada Boost Classifier, DT K Neighbors, Naïve Bayes, Dummy Classifier, SVM, QDA, best performance: extremely randomized trees
	Questionnaire	Okada et al.[11]	2024	ML	Light GB machine classifier
	NL	Vandenbussche et al.[20]	2022	NLP/ML	NLP, LR, SVM
	NL (EHR)	Riskin et al.[19]	2023	NLP/ML	Not specified
	Questionnaire/MRI	Chong et al.[23]	2021	ML	PCA, logistic classifier
	Clinical data/MRI	Dumkrieger et al.[24]	2023	ML	Ridge LR on principal component
	MRI	Rahman Siddiquee et al.[25]	2022	DL	ResNet-18
	MRI	Mitrović et al.[21]	2023	ML	LDA
	MRI	Mitrović et al.[22]	2023	ML	SVM
	Resting-state fMRI	Chong et al.[29]	2017	ML	Diagonal QDA
	Resting-state fMRI	Yang et al.[31]	2018	ML, DL	SVM, CNN
	Resting-state fMRI	Tu et al.[26]	2020	ML	Recursive feature elimination, SVM, LOOCV
	Resting-state fMRI	Nie et al.[27,28]	2021; 2023	ML	K-means clustering, hierarchical clustering, SVM
	Resting-state fMRI	Fernandes et al.[30]	2024	ML	Gaussian Process Classifier
	MEG	Hsiao et al.[32]	2022	ML	SVM
	MEG	Hsiao et al.[33]	2023	ML	DT, discriminant analysis, naïve Bayes classifiers, SVM, KNN
	EEG	Akben et al.[39]	2012	ML	MLP
	EEG (wearable)	Cao et al.[40]	2018	ML	LDA, KNN, MLP, Bayesian classifier, SVM
	EEG	Frid et al.[37]	2020	ML	Relif Family algorithm, SVM
	EEG	Aslan[38]	2021	ML	Rotation Forest, BFTree, RF, Bagging, AdaBoost, SPAARC, MultiBoost, Random Tree, NBTree ensemble classifiers
	EEG	Hsiao et al.[35]	2023	ML	DT, discriminant analysis, naïve Bayes classifiers, SVM, KNN
	EEG	Orhanbulucu et al.[36]	2023	DL	AlexNet, ResNet50, SqueezeNet
	SEP	Zhu et al.[42]	2019	ML, DL	RF, XGBoost trees, SVM, KNN, MLP, LDA, LR, CNN
	ECG	Chiang et al.[41]	2022	DL	CNN
	Headache diary application/wearable device	De Brouwer et al.[43]	2022	ML	Knowledge-based classification, ML-based detection of activity, stress, sleep events

(Continued to the next page)

Table 1. Continued

Purpose	Data source	Study	Year	AI method	AI method specification
	Functional near-infrared spectroscopy	Chen et al.[44]	2022	ML	LDA, QDA
Treatment efficacy/response					
	Web-based survey	Ashina et al.[47]	2024	ML	RF, LASSO
	NL (EHR)	Hindiyeh et al.[48]	2022	NLP	Not specified
	NL (social media)	Guo et al.[49]	2023	NLP	Transformer-based models
	NL (EHR)	Chiang et al.[50]	2024	NLP framework	ClinicalBERT regression model, GPT-2 Question Answering model zero-shot, GPT-2 QA model few-shot training fine-tuned on clinical notes, GPT-2 generative model few-shot training fine-tuned on clinical notes
	NL (generative LLM)	Moskatel and Zhang[52]	2023	LLMs	ChatGPT-3.5
	NL (generative LLM)	Li et al.[51]	2024	LLMs	ChatGPT-3.5, ChatGPT-4.0, Google Bard, Meta Llama2, and Anthropic Claude2
	Clinical dataset	Ferroni et al.[57]	2020	ML	SVM, random optimization
	Clinical dataset	Lu et al.[53]	2022	ML	SVM, DT, MLP
	Clinical dataset	Gonzalez-Martinez et al.[55]	2022	ML	RF, Bayesian search optimization method
	Clinical dataset	Stubberud et al.[56]	2022	ML, NLP	Multitask Gaussian process model, NLP
	Clinical dataset	Ciancarelli et al.[58]	2022	Neural network	ANN
	Clinical dataset	Martinelli et al.[54]	2023	ML, neural network	RF, SVM, ANN, adaptive neuro-fuzzy inference system, fuzzy c-means clustering
	Clinical dataset/MRI	Tso et al.[62]	2021	ML	PCA, t-distributed stochastic neighbor embedding, KNN, XGBoost implemented GB DT
	MRI, fMRI	Wei et al.[59]	2023	DL, ML	ResNet34, ResNet50, RexNeXt50, DenseNet121, 3D ResNet18,, best performance: ResNet-18 /SVM
	Multimodal MRI	Wei et al.[60]	2024	ML	LASSO, LR, SVM-recursive feature elimination for Feature selection / LR, SVM, RF, DT, KNN, MLP elastic network, light GB machine, XGBoost for classification, best performance: RF
	PET	Marino et al.[61]	2023	ML	CBDA
Migraine attack prediction					
	Wearable device	Siirtola et al.[65]	2018	ML	QDA, LDA
	Headache diary application/wearable device	Stubberud et al.[64]	2023	ML	LR, SVM, RF, GB, Adaptive boosting, XGBoost, best performance: RF
	Headache diary application/weather data	Katsuki et al.[9]	2023	ML, neural network	Generalized linear mixed model, feedforward neural network, XGBoost
Research					
	Cortical-evoked potentials in response to repetitive visual/auditory stimulus	Thomas et al.[68]	2002	Neural network	Neural network model
	Mouse grimace scale	Chiang et al.[67]	2022	DL	ResNet-18
	Temporal multi-omics profile	Kogelman et al.[66]	2023	ML	Qlattice

AI, artificial intelligence; ML, machine learning; XGBoost, extreme gradient boosting; LASSO, least absolute shrinkage and selection operator; RF, random forest; GB, gradient boosting; LR, logistic regression; SVM, support vector machine; NL, natural language; DL, deep learning; NLP, natural language processing; ANN, artificial neural network; DT, decision tree; LDA, linear discriminant analysis; QDA, quadratic discriminant analysis; EHR, electronic health records; MRI, magnetic resonance imaging; PCA, principal component analysis; fMRI, functional MRI; CNN, convolutional neural network; LOOCV, leave-one-out cross-validation; MEG, magnetoencephalography; KNN, K-nearest neighbor; EEG, electroencephalography; MLP, multilayer perceptron; BFTree, best first decision tree; SPAARC, sequential pattern-aided adaptive response classification; NBTree, naïve Bayes decision tree; SEP, somatosensory evoked potentials; ECG, electrocardiogram; ClinicalBERT, clinical bidirectional encoder representations from transformers; GPT, generative pre-trained transformer; LLMs, large language models; PET, positron emission tomography; CBDA, Compressive Big Data Analytics.

were selected from the self-reported data at each layer using the least absolute shrinkage and selection operator (LASSO). The model achieved an accuracy of 81% for the test set. The sensitivity and specificity for migraine, TTH, TAC, epicranial headache, and thunderclap headache were 88% and 95%, 69% and 55%, 65% and 46%, 53% and 48%, and 51% and 51%, respectively.[13]

In contrast, Simić et al.[7] proposed a hybrid system incorporating the Calinski-Harabasz index, Analytical Hierarchy Process, and Weighted Fuzzy C-means Clustering algorithm, an unsupervised ML method. The accuracy rates were 67% for migraine, 74% for TTH, and 86% for other primary headaches, with corresponding F1 scores of 75%, 74%, and 75%, respectively.[7]

The Japanese research group, led by Katsuki, Yamamoto, Sasaki, and Okada, along with other co-authors, has published multiple articles utilizing questionnaires and AI methods. In their first study, published in 2020, they used a combination of questionnaires, unstructured descriptions, and DL methods to classify primary headaches among 848 participants, with 46% diagnosed with migraine, 47% with TTH, and 5% with TAC.[14] Natural language processing (NLP) was employed using the commercial DL framework, Prediction One, and an ANN model was applied. The model achieved an accuracy of 0.7759, a mean precision of 0.8537, a mean recall of 0.6086, and a mean F1 score of 0.6353.

In subsequent studies, the same group used a 17- or 22-item questionnaire along with multiple AI methods to classify five to six different outcomes: migraine and medication-overuse headache (MOH) separately or together as migraine/MOH, TTH, TACs, other primary headaches, and other headaches.[10] Among the 6,058 participants, there were 4,829 cases of migraine, 834 cases of TTH, 78 cases of TACs, 38 cases of other primary headache disorders, and 279 cases of other headaches. The GB classifier yielded the highest c-statistic of 0.88. The c-statistic, equivalent to the AUROC, measures a classification model's ability to discriminate between classes, with higher values indicating better performance. The model's accuracy, sensitivity, specificity, precision, and F1-score were 93.7%, 84.2%, 84.2%, 96.1%, and 84.2%, respectively.

The AI model's performance was compared with that of non-headache specialists, and its usefulness in aiding headache diagnosis was evaluated using data from a study of 4,000 patients.[8] The light GB machine classifier achieved the highest c-statistic of 0.9203. The diagnostic accuracy of five non-headache specialists was then compared to that of the AI model using a sample of 50 patients. Without the AI model, the non-specialists' overall diagnostic accuracy was 46%, with a kappa value of 0.212. With the aid of the AI model, their accuracy and kappa value improved significantly to 83.2% and 0.678, respectively. External validation of the AI model's diagnostic performance using a sample of 59 participants demonstrated an overall accuracy of 94.92% and a kappa value of 0.65 (95% confidence interval [95% CI], 0.21–1.00) when compared to the ground truth. The sensitivity, specificity, precision, and F1-score for diagnosing migraines were 98.21%, 66.67%, 98.21%, and 98.21%, respectively.[11]

The application of the system in pediatric and adolescent populations was also validated. Sasaki et al.[12] used multiple AI models to diagnose 909 participants aged 6 to 17 years, including 234 individuals with migraine. For the test dataset, the model achieved an accuracy of 94.5%, sensitivity of 88.7%, specificity of 96.5%, precision of 90.0%, and an F1-score of 89.4%.

However, non-AI methods and rule-based decision systems have also demonstrated impressive results. For example, a web-based headache diagnosis questionnaire validated by telephone interviews showed a sensitivity of 92.6%, a specificity of 94.8%, and a kappa coefficient of 0.875 for diagnosing migraine among 256 participants. For the diagnosis of TTH and probable migraine (PM), the sensitivity, specificity, and kappa coefficients were 78.4%, 98.4%, and 0.809, and 85%, 92.9%, and 0.757, respectively.[15]

Computerized systems based on expert opinions have also proven effective. In 2008, Maizels and Wolfe[16] developed a Computerized Headache Assessment Tool (CHAT) using web-based questionnaires with branching questions based on headache frequency, duration, and ICHD criteria. Among 135 participants who completed CHAT and 117 who completed a diagnostic interview, CHAT correctly identified 35/35 cases (100%) of episodic migraine (EM), 42/49 cases (85.7%) of transformed migraine, 11/11 cases of chronic TTH, 2/2 cases of episodic TTH, and 1/1 case of episodic cluster headache (CH). It also identified medication overuse in 43/52 cases (82.7%), with the most common misdiagnosis being transformed migraine or new daily persistent headache.

In another study by Cowan et al.[17], the concordance between a self-administered, computer-based diagnostic engine (CDE) and a semi-structured interview conducted by a headache specialist was assessed. The CDE, developed by the authors using a detailed DT, was completed by 212 participants, who also underwent an interview. For diagnosing migraine and PM, the CDE demonstrated a sensitivity of 90.1% and a specificity of 95.8%, with a concordance rate with SSI of κ=0.83 (95% CI, 0.75–0.91).

These expert-based systems, built on transparent decision-making processes using ICHD-3 criteria, exhibit high sensitivity and specificity. In contrast, AI operates as a "black-box" system, where the decision-making process is not easily interpretable. While AI models may demonstrate high accuracy, careful interpretation according to current knowledge is necessary, and biases of the data may result in subpar prediction results.[18] Questions remain as to whether current AI offers real advantages beyond being novel and innovative. The challenge remains validating AI models and ensuring their effective application in real-world settings.

2. Natural language

Natural language as a data source in headache research holds significant potential, especially in aiding practitioners and saving time. Many patient interviews are naturally conducted in unstructured language, which doctors traditionally summarize and interpret to make a diagnosis. While structured questionnaires have been used to standardize this natural language, the raw language itself may contain even more valuable information. In this context, natural language includes any unstructured text, such as EHRs and generative large language models (LLMs). However, studies utilizing generative LLMs have predominantly focused on assessing treatment response rather than diagnosis and classification. Three studies were identified in the area of diagnosis and classification, with one integrating questionnaire data and natural language, as previously discussed in the questionnaire section.

Riskin et al.[19] used US claims and EHR data from 2010 to 2012 to compare the efficacy of migraine identification. They defined "Traditional Real-World Evidence (RWE)" as the use of insurance claims or structured EHR data, while "Advanced RWE" was defined as the use of unstructured EHRs. Although the exact AI-based technology was not specified, an ML algorithm was employed. Based on manual annotation by seven annotators, 2,642 migraine and 6,530 headache-related concepts were identified, and their recall rates were compared. "Traditional RWE" achieved recall rates of 66.6% and 29.6%, while "Advanced RWE" recalled 96.8% and 92.9%, respectively. The superior performance of "Advanced RWE" was consistent across the identification of six migraine-associated symptoms, with F1 scores ranging from 80.7% to 95.6%.

Vandenbussche et al.[20] conducted a web-based survey in which 81 migraine and 40 CH patients were asked to describe their headache disorders in detail. NLP was applied to analyze the narrative self-reports, focusing on lexical, semantic, and thematic properties. Lexicon-based sentiment analysis of attack descriptions revealed predominantly negative sentiments. For the classification of migraine and CH using features from the attack descriptions, LR and SVM algorithms demonstrated the best performance, with F1 scores ranging from 0.6 to 0.8. There was a significant difference between Dutch-speaking migraine and CH patients in how they described their disorder. Migraine patients used the Dutch word for "headache" more often, while CH patients more frequently used the word "pain."

3. Imaging

Numerous studies have employed brain imaging techniques, such as MRI, functional MRI (fMRI), and PET, analyzed with ML and DL methods to differentiate and classify headache disorders, particularly migraine.

Mitrović et al.[21] analyzed brain MRI data from a cohort including healthy controls (HCs) and patients with migraine with aura (MwA). Cortical thickness, surface area, and volume were compared using various ML methods.[21] The best classification results were obtained with linear discriminant analysis (LDA), achieving 97% accuracy for MwA. Left temporal pole, right lingual gyrus, and left pars opercularis thickness were notable distinguishing features. Further research used the average Migraine Aura Complexity Score (MACS) from multiple MwA attacks and evaluated its correlation with 340 MRI features.[22] Applying ML methods including SVM, a high coefficient of determination (0.89) was achieved, with 26 significant features including left parahippocampal mean Gaussian curvature,

left transverse temporal mean Gaussian curvature, left transverse temporal thickness, and left pars opercularis thickness ($p<0.01$) strongly correlating with average MACS ($p<0.05$).

Chong et al.[23] combined questionnaire data with T1-weighted MRI and diffusion tensor imaging, to distinguish between migraine and persistent post-traumatic headache (PTH) attributed to mild traumatic brain injury. A logistic classifier achieved an overall accuracy of 78%, with 97.1% accuracy for migraine and 64.6% for PTH. Critical features contributing to accuracy included responses related to anxiety on sports concussion Assessment Tool and decision-making difficulty on Beck Depression Inventory-13, as well as cortical brain regions such as the bilateral superior temporal gyrus, inferior parietal lobe, posterior cingulate cortex, and fiber tracts like the right anterior thalamic radiations and right superior longitudinal fasciculus. Additional study utilized clinical data, along with MRI measures of brain structure and functional connectivity.[24] A classifier using ridge LR on principal components achieved an average accuracy of 72% when using functional connectivity data, and 63.4% without it. In addition, a DL method was developed using a 3D ResNet-18 classifier to automatically identify features that differentiate MRIs of 95 migraine patients, 48 with acute PTH, 49 with persistent PTH, and 532 HCs. The 3D ResNet-18 classifier, an 18-layer CNN based DL architecture for image analysis, adapted for 3D convolutions, achieved an accuracy of 75%, a sensitivity of 66.7%, and a specificity of 83.3% in distinguishing migraine from HCs. The most significant biomarkers identified by the migraine classifier included the caudate, caudal anterior cingulate, superior frontal gyrus, thalamus, and ventral diencephalon.[25]

Resting-state fMRI has been frequently analyzed in migraine research, utilizing various ML and DL techniques for feature extraction and classification. Several studies compared migraineurs and HCs.

Tu et al.[26] examined 70 migraine without aura (MwoA) patients and 46 matched HCs, identifying abnormal functional connectivity within the visual network (VN), default mode network (DMN), sensorimotor network (SMN), and fronto-parietal networks that distinguished migraineurs from HCs using an SVM model with 93% sensitivity and 89% specificity. The model was validated on an independent cohort of 19 MwoA patients and 19 additional controls, achieving 84% sensitivity and specificity. To verify specificity, the model was tested on 18 MwoA patients and 76 non-migraine pain patients (with chronic lower back pain and fibromyalgia), demonstrating 78% sensitivity and 76% specificity for distinguishing migraineurs from non-migraineurs.

Nie et al.[27] applied both unsupervised and supervised ML techniques. Using an automatic segmentation algorithm, K-means clustering combined with hierarchical clustering identified 17 dynamic functional connectome patterns (DFCPs).[27] SVM was used to select optimal features from static functional connectivity strength and DFCP features and to classify migraine patients and HCs.[28]

Chong et al.[29] used diagonal quadratic discriminant analysis (QDA), an ML algorithm to analyze functional connections from 33 seeded pain-related regions of 58 migraine patients and 50 HCs. Notably, those with an disease duration of more than 14 years were classified more accurately (96.7% vs. 82.1%).

MwA was also examined in several studies. Fernandes et al.[30] used Gaussian Process Classifier to differentiate between ictal and interictal periods in two patients with MwA.

Yang et al.[31] analyzed the amplitude of low-frequency fluctuations, regional homogeneity, and regional functional correlation strength to distinguish 21 patients with MwoA, 15 with MwA, and 28 HCs. SVM classifier achieved an accuracy of 83.67%, whereas a CNN approach based on the Inception module improved accuracy to 86.18%.

4. Electrophysiology and magnetoencephalography

Wavelet data from electrophysiology studies, including EEG and SEP, have also been utilized for the diagnosis and classification of migraine. Analyzing these data often requires transformations, such as Fourier transformation, to process the complex signals. MEG has also been employed in the analysis of headache disorders and, in this review, is included in this section due to its time-dependent data acquisition characteristics. Studies utilizing EEG and MEG signals have been conducted to differentiate migraine from other conditions.

Hsiao et al.[32] conducted multiple studies utilizing MEG. In 2022, resting-state MEG data from 70 HCs, 100 chronic migraine (CM) patients, 35 EM patients, and 35 FM pa-

tients were analyzed to calculate source-based oscillatory connectivity in relevant cortical regions.[32] Using a SVM classifier, a model was developed to identify CM. The salience, SMN, and parts of the DMNs were key features differentiating CM from HCs, with classification performance showing an accuracy of ≥86.8% and an area under the curve (AUC) of ≥ 0.9. When comparing CM to EM, the model achieved an accuracy of 94.5% and an AUC of 0.96, and for CM versus FM, an accuracy of 89.1% and an AUC of 0.91. In 2023, resting-state MEG data of 70 HCs, 100 CM, 40 CM with FM, 35 FM, 30 chronic TTH, and 75 EM were analyzed.[33] Features were extracted and classified using ML algorithms including DT, discriminant analysis, naïve Bayes classifiers, SVM, and K-nearest neighbor (KNN). The best classification model distinguished CM from HCs with an accuracy of over 92.6% and an AUC of over 0.93. When validating CM classification against other groups, accuracy exceeded 75.7%, with an AUC greater than 0.8.

Although EEG is not routinely recommended in headache practice, its application in headache research has persisted.[34] EEG signals have been utilized to classify HCs, migraine patients, CM patients,[35,36] and to differentiate between MwA and MwoA.[37] EEG signals were recorded during resting state, visual or auditory stimulation tasks, or non-painful, painful, and repetitive painful electrical stimulation. Various signal processing techniques were applied, such as the tunable Q-factor wavelet transform method to decompose EEG signals into sub-bands[38] and segmentation of a 3-minute EEG into 120 1-second segments, generating 325 functional connectivity values between electrode pairs.[37] Most studies employed ML models. However, in one study, EEG signals were transformed into scalogram-spectrogram images and classified using CNN architectures, including AlexNet, ResNet50, and SqueezeNet.[36]

Akben et al.[39] in 2012 compared different flash stimulation frequencies (2 Hz, 4 Hz, and 6 Hz) and durations (2 seconds, 4 seconds, 6 seconds, and 10 seconds) to determine the most effective conditions for detecting migraine. EEG was recorded during flash stimulation in 15 migraine patients and 15 HCs. The power spectral density estimate was computed, and a multilayer perceptron (MLP) neural network was used for classification. The study found that a 4 Hz flash stimulation frequency and an 8-second duration were most effective in detecting migraine, particularly at the beta band of the T5-T3 channel.

In another study by Cao et al.[40], a wearable, wireless EEG device (Mindo-4S) was used to record EEG signals from the prefrontal (Fpz) and occipital (O1, Oz, O2) regions to differentiate 40 MwoA patients from 40 HCs. EEGs from interictal, pre-ictal, ictal, and post-ictal phases were processed, and a binary classification model was developed using LDA, KNN, MLP, Bayesian classifier, and SVM. The SVM demonstrated the highest accuracy (76%±4%) for classifying interictal and pre-ictal phases using prefrontal EEG complexity.

Chiang et al.[41] analyzed the electrocardiogram (ECG) data of 17,840 participants with MwA and 22,162 participants with MwoA, excluding those with a history of atrial fibrillation (AF). The team employed an AI-ECG algorithm, developed using a CNN-based approach, to calculate the probability of concurrent paroxysmal or impending AF in ECGs showing normal sinus rhythm. The AF prediction model output was significantly higher in the MwA group compared to the MwoA group (mean [standard deviation], 7.3% [15.0%] vs. 5.6% [12.4%]; mean difference [95% CI], 1.7% [1.5%–2.0%]; p<0.001). These differences remained significant even after adjusting for vascular comorbidities, suggesting a higher probability of concurrent paroxysmal or impending AF in individuals with MwA compared to those with MwoA.

Although not as extensively researched, SEP have also been investigated in the context of migraine. Zhu et al.[42] utilized SEP data to differentiate between 42 migraine patients (29 in the interictal phase and 13 in the ictal phase) and 15 HCs. The right median nerve SEPs were recorded, and features in both the time and frequency domains were selected through a feature selection method. The data were then classified using various ML algorithms, including RF, XGBoost trees, SVM, KNN, MLP, LDA, and LR. The classification accuracies for distinguishing HCs, ictal, and interictal phases ranged from 51.2% to 72.4%. After model and feature selection, the accuracy improved to 89.7% for HC-ictal, 88.7% for HC-interictal, 80.2% for ictal-interictal, and 73.3% for HC-ictal-interictal classification. Interestingly, a tested CNN-based model showed lower performance compared to the ML-based models.

5. Wearables and other devices

De Brouwer et al.[43] utilized the Empatica E4 wearable device (Empatica Inc., Cambridge, MA, USA) along with a custom-made application to maintain a diary of headache-specific data. The device employed data-driven ML algorithms to detect activity, stress, and sleep events. Individual headache attacks were classified based on a knowledge-based classification system, focusing on migraine, CH, and TTH. A total of 133 headache attacks from 14 migraine and four CH patients were analyzed. The strict application of ICHD-3 criteria resulted in the classification of eight out of 98 MwoA attacks and 0 out of 35 CH attacks. However, an adapted version of the criteria, which modified the headache duration for treated and terminated episodes, improved classification to 28 out of 98 MwoA attacks and 17 out of 35 CH attacks. The device also collected data on activities and stress events, which were confirmed in 46% and 59% of cases, respectively, indicating the potential link between headache and physiological data, although further improvement is warranted.

Functional near-infrared spectroscopy was employed to measure changes in hemoglobin levels in the prefrontal cortex during a mental arithmetic task, with the data used to classify 13 HCs, nine CM patients, and 12 MOH patients.[44] ML techniques, including LDA and QDA, were applied in both direct and stepwise classifications. The resulting model achieved a sensitivity of 100% and a specificity of 75% in classifying CM patients.

The statistical application of AI is particularly well-suited for use in classification tasks, especially when applied to data sources such as brain imaging, electrophysiology, wearable devices, or other measurable inputs. These data sources provide numerous inputs, and the diagnosis of headache disorders offers clearly defined target labels, facilitating the use of AI in generating accurate classifications. As demonstrated in the studies presented, these methods often yield favorable accuracies and show significant potential. However, the application of these AI methods in real-world clinical settings remains uncertain. A meta-analysis on the real-world accuracy of wearable activity trackers for detecting COVID-19, AF, and falls reported sensitivities of 79.5%, 94.2%, and 81.9%, and specificities of 76.8%, 95.3%, and 62.5%, respectively.[45] Notably, the highest accuracy was observed in detecting AF, which is primarily diagnosed using wavelet-transformed data from ECG signals. In contrast, the gold standard for diagnosing headache disorders is patient interviews, and interpreting headache diagnoses classified by complex wavelet data presents significant challenges. Additionally, randomized controlled studies are limited in demonstrating the benefits of AI or comparing with gold standard methods.[18] Also most studies, except for the ECG study by Chiang et al.[46], involved a small number of participants, raising concerns about the generalizability of these AI applications to broader populations.

ARTIFICIAL INTELLIGENCE APPLICATIONS IN THE ASSESSMENT OF TREATMENT EFFICACY AND RESPONSE IN HEADACHE DISORDERS

Assessing treatment response is a crucial aspect of clinical practice. Identifying responders and non-responders helps avoid ineffective therapies and minimize adverse effects, which is the core principle of precision medicine. This is particularly important when treating patients with headache disorders, especially CM, using costly therapies such as OnabotulinumtoxinA and anti-calcitonin gene-related peptide monoclonal antibodies (anti-CGRP mAb), where non-responders can have significant implications. AI methods have been increasingly utilized to assess or predict the need for treatment, evaluate treatment response, and identify potential good responders.

1. Questionnaire/survey

Ashina et al.[47] conducted a web-based survey involving 31,529 out of 61,826 individuals (51.0%) who had sought medical care for migraine in the previous 12 months. Using ML techniques, including RF and LASSO, the study identified 13 sociodemographic and clinical factors most strongly associated with seeking medical care for migraine. Among these, higher interictal burden, disability, and allodynia were particularly significant factors.

2. Natural language

NLP of EHRs, generative LLMs have been utilized to assess treatment response, evaluate current treatment status, and analyze patient feedback.

Hindiyeh et al.[48] constructed a migraine outcome model based on headache severity (mild, moderate, severe), headache descriptors (pulsating, debilitating, stabbing), headache progression, and associated symptoms (nausea, vomiting, photophobia, and phonophobia). Each data element was weighted to define a 10-point scale. EHR data from 2018 to 2020 were reviewed, and trained annotators assigned scores. The accuracy of "traditional approaches" and "advanced approaches" was compared. From 2,006 encounters, the average F1 score for automated extraction was 92.0% for AI applied to unstructured data (advanced approach).

Guo et al.[49] developed a platform-independent text classification system to automatically detect and analyze self-reported migraine-related posts. Texts from Twitter and Reddit were manually labeled, and six transformer-based models were used to classify posts as positive if at least one sentence within the post was identified as self-reporting. The best system achieved an F1 score of 0.9 on Twitter and 0.93 on Reddit, demonstrating minimal bias. Treatment-related information and associated sentiments were also analyzed. This study suggests the potential for analyzing treatment response based on real-time, real-world self-reports, outside of traditional hospital settings or headache diaries, which could reduce recall bias.

Chiang et al.[50] performed a retrospective cross-sectional study from two tertiary headache referral centers. A total of 1,915 neurology consultation notes written by 15 specialized clinicians between 2012 and 2022 were extracted. Four NLP frameworks were applied to generate answers and extract headache frequency. Among these, the generative pre-trained transformer 2 (GPT-2) generative model showed the best performance, with an accuracy of 0.92 (95% CI, 0.91–0.93) and an R^2 score of 0.89 (95% CI, 0.87–0.90). All GPT-2–based models outperformed the ClinicalBERT (Bidirectional Encoder Representation from Transformers) model in terms of exact matching accuracy.

Li et al.[51] provided 30 migraine-related queries, including evaluation, definition, testing, diagnosis, treatment, follow-up, prognosis, and special population considerations, to five LLMs (ChatGPT-3.5, ChatGPT-4.0, Google Bard, Meta Llama2, and Anthropic Claude2). The answers were randomly ordered and rated by neurologists.[51] Although the difference in performance was not statistically significant, ChatGPT-4.0 received the highest accuracy ratings, whereas Google Bard had a relatively higher proportion of 'poor' ratings. Notably, there were erroneous recommendations, such as proposing hemicraniectomy for persistent and severe migraine by ChatGPT-3.5.

This study highlights the need for caution among clinicians, researchers, and potential patients when using LLMs for medical purposes. These erroneous recommendations are not just incorrect; they have the potential to cause patient harm. Therefore, the use of LLMs must be managed with caution and public awareness, and further research is warranted.

Another significant caution regarding the use of LLMs for medical advice arises from a study by Moskatel and Zhang.[52] They queried ChatGPT-3.5 on the efficacy of 47 medications for the prevention of migraine and evaluated its responses and citations. The assessments of 33 medications were found to be unreliable, with 66% (76/115) of the citations being hallucinations and 5% (6/115) being erroneous.

3. Clinical dataset

Lu et al.[53] evaluated 610 migraine patients, including 326 who responded to non-steroidal anti-inflammatory drugs (NSAIDs) and those who did not. They extracted potential predictors among demographic and clinical features using multivariable LR analysis.[53] The SVM, DT, and MLP algorithms were used to predict NSAID responsiveness, with the AUC for the test cohort ranging from 0.712 to 0.744 across the three ML methods. Significant predictors identified included disease duration, headache intensity, frequency, anxiety, depression, and sleep disorders.

Martinelli et al.[54] attempted to predict treatment response to OnabotulinumtoxinA in patients with CM and high-frequency episodic migraine. Among the 212 enrolled patients, 35 were classified as excellent responders and 38 as non-responders. The Relif Family feature selection algorithm was used to select demographic and clinical data, which were then analyzed using various ML methods. Although ML methods failed to distinguish good responders from non-responders overall, the RF algorithm in the high-frequency EM group achieved a high classification accuracy of 85.71%. Key predictors of response in the high-frequency EM group included age at migraine onset, opioid use, anxiety subscore on the Hospital Anxiety

and Depression Scale, and Migraine Disability Assessment (MIDAS) score.

Gonzalez-Martinez et al.[55]'s team utilized prospectively collected multicenter dataset of 712 migraine patients receiving anti-CGRP mAb therapies to predict treatment response. The study population was predominantly female (93%), with 84% having CM. A RF-based approach was employed, with hyperparameters selected using a Bayesian search optimization method. Prediction models at 6, 9, and 12 months utilized variables such as headache days per month at each time point and their reduction, migraine days per month at baseline and 3 months, and headache impact test (HIT-6) scores. The F1 scores of the models ranged from 0.70 to 0.97, with AUROC values between 0.87 and 0.98. A calculator tool was subsequently developed and made available online (https://portal.brainguard.life/tools/cgrp.php).

Stubberud et al.[56] utilized clinical data from a retrospective cohort of 1,446 CM patients to estimate individual treatment effects across 10 classes of preventive therapies, including OnabotulinumtoxinA, flunarizine, candesartan, serotonin-noradrenaline reuptake inhibitors, topiramate, tricyclic antidepressants, acupuncture, valproate, beta blockers, and serotonergic agents. The analysis was performed using a causal multitask Gaussian process model. Data were collected through automated extraction using NLP of Microsoft Word template-based clinical records, achieving an accuracy of 90.73% compared to manual extraction. Individual treatment effects were then used to rank the preventive therapies for machine-guided prescription. The machine prescription policy was estimated to reduce time-to-response by 35% (3.750 months; 95% CI, 3.507–3.993; p<0.0001) compared with expert guidelines, with no substantive increase in expense per patient.

Ferroni et al.[57]'s research utilized a dataset of 777 migraine patients with 21% (162) of whom reported MO lasting for at least 2 years, to predict the risk of developing MO. The team developed a customized ML-based decision support system combining SVM and Random Optimization (RO-MO), which was compared to a baseline SVM model. The final RO-MO decision support system, incorporating the top four models, achieved a c-statistic of 0.83, with sensitivity and specificity of 0.69 and 0.87, respectively, and an accuracy of 0.87. LR analysis confirmed the system's effectiveness in predicting MO, with odds ratios of 5.7 and 21.0 for patients classified as probably (three predictors positive) and definitely at risk of MO (four predictors positive), respectively.

Ciancarelli et al.[58] used ANN to predict the effect of EMG-biofeedback treatment in 20 CM patients. The ANN predicted post-treatment MIDAS scores with 75% accuracy. A significant correlation between NOx (nitrite and nitrate) levels and MIDAS (R=–0.675, p=0.011) suggested that higher nitric oxide levels pre-treatment were associated with lower post-treatment MIDAS scores, particularly when peroxide levels are within a specific range (116–205 U/mL).

4. Imaging

Wei et al.[59] evaluated 111 migraine patients, of whom 62 were responders to NSAIDs and 49 were non-responders. Their 3D-T1 weighted images were analyzed using DL with the ResNet-18 model demonstrated the best accuracy of 0.78. In a subsequent study, the static functional connectivity was compared among 35 NSAID-responsive episodic MwoA patients, 35 NSAID-non-responsive MwoA patients, and 33 HCs. Clinical characteristics and functional network connectivity features were applied to a SVM model to classify NSAID responsiveness, yielding a sensitivity of 0.88, specificity of 0.89, and an AUROC of 0.93. NSAID-responsive patients exhibited reduced connectivity between the DMN and VN, as well as between the SMN and VN, while showing enhanced VN-auditory network connections.

In a follow-up study, the team compared 59 NSAID responders with 59 non-responders among migraine patients, using propensity score matching.[60] Multimodal MRI was employed to extract percentage amplitude oscillations and gray matter volume from six brain areas, with multiple ML models applied. The RF model, which had the lowest predictive residuals, was selected. The model metrics in the training and testing groups were as follows: AUROC 0.982/0.711, sensitivity 0.976/0.667, and F1 score 0.930/0.649. The choice of AI algorithm is noteworthy. ResNet-18, a CNN based DL architecture, is advantageous for direct image analysis. When features extracted from MRI were used, ML methods were applied. Marino et al.[61] utilized Compressive Big Data Analytics (CBDA), a semi-supervised ML technique, to identify predictive migraine biomarkers at the molecular level using a PET

dataset from 38 migraine patients and 23 HCs. The CBDA method classified migraineurs from HCs with accuracy, sensitivity, and specificity above 90% for both whole-brain and region-of-interest analyses. The putamen was identified as the most predictive region for migraine, particularly regarding μ-opioid and D2/D3 dopamine receptors.

Tso et al.[62] predicted verapamil responsiveness in 708 CH and probable CH patients, comprising 317 episodic and 391 chronic cases, using 72 clinical features from 410 patients and imaging data from 194 patients. Non-linear dimensionality reduction techniques, including principal component analysis and t-distributed stochastic neighbor embedding, were applied to the clinical data, identifying two large clusters. KNN was then used to define these clusters. The voxel-based morphometry analysis revealed a gray matter cluster in lobule VI of the cerebellum (–4, –66, –20) that exhibited increased gray matter concentration in verapamil non-responders compared with responders (p=0.008). The XGBoost-implemented GB DT was used to predict verapamil response, achieving AUROC of 0.689 on cross-validation (95% CI, 0.651–0.710) and 0.621 on held-out data.

While there are still relatively few studies and the results have not yet been particularly compelling, the potential for utilizing AI in this area has been demonstrated. Further research and development are needed to refine these methods and make them more accessible for clinical application in the future.

ARTIFICIAL INTELLIGENCE APPLICATIONS IN MIGRAINE ATTACK PREDICTION

1. Forecasting migraine attack

Migraine sufferers often have a strong desire to predict both the onset and intensity of a migraine attack. Despite knowing that acute-phase migraine medication should be taken immediately when a headache begins (as reported by 184 out of 207 participants), many delay treatment. This hesitation is largely due to the desire to confirm whether the headache is indeed a migraine (68.7%) and to reserve medication for cases that develop into severe migraine attacks (46.2%).[63] The application of AI holds great potential in forecasting migraine attacks, given its strength in classification and prediction.

In a study by Stubberud et al.[64], 18 migraine patients were prospectively included, completing 388 headache diary entries and self-administering app-based biofeedback sessions that wirelessly measured heart rate, peripheral skin temperature, and muscle tension. The primary outcome was the presence or absence of any headache on the day following a completed headache diary entry and biofeedback session. The RF model was the top-performing model in the out-of-sample test set, achieving an AUROC of 0.62, with accuracy, sensitivity, and specificity of 0.56, 0.0, and 1.0, respectively. A GB classifier showed similar results. Using SHapley Additive exPlanations, the most important features for predicting the next day's headache were identified as premonitory symptoms (craving, swelling, and feeling cold), the amount of sleep, the presence and intensity of headache, the impact of the headache on daily functioning, the length of the biofeedback session, and mean heart rate.

Siirtola et al.[65] utilized wearable sensors from the wrist-worn Empatica E4 device, along with sleep data, to predict migraine attacks. Data from seven participants, including headache diaries and sleep metrics, were used. The wearable device collected data from a 3D accelerometer, thermometer, electrodermal activity sensor (galvanic skin response), and photoplethysmography sensor (measuring blood volume, heart rate, and heart rate variability). Features were derived by comparing nights before a migraine attack to nights without an attack, and nights before a day without a migraine were also compared with each other. QDA and LDA were used as classifiers, with QDA producing better results than LDA. The personal model outperformed the balanced user-independent model, with accuracy for detecting attacks one night prior exceeding 82% in five individuals, while accuracy varied significantly, ranging from 60.4% to 69.6% in the other two individuals.

Katsuki et al.[9] utilized a smartphone application to collect hourly headache occurrences from 4,375 migraine sufferers, integrating this data with local weather information. The variables were analyzed using a generalized linear mixed model, feedforward neural network, and XGBoost. The study found that headache occurrences were associated with lower barometric pressure (p<0.001, gain=3.9) and significant decreases in barometric pressure (p<0.001, gain=11.7), higher barometric pressure at 6 a.m. (p<0.001, gain=4.6), higher humidity (p<0.001, gain=7.1), and in-

creased rainfall (p<0.001, gain=3.1).

Further research is needed to enhance accuracy, ease of use, and generalizability, but the significant patient demand and industrial potential underscore the importance of this field.

ARTIFICIAL INTELLIGENCE APPLICATION IN RESEARCH OF HEADACHE DISORDERS

1. Basic research

Kogelman et al.[66] collected temporal multi-omics profiles from 24 migraine patients during spontaneous migraine attacks, 2 hours after triptan treatment, during headache-free periods, and after a cold-pressor test. Relevant metabolites were evaluated using an ML method based on symbolic regression, QLattice.[66] The study detected lower cortisol levels, higher sumatriptan levels, and elevated glutamine levels following treatment. Changes in sumatriptan levels were correlated with changes in GNA1 and VIPR2 gene expression, both of which are known to regulate cAMP levels.

Chiang et al.[67] developed a DL model for the mouse grimace scale (MGS) called DeepMGS, utilizing the ResNet-18 architecture. This model automatically crops mouse face images, predicts action unit scores and total scores on the MGS, and infers the presence of pain. The system was tested on six migraine and six control mice, with performance compared to human scorers. The model achieved an accuracy of 70% to 90% and demonstrated a high correlation with human scorers in total MGS score (correlation coefficient=0.83).

Thomas et al.[68] used a neural network model to replicate the neurophysiological dysfunction observed in migraine sufferers, specifically analyzing cortical-evoked potentials in response to repetitive visual and auditory stimuli. They developed normal and migraine synapse models for comparison. Upon repetitive presentation of stimuli at 40 dB and 70 dB input levels, the migraine model exhibited sensitization, with higher potentiating synapse strength resulting in a greater output.

2. Imaging

Hong et al.[69] developed a system for the segmentation of deep white matter hyperintensities (WMHs) using a deep neural network based on the U-Net architecture. The model, applied to 148 migraine patients, comprised two networks: the first identified potential deep WMH candidates, and the second reduced false positives among these candidates. The models achieved a true positive rate of 0.88, a false discovery rate of 0.13, and an F1 score of 0.88 for segmenting deep WMHs.

CONCLUSIONS AND FUTURE PERSPECTIVES

The application of AI in the field of headache disorders is on the rise and has shown promising results. However, significant challenges remain in improving accuracy, generalizability and validation, ease of application, and linking findings to clinical relevance. Further research is needed in areas such as digital twins, which have been suggested as a potential tool in migraine management but have yet to be thoroughly explored.[70]

The appropriate use of AI holds great potential to enhance diagnosis, treatment, and research processes in the headache field. However, it is important to recognize that DL, ML, and various supervised and unsupervised methods do not always produce optimal results. No single approach—whether ML, DL, or supervised/unsupervised methods—is inherently superior to the other. Therefore, selecting the most appropriate method with careful consideration of study design is recommended. Caution is necessary when interpreting results, particularly with generative AI models such as LLMs.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: WL, MKC; Data curation: WL, MKC; Formal analysis: WL, MKC; Investigation: WL, MKC; Methodology: WL; Writing–original draft: WL; Writing–review & editing: WL, MKC.

CONFLICT OF INTEREST

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Headache and Pain Research

Morning Headaches: An In-depth Review of Causes, Associated Disorders, and Management Strategies

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Abstract

Morning headaches, which are defined by occurrence upon or shortly after waking up in the morning, range from mild discomfort to severe pain and significantly impact an individual's quality of life. Although morning headaches are a prevalent and potentially debilitating condition, the criteria for defining these headaches vary. The lack of universally accepted diagnostic criteria complicates understanding their etiology, associated factors, and potential interventions. The causes of morning headaches are multifaceted, including primary headache disorders like migraines and cluster headaches, and secondary causes such as sleep disorders, hypertension, abnormal intracranial pressure, and brain parenchymal diseases. Psychological factors, including anxiety and depression, as well as substance use, further complicate the clinical presentation, often requiring a multidisciplinary approach for effective diagnosis and treatment. This review provides a comprehensive overview of morning headaches, examining their various aspects and possible treatment options, with the goal of enhancing clinicians' understanding and management of this common yet often overlooked condition.

Keywords: Depression, Morning headache, Primary headaches, Secondary headaches, Sleep apnea syndromes

INTRODUCTION

Morning headache, characterized by their occurrence upon waking, can range from mild discomfort to severe pain and have profound implications on an individual's quality of life. This prevalent and often debilitating condition affects 5% to 8% of the general population, with women reporting morning headaches more frequently than men. The prevalence is also higher among individuals aged 45 to 64 years.[1,2]

The criteria for defining morning headaches differ across studies, but various criteria have been used, including experiencing three or more morning headaches in the past year, the presence of any morning headache, having a morning headache once a week or more, and frequency descriptors such as 'always,' 'often,' or 'sometimes' having

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headaches upon waking.[1,3] Additionally, some studies specify criteria like 'often' or 'very often' experiencing headaches upon waking.[4] Since there are no universally accepted diagnostic criteria for 'morning headache,' understanding their causes, related factors, and possible treatments is essential for creating effective management strategies.

The causes of morning headaches are multifaceted and can include primary headache disorders such as migraines and cluster headaches (CH), as well as secondary causes like sleep disorders, hypertension, and brain parenchymal disease.[1] For primary headache, hormonal fluctuations such as cortisol, which peaks in the early morning, the effect of medications wearing off overnight or morning movement such as from a lying to a standing position or sudden/vigorous physical activity also can trigger morning headache. Sleep-related factors, including obstructive sleep apnea (OSA), circadian disruption, and poor sleep hygiene, are particularly significant, given their direct impact on sleep quality and overall health. A natural morning surge in blood pressure combined with or without uncontrolled hypertension can result morning headache suggesting secondary brain parenchymal disease such as hemorrhagic stroke or changes of intracranial pressure (ICP) or brain tumors.[5] Moreover, psychological aspects, including anxiety and depression, further complicate the clinical picture, often necessitating a multidisciplinary approach to diagnosis and treatment. Consulting with a professional can help identify the underlying cause and appropriate treatment.

This article aims to provide a comprehensive overview of morning headaches, exploring their various aspects and possible treatment options. We present a comprehensive review of morning headaches which can result from a combination of factors, including primary headaches like migraines or tension-type headaches (TTH), secondary headaches like brain parenchymal disease, hypertension, and linked to underlying conditions such as sleep disorders or poor sleep quality or sleep apnea, and behavioral aspects such as mood, stress levels and medication/substance overuse.

HEADACHE DISORDERS IN MORNING HEADACHE

Morning headaches are frequently reported by individuals suffering from primary and secondary headache disorders. Recent research has explored the intricate connections between morning headaches and these other types of headaches.

1. Primary headache manifesting as morning headache

1) Migraine

Migraines are common issues that significantly impact daily life. The prevalence of morning headaches among migraine sufferers varies. Studies reported that about 60% to 70% of migraine patients experience morning headaches,[6-8] suggesting that these two conditions are closely related and often share common underlying causes.[9]

Several mechanisms may explain the connection between these two types of headaches. First, changes in blood vessels, such as constriction and dilation, can influence the mechanisms behind morning headaches and migraines. Migraines are often associated with abnormal vascular expansion and contraction, which can significantly contribute to morning headaches. Recent studies have delved deeper into how these physiological changes impact the occurrence of morning headaches and migraines.[10] Second, hormonal changes play a crucial role in the relationship between morning headaches and migraines. Hormonal fluctuations are known to be major triggers for migraines, especially in women,[11-13] who may experience headaches due to menstrual cycles, pregnancy, or menopause.[14,15] These hormonal changes can be particularly pronounced in the morning, increasing the likelihood of both morning headaches and migraines.[13]

Specific genetic factors may contribute to both morning headaches and migraines.[9,16] New theories suggest that central nervous system hypersensitivity, inflammatory responses, and hormonal imbalances could be shared triggers. It is proposed that hypersensitivity and inflammatory responses may provoke both conditions, while hormonal imbalances could also play a role in their simultaneous occurrence.[17,18]

2) Cluster headache

CH is characterized by its striking circadian and circannual rhythmicity.[19] These headaches often occur at the same time each day, predominantly in the early morning hours.

Previous studies reported that about 80% of patients with CH had headache awakening and these patients reported nocturnal sleep as a trigger of attacks.[20,21]

This have been linked to disruptions in the body's internal biological clock. Research has demonstrated that the hypothalamus, which regulates circadian rhythms, plays a critical role in the pathophysiology of CH.[22,23] This connection to the hypothalamus helps explain why CH frequently occurs in the early morning, aligning with the peak of melatonin secretion and other circadian processes.[24,25]

Understanding the association between morning headaches and CH is crucial for developing effective treatment strategies. Clinicians should consider evaluating patients with CH for underlying sleep disorders, such as OSA, and address any sleep disturbances that may contribute to headache occurrence.[19] Treatments aimed at regulating circadian rhythms, such as melatonin supplementation or chronotherapy, may also be beneficial for patients with CH.[24,26] Additionally, the use of continuous positive airway pressure (CPAP) therapy in patients with comorbid sleep apnea could help reduce the frequency and severity of CH attacks.[27]

3) Tension-type headache

TTH are one of the most common forms of primary headaches and are often characterized by a bilateral pressing or tightening pain. Research indicates that up to 40% of individuals with TTH experience morning headaches, highlighting the close association between these conditions.[28] The relationship between TTH and morning headaches is clinically significant, as they share common contributing factors such as muscle tension, stress, and poor sleep quality. Morning headaches, specifically, can frequently occur in individuals with TTH, especially when muscle tension builds up during sleep or due to inadequate sleep posture. Moreover, the cyclical relationship between poor sleep and TTH is well-documented.[28] Poor sleep quality can exacerbate TTH, leading to an increased likelihood of waking with a headache. In turn, the pain and discomfort from TTH can further disrupt sleep, perpetuating a cycle that can be challenging to break without targeted interventions.

Understanding the prevalence of morning headaches in patients with TTH is critical for developing comprehensive treatment strategies. Addressing underlying issues such as sleep hygiene, stress management, and muscle relaxation can be effective in reducing the frequency and severity of both morning headaches and TTH.

4) Hypnic headache

Hypnic headache (HH), known as "alarm clock headache," is a rare condition affecting 0.07% to 0.3% of individuals, primarily those over 50, and is more common in women.[29,30] Attacks typically occur early in the morning, between 2 am and 4 am, lasting from 5 minutes to 12 hours, with pain described as dull, sharp, or throbbing. HHs and morning headaches are distinct conditions, but they can overlap in some cases. If a patient wakes up due to an HH and is unable to go back to sleep, the headache may also be categorized as a morning headache, especially if it persists into waking hours. Many patients report difficulty falling back asleep due to the intensity of the headache. Although the exact percentage of those affected is not well-documented, sleep disruption is a well-known feature of HHs.

The pathophysiology of HH is not well understood but it may share some predisposition with migraines, which thought to involve hypothalamic disruptions, particularly in areas regulating circadian rhythm, pain processing, and melatonin release, which may be related to aging.[31,32] Its connection to sleep suggests it could be a chronobiological disorder involving hypothalamic changes. Diagnosing HH involves excluding other causes, particularly sleep-related headaches. Unlike migraine sufferers, who tend to rest in a dark room, HH patients often get up to relieve pain. HH is distinct from CH, which have autonomic symptoms like tearing or nasal congestion. HH is unique as it occurs only during sleep.[30]

Treatment for HH includes abortive therapies like caffeine, effective due to its vasoconstrictive properties but potentially causing insomnia.[33] Caffeine-containing analgesics and serotonin receptor agonists (triptans) show variable results. Preventive options include caffeine before sleep, lithium, indomethacin, and melatonin, though outcomes vary.[29,34,35] Amitriptyline and anticonvulsants like topiramate, lamotrigine, and pregabalin have shown efficacy in some cases.[36,37] Other medications, such as beta-blockers, verapamil, and glucocorticoids, yield mixed results. Nonpharmacologic approaches like physical activity at onset, occipital-nerve stimulation, occipital-nerve block, and oxygen therapy may also be beneficial.[38-40]

2. Secondary headache manifesting as morning headache

1) Intracranial pressure

Cerebral autoregulation is the process by which the brain maintains a consistent blood flow despite changes in systemic blood pressure (Figure 1). Morning headaches can be associated with changes in ICP, a condition characterized by low or high cerebrospinal fluid (CSF) pressure.[41] One previous study showed 62% of patients with idiopathic intracranial hypotension documented their headache with awakening and 73% of patients reported daily headache.[42]

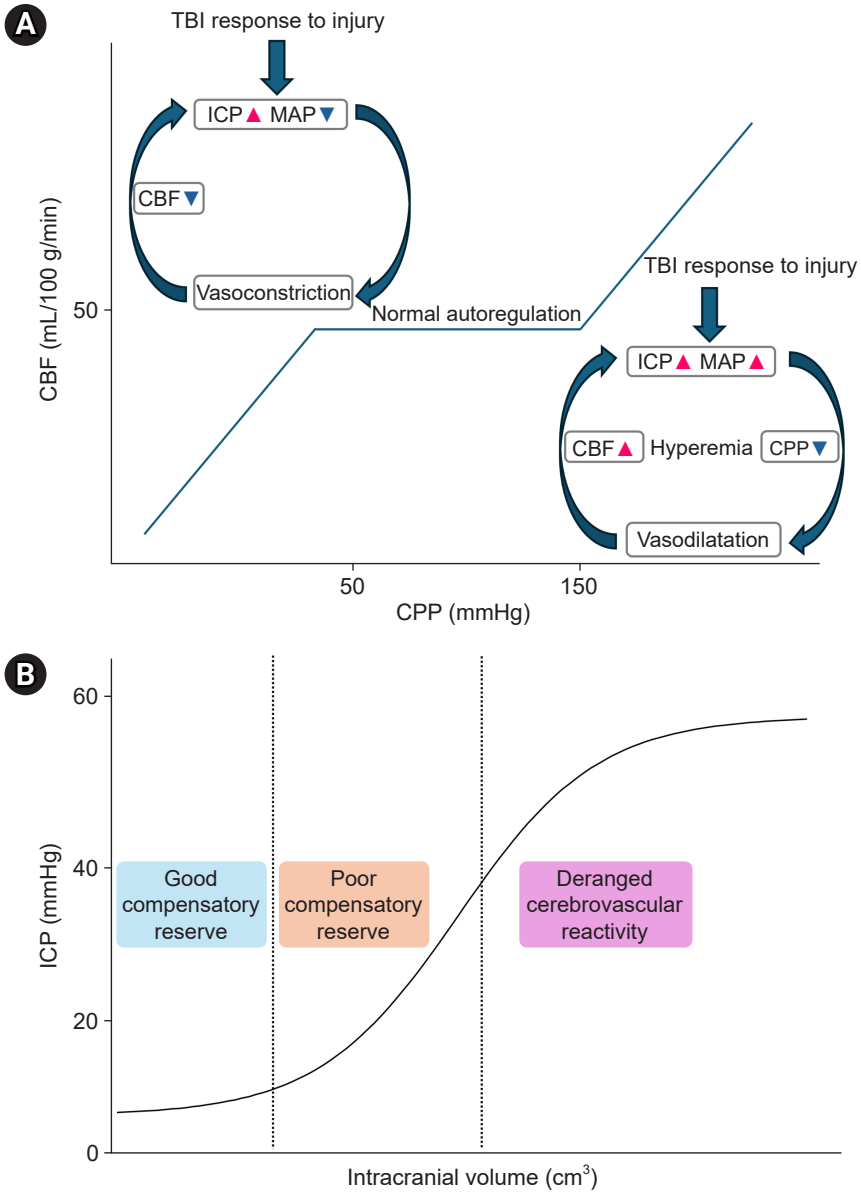

Figure 1. Cerebral autoregulation and increased ICP. (A)The Monro-Kellie doctrine states that because the cranial volume is fixed, increases in brain tissue, CSF, or blood must be offset by decreases in one or more of the others to prevent a rise in ICP. Autoregulation maintains CBF within a mean arterial pressure of 50 to 150 mmHg, with this range shifting higher in chronic hypertension. (B) ICP–volume compliance curve: When compensatory mechanisms are disrupted, the ICP rises sharply, risking brain herniation.
CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; ICP, intracranial pressure; MAP, mean arterial pressure; TBI, traumatic brain injury.

First, Intracranial hypertension, defined as CSF opening pressure ≥250 mm H_2O, physiologically can worsen headache at morning because, during sleep, particularly in a lying down position, blood flow to the brain can increase, leading to a slight rise in ICP.[43] This can be more pronounced in individuals with conditions that already elevate ICP. Also, hormonal changes and fluid retention during lying down while sleeping can also contribute to increased ICP. Otherwise, intracranial hypotension defined as a lumbar puncture opening pressure below 60 mm H_2O.[44] It typically results from a CSF leak, which can occur spontaneously or due to trauma, medical procedures, or certain connective tissue disorders. These headaches are 'positional' or 'orthostatic,' which is typically worsen when upright and improve when lying down, so patients frequently mention that their headache is either absent or minimal upon waking and gradually worsen as the day progresses. But they can also be present upon waking due to positional changes during sleep.

Diagnosis of issues related to ICP typically involves imaging studies such as magnetic resonance imaging (MRI)[45] or computed tomography (CT) scans, lumbar punctures to measure CSF pressure, and possibly other tests to identify underlying causes. In a large study involving 568 patients who underwent imaging with either CT myelography or spinal MRI, a CSF leak was identified in 51% of the cases. Treatment varies depending on whether the problem is increased or decreased ICP. For increased ICP, treatment might include medications to reduce pressure, surgical interventions, or lifestyle changes. For decreased ICP, treatments may focus on sealing CSF leaks, bed rest, hydration, caffeine intake, or procedures like an epidural blood patch. Recognizing the connection between morning headaches and ICP can facilitate timely diagnosis and management of this potentially serious condition.

2) Hypertension and its complications

According to the International Classification of Headache Disorders (ICHD)-3, headache attributed to arterial hypertension is classified as a secondary headache disorder of hemostasis.[44] In a study of prevalence and risk factors of morning headaches in the general population, hypertension (11.0% vs. 7.2%) is one of the significant associated factors with morning headache.[1]

Guidelines specify that such headaches are linked to abruptly elevated blood pressure (systolic blood pressure 180 mmHg or higher, or diastolic blood pressure 120 mmHg or higher). Mild to moderate chronic arterial hypertension does not appear to cause of headache.[46] The relationship between headache and hypertension was first examined in 1913. Hypertensive headache was described as non-migrainous headaches that occur in the morning and gradually resolve.[47] However, these findings had limitations because they were based on patients with malignant hypertension.

A non-dipping blood pressure pattern may contribute to early morning headaches. This pattern means that blood pressure does not significantly decrease at night, leading to higher blood pressure in the early morning. Morning headache is secondary symptom of OSA.[48] A non-dipping blood pressure is independently associated with OSA.[49] This can cause increased ICP and subsequently result in headaches upon waking. Additionally, the higher blood pressure in the morning can be a trigger for these headaches due to the stress it places on the cardiovascular and cerebrovascular systems.[50]

The pathophysiology underlying the onset of headaches related to sudden rises in blood pressure appears to be at the cellular level. Abrupt high blood pressure can cause endothelial dysfunction, reducing vasodilator substances (such as nitric oxide) and increasing vasoconstrictive factors, thereby contributing to hypertension and headaches. Additionally, increased ICP, and the modulation of pain by the baroreflex system in the brainstem contribute to the complex interaction between cardiovascular regulation and pain perception (Figure 2). These mechanisms highlight the intricate relationship between cardio-cerebrovascular health and headache disorders, particularly migraines.[46,51-53]

Understanding these complex relationships is important for proper diagnosis and management of patients with both hypertension and headaches. Effective blood pressure management can alleviate headaches and reduce overall cardio and cerebrovascular risk.

3) Brain tumor

Brain tumor is rare but serious causes of secondary headaches. Headache is reported in 32.2% to 71% in patients with brain tumor,[54-58] often accompanied by various neurological symptoms. Morning headaches are one of the char-

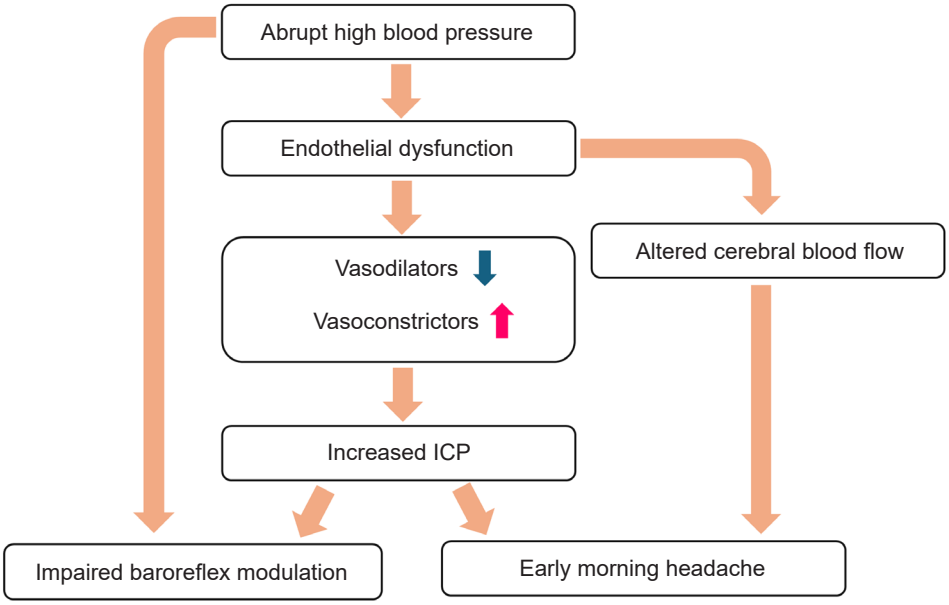

Figure 2. Pathophysiology of headache and arterial hypertension. Abrupt high blood pressure can cause endothelial dysfunction, reducing vasodilator substances (such as nitric oxide) and increasing vasoconstrictive factors, thereby contributing to hypertension and headaches. Additionally, increased intracranial pressure (ICP) and the modulation of pain by the baroreflex system in the brainstem contribute to the complex interactions between cardiovascular regulation and pain perception.

acteristic signs in brain tumors, presenting as worse headache in the early morning upon waking. Headache is often worsening during the sleep. These morning or nocturnal headaches are attributed to the exacerbation of increased ICP during sleep, through sustained recumbency and cerebral vasodilatation due to nocturnal hypoventilation with raised the partial pressure of carbon dioxide.[59] Also, tumor headache is often exacerbated by lying down or bending, and by Valsalva-like maneuvers such as cough, exercise, or straining. Nausea or vomiting is another common accompanying symptom. However, the clinical characteristics of tumor headache are heterogeneous with various severity,[57,58,60] and headache specifically occurring in the morning or night were only reported in 25.5% and 3.1% of cases, respectively.[58]

Factors associated with morning headache in patients with brain tumor headache is uncertain, but large-sized brain tumor and tumor with increased ICP showed higher prevalence of morning headache.[58] The location of tumor and the distribution of the headache do not always correlate precisely, but infratentorial tumors are associated with occipital headaches. Also, intraventricular and infratentorial tumors have higher prevalence of headache compared to supratentorial tumor.[55] Tumors with rapid-growing characteristics are more likely to cause headache. Based on the ICHD-3 diagnostic criteria for headache attributed to intracranial neoplasia, patients presenting with progressive headache, headache worsening in the morning and/or lying down, aggravated by Valsalva-like maneuvers, accompanied by nausea/vomiting or cranial nerve palsies should be promptly screened, and appropriate brain imaging studies should be performed.[44]

To alleviate headaches related to brain tumors, managing the brain tumor itself is the most important and effective approach. Specifically, for headaches that worsening in the morning, corticosteroid therapy is effective in relieving increased ICP. Among corticosteroids, dexamethasone is preferred due to its strong potency, long half-life and minimal mineralocorticoid effect.[61] If headache is not associated with brain edema or increased ICP, non-steroidal anti-inflammatory drugs and/or opioids may be used.[62]

SLEEP AND CIRCADIAN DISORDERS IN MORNING HEADACHE

Headache and sleep disorders are closely related, with a

complex and multidimensional relationship. The comorbidity of these two conditions leads to their chronification and increases the overall burden, worsening both disorders. This results in a decreased quality of life, a higher frequency of complications, and reduced treatment effectiveness. Especially, morning headache is often recognized as a common manifestation of sleep disorders.

1. Insomnia and sleep deprivation manifesting as morning headache

Population-based studies have shown an increased prevalence of sleep disorders among individuals with headache.[63,64] Among the various sleep disorders, insomnia stands out as being closely associated with headaches. Insomnia, much like headaches, is remarkably common in the general population. The prevalence of insomnia ranges from 30%–48%, and 16%–21% of the population experiences insomnia often or always, or three or more days a week.[65] This high prevalence underscores the importance of understanding the relationship between insomnia and headaches. People with insomnia have a two- to threefold increased risk of migraines,[66] TTH,[67] and chronic daily headaches.[68] This elevated risk highlights the potential causal or exacerbating role that sleep disturbances may play in headache disorders.

A comprehensive study on this topic yielded interesting results regarding the co-occurrence of headaches and sleep problems. The study found that 18.1% of people had both headaches and insomnia, 16.3% had headaches only, and 21.1% had sleep problems only.[69] In particular, the association between morning headaches and insomnia disorders or other sleep disorders involving sleep deprivation is a well-known cause of headaches.[70,71] This connection is well-established in the medical community and is recognized as a common cause of headaches. The timing of these headaches—occurring in the morning—points to the potential role of nighttime sleep disturbances in their onset.

Further emphasizing this relationship, previous study reported that morning headache is more common in patients with Diagnostic and Statistical Manual of Mental Disorders-IV insomnia disorders (18.4%) than in those without (6.9%).[1] This difference was statistically significant, providing strong evidence for the link between insomnia and morning headaches. The most recent study conducted in adults and children has provided additional insights.[72] It reported that worse sleep quality was associated with morning-onset headaches but not afternoon-onset headaches. Furthermore, the study suggested that morning-onset headaches may be more representative of a migraine phenotype rather than a TTH phenotype.

Also, disturbances in sleep quality, including insomnia and altered sleep architecture, are also commonly reported by patients with CH. Actigraphy and sleep diary studies have shown that patients with CH often experience lower rapid eye movement sleep density and longer sleep latency compared to healthy controls, indicating poor sleep quality.[73,74] This disruption in sleep may act as a trigger for CH attacks, although the exact mechanisms remain unclear.

These findings collectively underscore the complex interplay between sleep disorders, particularly insomnia, and headaches. They suggest that addressing sleep issues may be a crucial component in managing and potentially preventing certain types of headaches, especially those occurring in the morning. Further research in this area could provide valuable insights into the mechanisms underlying this relationship and inform more effective treatment strategies for both sleep disorders and headaches.

2. Sleep apnea manifesting as morning headache

Many patients with sleep apnea experience morning headaches, believed to be a secondary symptom of OSA.[44] The repeated interruptions in breathing during sleep lead to oxygen deprivation and carbon dioxide build-up in the body, which contributes to these headaches.[48] For several decades, morning headaches have been considered to be a symptom of OSA syndrome.[71,75] Research has primarily focused on the relationship between morning headaches and heavy snoring and OSA, which can cause hypoxia and blood pressure changes during sleep.[2] These conditions are believed to provoke headaches that persist upon waking. It has also been reported that patients with OSA who experience morning headaches significantly improve their morning headaches after CPAP treatment.[76] However, it is important to note that while morning headaches are similar to sleep apnea headaches (Table 1), they are not exclusively caused by OSA. This distinction highlights the complex nature of the relationship between sleep disor-

Table 1. Diagnostic criteria for sleep apnea headaches according to the International Classification of Headache Disorders 3 (ICHD-3)

1. Headache has developed in temporal relation to the onset of sleep apnea
2. Either or both of the following:
a) headache has worsened in parallel with worsening of sleep apnea
b) headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnea
3. Headache has at least one of the following three characteristics:
a) recurring on ≥15 days/mo
b) all of the following:
– bilateral location
– pressing quality
– not accompanied by nausea, photophobia or phonophobia
c) resolving within 4 hours
4. Not better accounted for by another ICHD-3 diagnosis.

Adapted from the article of Headache Classification Committee of the International Headache Society (Cephalalgia 2018;38:1-211).[44]

ders and morning headaches.

Morning headaches are a common symptom of sleep apnea, and sleep apnea headache is a specific diagnosis. The criteria for sleep apnea headaches, as set by the ICHD-3, are that they occur 15 or more days per month, typically resolve within 4 hours of waking up, and are characterized by a pressure-like sensation, usually bilateral. In contrast, morning headaches in sleep apnea also occur upon waking, but can last longer than for hours and are often accompanied by additional symptoms such as dry mouth or sore throat. These types of headaches are typically described as dull, diffuse pain.[77,78] Both types are related to the physiologic effects of sleep apnea, such as intermittent hypoxia and changes in ICP, and often improve with effective sleep apnea treatment, such as CPAP therapy.[79,80] However, improvement with treatment is a diagnosis for sleep apnea headaches, not common morning headaches. Therefore, if you have a morning headache, sleep apnea should be suspected, and further evaluation is needed to determine if you meet the criteria for sleep apnea headaches.

Several studies have investigated the prevalence and characteristics of morning headaches in relation to sleep apnea. A cross-sectional study of people suffering from snoring and OSA syndrome found that 18% experienced headache often or very often upon awakening, while only 5% of the general population experienced the same type of headache.[81] This suggests that snoring and OSA increase the risk of sleep apnea headaches three- to four-fold. A study across five European countries (Germany, Italy, Portugal, Spain, and the United Kingdom) revealed that 7.6% of the general population experienced chronic morning headaches, while this increased to 15.2% among those with breathing-related sleep disorders.[1] A Norwegian epidemiological survey using polysomnography found that 11.8% of participants with OSA had sleep apnea headaches, compared to 4.6% of those without OSA who had similar morning headaches.[82]

An older study conducted to determine whether morning headaches were a consistent symptom of sleep apnea, 18% of patients with sleep apnea experienced morning headaches frequently, compared with 21% to 38% of patients with other sleep disorders and 6% of controls.[83] Interestingly, morning headaches were most common in those with mild non-obstructive apnea, with no significant difference among patients with moderate to severe sleep apnea. These findings suggest that frequent morning headaches may be a non-specific symptom of various sleep disorders, rather than a consistent symptom of sleep apnea syndrome alone. This is further supported by another study which found that morning headaches, while frequently reported among OSA patients, may not necessarily be related to OSA itself. This study found no statistically significant association between the apnea-hypopnea index, arousal index, or oxygen saturation parameters and the probability of morning headaches.[48] These results partially confirm previous findings from a case-control study that concluded that there was no relationship between severity of OSA syndrome and headaches.[82,84] Therefore, more comprehensive research is needed to understand the complex relationship between sleep disorders and morning headaches. These results partially confirm previous case-control study findings that concluded there was no relationship between the severity of OSA and headaches.

The lack of a clear correlation between OSA severity and morning headaches suggests a more complex relationship between sleep disorders and headaches than previously thought. Given these findings, it's evident that more comprehensive research is needed to fully understand the intricate relationship between sleep disorders, particularly OSA, and morning headaches. Future studies should aim to elucidate the mechanisms underlying this relationship

and explore potential confounding factors that may influence the occurrence of morning headaches in individuals with sleep disorders.

3. Circadian rhythm disorders manifesting as morning headache

The relationship between morning headaches and circadian rhythm has been a subject of increasing interest in headache research. Several studies have shown that headache attacks, particularly migraines and CH, exhibit seasonal and circadian periodicity.[85,86] This periodicity suggests a strong link between our body's internal clock and the onset of certain types of headaches.[87,88] Notably, migraine attacks have been found to occur more frequently in the early morning hours.[87] This temporal pattern aligns with various physiological changes that occur during the transition from sleep to wakefulness, such as fluctuations in hormone levels, neurotransmitter activity, and autonomic nervous system function.[89,90] The consistency of this early morning peak in migraine occurrence across multiple studies underscores the potential role of circadian rhythm disturbances in headache pathophysiology.[28,91,92]

Understanding this connection could have significant implications for both the prevention and treatment of morning headaches. For instance, interventions targeting circadian rhythm regulation, such as light therapy or melatonin supplementation, might prove beneficial in managing these types of headaches. Furthermore, this circadian influence on headache patterns highlights the importance of considering timing in headache management strategies, potentially leading to more personalized and effective treatment approaches. As research in this area continues to evolve, it may provide new insights into the complex interplay between our body's internal clock, sleep-wake cycles, and the manifestation of morning headaches, ultimately contributing to improved quality of life for those affected by these conditions.

BEHAVIORAL PROBLEMS IN MORNING HEADACHE

1. Mood changes manifesting as morning headache

Mood may be one behavioral predictor of morning headache. Indeed, it is well-established that depression and anxiety disorders are highly comorbid with headache,[93] including migraine,[94] tension type headache,[95] and chronic daily headache.[96] Such comorbidity may reflect shared underlying brain regions between emotion and pain.[97] Although limited work has examined the association between mood and morning headache specifically, extant findings suggest a link similar to that observed for headache broadly. Consistent with the broader headache literature, a study conducted in a large community sample found chronic morning headache is likewise associated with higher prevalence of mood and anxiety disorders.[1] Similarly, in a large sample of habitual snorers, greater frequency of morning headache was associated with more severe general psychological distress.[6] Notably, mood and headache are dynamic processes that vary over time; thus, studies using prospective monitoring methods may provide more detailed insight into the relationship between mood and morning headache. One such study followed a sample of habitual snorers who monitored mood and morning headache incidence over 90 days. Results revealed that clinically significant anxiety symptoms, but not depression symptoms, predicted increased likelihood of experiencing morning headache, controlling for sleep quality.[98] In contrast, a recent study in a large sample of community adults with and without migraine who monitored mood and morning headache for 2 weeks found that worse mood and higher anxiety predicted higher incidence of morning headache in univariate models, but these effects were no longer significant when accounting for the effects of sleep quality and energy level.[72] Thus, additional research using prospective monitoring designs is needed to clarify the day-to-day association between mood and morning headache, over and above the effect of sleep.

2. Substance use manifesting as morning headache

Morning headaches are frequently linked to substance use, including alcohol, caffeine, and certain medications. Because alcohol is frequently consumed during evenings, weekends, or typically after work or school as a way to unwind and relieve stress after a long day and to socialize, excessive alcohol consumption can cause dehydration, hypoglycemia resulted from low blood sugar levels after an overnight fasting a common headache trigger, and

disrupt sleep patterns, leading to poor-quality sleep and resulting in morning headaches which is called 'hangover headache' or 'delayed alcohol-induced headache,' especially common in migraine.[99,100] Caffeine has a dual effect; while moderate intake can alleviate headaches, excessive consumption or abrupt withdrawal can cause rebound headaches, particularly upon waking.[101,102] Previous experimental studies and reports have shown that about 50% of patients experience headaches during caffeine withdrawal.[101,103,104] And higher daily caffeine intake is reported to be associated with more severe withdrawal headaches.[101,105] Even relatively low doses (around 100 mg/day) can cause withdrawal symptoms.[101,106]

Certain medications, especially those for chronic pain or psychiatric conditions, can also contribute to morning headaches.[107] Overuse of analgesics, for instance, can lead to medication overuse headaches, which are often worse in the morning. Medication overuse headaches often manifest in the morning, likely due to the decline of drug levels in the body overnight (called wearing-off).[108] Understanding the impact of substance use on morning headaches is crucial, as modifying these behaviors can significantly reduce the frequency and severity of headaches, thereby improving overall quality of life.

CONCLUSION

In conclusion, morning headache is a common condition that significantly impacts an individual's quality of life. The complex interplay of multiple factors contributing to morning headache necessitates a multidisciplinary approach to both diagnosis and treatment.

As a neurologist, your approach to morning headaches should be systematic and patient-centered (Table 2). Start

Table 2. Summary of risk factors and treatment options for morning headaches

Risk factors	Neurologist's considerations	Treatment options
Primary headaches	-Distinguish between primary headache disorders (e.g., migraine, cluster headache, hypnic headache) that may present as morning headaches -Rule out secondary causes of headaches	-Pharmacological management: pain-relieving, preventive medications -Non-pharmacological management: behavioral therapy (regular sleep, exercise, avoidance of trigger factors, Biofeedback)
Secondary headaches	-Distinguish between primary and secondary headache disorders -Rule out brain parenchymal lesion or abnormal intracranial pressure -Monitor for red flag symptoms -Evaluate stroke risk	-Imaging studies (MRI/MRA, CT) -Lumbar puncture if indicated -Medication to reduce intracranial pressure or antiplatelet therapy if indicated -Management of vascular risk factors -Monitor blood pressure regularly, lifestyle changes, medication as prescribed by a doctor
Sleep disorders	-Evaluate for secondary headaches & potential underlying neurological symptoms -Take a sleep history in detailed/assess the sleep quality -Consider polysomnography for diagnosis -Assess for mood disorders often comorbid with sleep issues	-PAP for sleep apnea -Sleep hygiene education for insomnia -Cognitive behavioral therapy for insomnia -Light therapy, chronotherapy -Melatonin or sleeping pills supplementation (*teeth grinding or sleep posture problems: use of a night guard, dental treatment, supportive pillows, physical therapy)
Cervicogenic factors	-Assess for cervical spine pathology -Consider contribution to other headache types -Evaluate for comorbid temporomandibular disorders	-Physical therapy -Occipital nerve blocks -Postural correction
Substance use (medication, caffeine/alcohol)	-Evaluate for medication-overuse headache -Assess for substance use disorders -Consider comorbid psychiatric conditions -Develop personalized withdrawal plans -Educate on caffeine's role in headaches	-Medication withdrawal under supervision -Preventive medications -Patient education on medication use -Gradual caffeine reduction -Alcohol moderation or abstinence -Hydration therapy
Psychiatric comorbidities	-Screen for psychiatric comorbidities -Consider impact on headache chronification -Evaluate need for a multidisciplinary approach	-Psychotherapy -Antidepressants with analgesic properties -Stress management

MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; CT, computed tomography; PAP, positive airway pressure.

by taking a detailed history and performing a comprehensive neurological examination. If you suspect a sleep disorders, don't hesitate to recommend a sleep study. Neuroimaging can be a useful tool to rule out structural causes, so consider a brain MRI or CT scan if clinically indicated. Encourage patients to keep a detailed headache diary, as this can identify important patterns and triggers of headache. Use the information you gather to make treatment decisions, including the possibility of preventive or acute medications. Patient education is paramount, so focus on teaching lifestyle modifications and strategies for trigger avoidance. Finally, recognize that managing morning headaches is an ongoing process. Schedule regular follow-up visits to assess the effectiveness of the treatment plan and make adjustments as needed to ensure a dynamic and personalized approach to patient care. By focusing on these key areas, healthcare professionals can better understand, treat, and ultimately alleviate the burden of morning headaches on patients.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: HJI; Data curation: YH, MKK, MSK, HM, RCC; Investigation: YH, MKK, MSK, HM, RCC; Writing–original draft: YH, MKK, MSK, HM, RCC; Writing–review and editing: YH, MKK, HJI.

CONFLICT OF INTEREST

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Review Article

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Headache and Pain Research

Advances in Primary Stabbing Headache: Diagnostic Criteria, Epidemiological Insights, and Tailored Treatment Approaches

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Abstract

Primary stabbing headache (PSH), characterized by sudden, localized stabbing headache pain, is a recognized primary headache disorder with evolving diagnostic criteria. Epidemiological studies show a wide range of prevalence, influenced by various factors. PSH is more common in females, frequently occurring in conjunction with migraine, and can manifest in children. Recent diagnostic criteria have changed the definition of sharp stabbing pain, which is no longer restricted to the first division of the trigeminal nerve. In addition, the criterion of "no accompanying symptoms" has been refined to "no cranial autonomic symptoms" specifically. These changes have increased the sensitivity for capturing PSH. Although it is generally considered benign, stabbing headache can be associated with secondary causes. Clinical red flag signs can be helpful in distinguishing secondary headaches from PSH. A recent prospective study has proposed the monophasic, intermittent, and chronic patterns as subtypes, and this division may be helpful for predicting the prognosis. Pharmacological treatment is typically not required for PSH, although indomethacin and other alternating agents can be used. The treatment should be selected based on individual clinical features and comorbidities. This review aims to highlight the necessity of recognizing the distinctive clinical profile of PSH and of tailoring treatment approaches to patients' individual needs.

Keywords: Diagnosis, Indomethacin, Primary headache disorders, Stabbing headache, Therapeutics

INTRODUCTION

Primary stabbing headache (PSH), first described by Lansche[1] in 1964 as "ophthalmodynia periodica," is a well-recognized primary headache disorder. PSH is a sudden, localized stabbing pain in the head, known by various names such as ice-pick pain, jabs and jolts, needle-in-the-eye syndrome, and sharp short-lived headache. As different clinical features have been reported compared to those previously documented, the diagnostic criteria for PSH have changed over time. Initially, it was believed that the headache was confined to the first division of the

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trigeminal nerve.[2] However, it has been reported that PSH can occur in extra-trigeminal areas, with PSH occurring in an extra-trigeminal area in approximately more than 70% of patients with PSH.[3,4] Additionally, the criteria for no accompanying symptoms have been refined to specifically no cranial autonomic symptoms.[5,6] The absence of cranial autonomic symptoms of PSH be helpful in differentiating it from short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA) or short-lasting unilateral neuralgiform headache attacks with conjunctival injections and tearing (SUNCT). Consequently, PSH is now defined in the International Classification of Headache Disorders, third edition (ICHD-3), as a primary headache characterized by a single stab or a series of stabs that last for a few seconds, occurring with irregular frequency and without any cranial autonomic symptoms.[6] Although the pathophysiology of PSH is unknown, current hypotheses include irritation of the trigeminal and extra-trigeminal nerves and/or intermittent impairment of central pain processing leading to neuronal hyperexcitability or spontaneous synchronous discharge of neurons. Previous studies have shown that most cases of stabbing headache are benign and self-limiting without treatment. However, a few studies have reported structural intracranial or extracranial disorders and systemic autoimmune disorders,[7,8] suggesting that neuroimaging may be necessary when clinical features do not match the typical features of PSH. With regard to treatment, PSH is regarded as one of the indomethacin-responsive headaches.[9] As indomethacin can demonstrate inadequate response and may contraindicate or be intolerable to individual patients, a number of different treatments have been attempted, with some demonstrating efficacy in clinical trials despite small case studies. Treatment may therefore be selected based on individual clinical features and comorbidities. This review aims to provide an up-to-date review of epidemiology, clinical features, diagnostic criteria, differential diagnosis, and treatment of PSH.

EPIDEMIOLOGY

The prevalence of PSH exhibit significant variability across different epidemiological studies. This variability is influenced by several factors, including age, sex, referral bias, the definition of PSH, and the presence of comorbid headache disorders. Reported prevalence rates for PSH range from 0.2% to 35.2% in general population and 1.5% to 26.7% in hospital- and clinic-based studies, respectively. In general population, the largest study specifically examining PSH prevalence was conducted in Vågå, Norway, where 1,779 parishioners were questioned about head pain described as jabs.[10] This study reported a high lifetime prevalence of 35.2%. In contrast, other studies have reported significantly lower prevalence. In a large study of primary headache disorders, 1,000 individuals in Copenhagen were interviewed, and only 2% reported a lifetime occurrence of stabbing headache.[11] Similarly, a population study in Porto involving 2,008 subjects found a lifetime prevalence of only 0.2%.[12] In addition, hospital- and clinic-based studies have been performed to investigate the prevalence. A study of 1,219 patients presenting to a tertiary neurology clinic in China found that isolated PSH had a prevalence of 1.5%.[13] In a Turkish headache clinic, a prevalence of 12.6% were reported.[14] In Spanish and Taiwanese headache clinics, 5% of 725 patients and 13% of 872 patients, respectively, were reported.[15,16] In Korea, the self-reported lifetime prevalence rates of PSH were 11.0% among patients with headache and 26.7% among neurologists in different hospitals.[17,18] These differences between patients and neurologists might reflect under diagnosis of PSH in general populations.

PSH is more common in females within the adult population, with a female-to-male ratio ranging from 1.49 to 6.6:1.[10,19] The mean age of onset for PSH in adults ranges from 28 to 53, with significant variation across previous studies.[10,16,20] A family history of migraine was reported in 34.8%–40.5% of patients with PSH.[21,22] PSH can occur in isolation or in association with other headache types, including migraine and tension-type headache, with migraine being the most common. A prevalence of approximately 40% has been reported in patients with migraine.[23]

In childhood, the prevalence of PSH ranges from 3.35% to 9.97%.[24-26] Age of onset for PSH is between 4.5 and 9 years, with 12.4% of cases occurring in children younger than 6 years old.[27] Recently, the prevalence of PSH were found to be 77 patients (9.97%) of 772 children and adolescents, indicating that it is not uncommon among thisagegroup.[26] In this study, 0.9% of patients experienced the onset of PSH before the age of six, with a mean onset age of 10.9±3.5 years (ranging from 4 to 16 years).[26] The sex distribution among children with PSH is not consistent across studies.

CLINICAL CHARACTERISTICS

Patients typically describe the pain as stabbing or piercing without a pulsatile component.[28] This stabbing pain occurs spontaneously and in irregular patterns, with no circadian or circannual rhythm, and can even wake patients from sleep.[16] The severity of pain reported by patients shows considerable variation across different studies. While the Vågå study found that 93% of patients described their pain as mild to moderate, other studies indicate that the majority of patients experience pain that is moderate to severe.[20] Pediatric studies show no significant difference in pain severity, with most patients reporting moderate to severe pain. Based on the previous epidemiological and clinical studies, 80% of attacks last 3 seconds or less, although occasionally they can last from 10 to 120 seconds.[16,19] The majority of patients experience single, brief stabs of pain, although they may also present with a series of stabs. Attacks of stabbing pain are typically infrequent, occurring one to a few times a day. However, on rare occasions, the pain can occur repeatedly for days to 1 week.[6,16,19] At times, patients may experience more than a dozen attacks per day. Initially, the pain was believed to be localized to the first branch of the trigeminal nerve, with previous studies indicating that 45%–62% of patients with PSH experienced pain exclusively in the V1 distribution.[16,19] However, more recent research indicates that up to 70% of patients also experience stabbing pain in areas other than the trigeminal nerve, including the occipital, nuchal, and parietal regions innervated by nerves C2–C4.[16] The stabbing pain may manifest unilaterally or bilaterally, with unilateral location reported in 59%–91.4% of patients.[3,29] During the stabs, symptoms such as jolts, allodynia, vocalization, and bodily jabs can be accompanied. Among them, jolts and allodynia are commonly observed. Jolts can accompany the stabbing pain in 38%–74% of cases, while allodynia is present in 19%–37% of patients with PSH.[4,16] Vocalization was observed in 18% of patients, while bodily jabs were seen in only 1.1% of those with PSH.[16,30] Nausea and vomiting (7%–11.1%), photophobia and phonophobia (8%–22.2%), and dizziness (5.6%–8%) were uncommon accompanying symptoms.[13,16,24] In contrast to trigeminal autonomic cephalalgias (TACs), PSH do not present with cranial autonomic features such as tearing or ptosis during the pain attacks. Although similar findings have been observed in pediatric studies, one study reported that vertigo, nausea, photophobia, and phonophobia can occur in as high as 47% of children with stabbing headache.[24]

In recent studies, clinical courses and patterns of PSH have been proposed, including monophasic, intermittent, and chronic.[4,31] The patterns were identified based on the frequency of stabbing pain, the clinical course, and the total disease duration. Stabbing pain in the monophasic pattern was characterized by greater severity, higher frequency, side-locked location, and single stabs that typically responded well to treatments such as indomethacin, steroids, gabapentin, or tricyclic antidepressants. In contrast, the chronic daily stabbing pain pattern was associated with a longer duration, variable location, multiple stabs, less responsiveness to treatment, and a higher prevalence among female patients.[4]

DIAGNOSTIC CRITERIA

The diagnosis of PSH is based on the clinical characteristics outlined in the ICHD criteria (Table 1).[6] Over time, there have been two significant changes to the diagnostic criteria for PSH. The first is the location of pain, and the second is the accompanying symptoms. In the ICHD-2 criteria published in 2004, the diagnosis of PSH was restricted to the first branch of the trigeminal nerve.[5] However, according to some later studies, PSH was localized in extra-trigeminal regions such as behind the ear, frontal, parietal, and occipital regions, implying that the head can be all involved. Consequently, in 2018, the ICHD-3 criteria, which limited the location of pain to the first branch of the trigeminal nerve, were abandoned.[6] In accompanying symptoms of ICHD-2, no accompanying symptoms were included for the diagnosis of PSH. However, accompanying symptoms such as allodynia, nausea and vomiting, and photophobia or phonophobia have been reported. Consequently, the ICHD-3 revised the diagnostic criteria for PSH, changing no accompanying symptom to no cranial autonomic symptoms.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for PSH encompasses a range of short-lasting, stabbing primary and secondary headache disorders. Among the primary headache disorders, the

Table 1. Diagnostic criteria of primary stabbing headache in the ICHD-3

Primary stabbing headache
A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B and C
B. Each stab lasts for up to a few seconds*
C. Stabs recur with irregular frequency, from one to many per day†
D. No cranial autonomic symptoms
E. Not better accounted for by another ICHD-3 diagnosis.
Probable primary stabbing headache
A. Head pain occurring spontaneously as a single stab or series of stabs
B. Two only of the following:
1. Each stab lasts for up to a few seconds
2. Stabs recur with irregular frequency, from one to many per day
3. No cranial autonomic symptoms
C. Not fulfilling ICHD-3 criteria for any other headache disorder
D. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3, International Classification of Headache Disorders, third edition.
*Studies show that 80% of stabs last 3 seconds or less; rarely, stabs last for 10–120 seconds. †The attack frequency is generally low, with one or a few per day. In rare cases, stabs occur repetitively over days, and there has been one description of stabs lasting 1 week.
Adapted from the article of Headache Classification Committee of the International Headache Society (IHS) (Cephalalgia 2018;38:1-211).[6]

short-duration primary headache category includes trigeminal neuralgia, TACs such as paroxysmal hemicrania, SUNA and SUNCT. Trigeminal neuralgia is a unilateral disorder characterized by brief electric shock-like attacks of pain limited to the distribution of one or more divisions of the trigeminal nerve. The attacks of pain are often precipitated by mechanical stimulation such as speaking, eating, or brushing teeth. The distribution of pain and provocative factors differentiate trigeminal neuralgia from PSH. TACs must have unilateral cranial autonomic features by definition. The presence or absence of autonomic symptoms represents a key differentiating factor between a TAC and PSH.

Stabbing headaches have been described as the presenting symptom in pituitary tumours,[32] intracranial meningioma,[33] herpetic meningoencephalitis,[34] stroke,[35] and giant cell arteritis.[36] Therefore, underlying pathology should be considered in patients presenting with new complaints of stabbing headaches. Furthermore, there have been reports of stabbing headaches in patients with autoimmune disorders, including multiple sclerosis, lupus, Behcet's disease, Sjogren's syndrome, vasculitis, antiphospholipid antibody syndrome, and Lyme disease.[8] A recent studies have identified clinical red flag signs that are associated with secondary causes. These include the recent onset of stabbing headache, which is exclusively unilateral (ipsilateral) at the same location, a crescendo pattern, which is triggered by head movements, or a Valsalva maneuver.[7]

Although the prevalence of secondary headache disorders manifesting as stabbing headaches was low, brain imaging such as computed tomography or magnetic resonance imaging could be considered to investigate for potential secondary structural disorders. It is also reasonable to perform blood evaluation, including erythrocyte sedimentation rate, in patients over the age of 50 who present with stabbing pain, particularly if they have additional features of giant cell arteritis.

PATHOPHYSIOLOGY

The pathophysiology of PSH remains unclear. Proposed theories include irritation of peripheral branches of the trigeminal nerve or other cranial nerves, as well as intermittent dysfunction of central pain processing leading to spontaneous synchronous discharges or hyperexcitability of neurons.[37,38] It is hypothesized that irritation or spontaneous firing of the peripheral branches of the trigeminal nerve cause stabbing pain. The pain of PSH, which is very short-lasting, focal, and not triggered by external stimuli, suggests a spontaneous and temporary firing of nociceptive nerve endings, specifically A-delta fibers, originating from sensory afferents in the head, such as the trigeminal and occipital nerves.[16] The intermittent nature of most PSH, characterized by infrequent stabs and normal sensory function between episodes, implies a nonpathological process without axonal damage. Nociceptive Schwann cells, recently identified in both mice and humans, might fail transiently in their pain gating function, leading to spontaneous nerve firing.[39] However, as the location of pain often does not correspond to the distribution of the trigeminal nerve, the pathogenesis is likely to be more complex.[37]

Dysfunction of central pain processing secondary to peripheral mechanisms can be another proposed mechanism. Extra-trigeminal stabbing headaches can occur in cephalic regions innervated by C2–C4. Pain signals from

these upper cervical areas, similar to those from trigeminal inputs, are transmitted to the trigemino-cervical complex. This suggests that both trigeminal and extra-trigeminal sources may converge on central pain control mechanisms that may be defective.[16] Central sensitization may be another central mechanism for intermittent and chronic daily PSH. This may explain the long-term course, migrating pain locations, allodynia, and bodily jabs observed in PSH patients. High prevalence of PSH with migraine has also suggested the proposed segmental disinhibition of central pain processing.[38]

TREATMENT

In patients with infrequent attacks, the explanation that PSH is a benign condition may be sufficient and treatment may not be necessary. However, high frequency of stabbing attacks may require intervention. Due to pain paroxysms, treatment is aimed at prophylactic suppression of the attacks. PSH is considered to be one of the indomethacin-responsive headache syndromes.[40] In PSH, the therapeutic mechanism of indomethacin may be its anti-inflammatory and vasoconstrictive properties.[41,42] It is a nonsteroidal anti-inflammatory drug that exerts its effects through reversible inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes. It also impedes polymorphonuclear leukocyte motility, reduces mucopolysaccharide synthesis, and may induce vasoconstriction.[42] Furthermore, indomethacin is known to inhibit nitric oxide release, decrease cerebral blood flow, and lower cerebrospinal fluid pressure.[41] Patients with PSH have been reported to respond quickly to indomethacin ranging from 75–250 mg/day given in divided doses. Dose-related side effects include dyspepsia, gastrointestinal bleed, and renal toxin.[40] Long-term treatment with indomethacin may also result in gastrointestinal and renal side effects. Furthermore, the response rate to indomethacin was found to be inconsistent across clinical studies, with remission rates ranging from 20% to 57%.[15,16,19] Therefore, other treatment options for patients who are unable to tolerate indomethacin or are not responsive to indomethacin.

Alternative agents reported to be effective in small series of patients include other COX-2 inhibitors,[43-45] prednisolone, melatonin,[46] gabapentin,[47] topiramate,[48] acetazolamide,[49] amitriptyline,[50] and onabotulinum toxinA.[51] In cases where a series of treatments utilizing selective COX-2 inhibitors such as celecoxib and etoricoxib were used, a favourable response was observed. Melatonin is a pineal hormone and marker of circadian function. Its chemical structure is very similar to that of indomethacin. In cases series, patients had complete remission with melatonin, 3–21 mg at night.[46] In this study, a strategy which starting with a bedtime dose of 3 mg and increasing by 3 mg every three to four nights until pain relief, with 24 mg as an upper dose limit was recommended. In other cases, gabapentin 400 mg every 12 hours have also been reported to be effective.[47] All patients had complete relief of pain already in the first days of treatment. The precise mechanisms of action of gabapentin are still not completely defined but are probably related to both peripheral and central pathways of pain suppression. Gabapentin may have an effect by inhibiting ectopic discharge activity from injured peripheral nerves.[52] In case reports, topiramate 100 mg per day and acetazolamide 250 mg twice per day was effective in the treatment of PSH.[48,49] In other case series, two patients were treated with amitriptyline, a single dose of 10–25 mg at bedtime with significant improvement within the first month of treatment.[50] Onabotulinum toxinA was studied in a prospective, unblinded study in 24 patients with PSH.[51] Patients received five units of onabotulinum toxinA into each area where they experienced the stabs with the mean dose 11.81±7.17 units. Among them, 22 patients showed partial-response and three patients full-response.

The treatment plan for PSH could be tailored according to the specific clinical pattern presented in a recent prospective study: monophasic, intermittent, and chronic.[4] For a monophasic pattern, characterized by a single episode, short-term treatment with indomethacin, COX-2 inhibitors and/or prednisolone can provide quick relief. For an intermittent pattern, involving sporadic episodes over weeks to months, preventive and abortive treatments with indomethacin and/or melatonin, gabapentin, topiramate, acetazolamide, or amitriptyline may reduce frequency and severity. Chronic patterns, defined by daily or near-daily episodes, require consistent preventive approaches with long-term use of indomethacin and/or botulinum toxinA injections, along with regular monitoring and dosage adjustments. Adjunctive therapies such as lifestyle modifications, including regular sleep patterns, stress management, and avoiding known triggers, can further help manage

headache frequency and severity.

While there is limited information available regarding the treatment of PSH in children and adolescents, it's noted that the number of reported cases is small. Nonetheless, the general treatment strategy should be similar to that of adult patients.

PROGNOSIS

Previous studies of PSH have indicated that both population-based and clinic-based subjects exhibited a wide variety of disease durations, ranging from a few days to several years.[10,16] Although there have been no prospective studies on the prognosis of PSH, it is generally regarded as a benign condition that may resolve over time. However, in a recent study, half of patients with PSH experienced spontaneous remission, while the other half required medical treatment to reach remission. This study has indicated that the prognosis of PSH may depend on the individual clinical courses.[4] Patients with the intermittent subtype may experience relapses at variable frequencies over several years. This subtype may progress to the chronic daily subtype, although this has been reported in a very small number of patients. In patients with the chronic subtype, the majority may not respond to treatment and continue to experience chronic daily headaches. The chronic daily pattern was associated with multiple or migrating locations, slightly longer-lasting stabs, frequent allodynia, and bodily jabs.[4]

SUMMARY

Clinical features of PSH were summarized on Table 2. The evolution of diagnostic criteria has expanded understanding of its clinical features and epidemiology, revealing a wide prevalence range influenced by demographic factors. While treatment options such as indomethacin and alternative agents exist, prognosis varies among patients. Further research is needed to elucidate the underlying pathophysiology and optimize management strategies for PSH. This comprehensive review serves to highlight the necessity of recognizing the distinctive clinical profile of PSH and of tailoring treatment approaches to the individual needs of patients.

Table 2. Summary of the clinical features of PSH

	Main feature
Prevalence	0.2%–35.2%
F:M ratio	Female predominance (1.49–6.6:1)
Mean age at onset (yr)	28–53
Comorbid headache	Migraine and tension-type headache, with migraine being the most common
Pain location	Can be anywhere on the head
Pain side	Can be bilateral or unilateral and switch between attacks
Severity	Mild to severe
Accompanying symptoms	Jolts (38%–74%)
	Allodynia (19%–37%),
	Vocalization (18%)
	Bodily jabs (1.1%)
	Photophobia and phonophobia (8%–22.2%)
	Nausea (7%–11.1%)
	Dizziness (5.6%–8%)
Treatment	Indomethacin (75–250 mg/day) is most widely used
	Cyclooxygenase type 2 inhibitors, prednisolone, melatonin, gabapentin, topiramate, acetazolamide, and onabotulinum toxinA

PSH, primary stabbing headache; F:M, female-to-male.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: SC; Data curation: SC; Investigation: SC; Writing–original draft: AC (Ayush), SC; Writing–review and editing: AC (Avinash), SC.

CONFLICT OF INTEREST

Soohyun Cho is the Editor of *Headache and Pain Research* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

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Letter to the Editor

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하나로[1] 더 강력하게![2,3]

수벡스정

수벡스정
(Sumatriptan/Naproxen sodium)

† SUMATRIPTAN, SUMATRIPTAN SUCCINATE.
§ NAPROXEN, NAPROXEN SODIUM

REFERENCES 1. 의약품안전나라_의약품등 정보검색(검색어: 수벡스정). Available at https://nedrug.mfds.go.kr/searchDrug. Accessed on 29 of Jul, 2024. 2. 대한두통학회. 편두통 진료지침 제2판. 2009 Nov. Available from: https://www.headache.or.kr/bbs/board.php?bo_table=3_1_1&wr_id=1. 3. Brandes JL, et al. Sumatriptan–naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007 Apr 4;297(13):1443-54.

수벡스정 제품요약정보

[제품명] • 수벡스정 **[원료약품 및 그 분량]** 이 약 1정 중 유효성분: 수마트립탄숙신산염·119mg (수마트립탄으로서 85mg), 나프록센나트륨·500mg **[효능·효과]** 18세 이상의 성인 환자에서 전조증상을 수반하거나 수반하지 않는 편두통의 급성 치료 **[용법용량]** 이 약은 꼬개거나 씹거나 또는 부수지 말고 물과 함께 그대로 삼켜서 복용한다. 이 약은 편두통 예방 목적으로는 복용하지 않는다. ○ 성인 : 이 약의 권장 복용량은 1일 1정(수마트립탄 85mg/나프록센나트륨500mg)이다. 24시간 동안 최대 권장 용량은 2정을 초과해서는 안된다. 이 때, 투여 간격은 최소 2시간 간격을 두고 복용해야 한다. 최초 1정 투여 후 재투여에 대한 효과는 체계적으로 평가되지 않았다. 최초 1정 투여 후 재투여를 고려하는 경우 재투여에 대한 효과는 확립되지 않았다. 30일 동안 평균 5회 이상의 편두통에 대한 이 약의 안전성은 확립되지 않았다. 이 약은 수마트립탄숙신산염의 최소 유효용량보다 높은 용량을 포함하고 있으므로 환자별로 높은 용량의 수마트립탄에 대한 유익성과 더 높은 이상반응의 위험성을 고려하여 이 약의 사용하여야 한다. 개별 환자 치료목적에 맞게 최소 유효용량을 최단기간 동안 사용해야 한다. ○ 신 장애 환자 : 이 약은 신부전 환자와 중증의 신 장애(크레아티닌 청소율 < 30 mL/min) 환자에게 투여해서는 안된다. 이 약은 경증–중등증의 신 장애 환자에서의 투여는 권장되지 않는다. ○ 간 장애 환자 : 이 약은 중등도–중증(Child-Pugh B and C) 간 장애 환자에게 투여해서는 안된다. 이 약은 경증의 간장애 환자에서의 투여는 권장되지 않는다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 : 1) 수마트립탄, 나프록센 및 이 약의 구성성분에 과민증이 있는 환자 2) 설폰아미드에 과민반응 병력이 있는 환자(중각) 3) 아스피린이나 기타 비스테로이드성 소염진통제의 투여에 의하여 천식, 비염, 코의 용종, 두드러기, 알레르기 반응 또는 그 병력이 있는 환자 (중각) 4) 허혈성 관상동맥질환(중각), 심근박질환, 부정맥(특히 빈맥)의 증상, 징후 또는 그 병력이 있는 환자 또는 프린즈메탈 협심증을 포함한 관상동맥연축 병력이 있는 환자 5) 장각적인 상처관 질환 환자(중각) 6) 관상동맥 우회로술(CABG)을 받기 직후의 환자 7) Wolff-Parkinson-White 증후군 또는 기타 심장 부전도 경로 장애가 있는 환자 8) 조절되지 않는 고혈압 환자, 중등도 또는 중증 고혈압 환자 9) 심한 심기능부전 환자 10) 뇌혈관성 우발증상(CVA), 뇌졸중, 일시적인 허혈성 발작(TIA) 병력이 있는 환자 11) 편마비, 경련, 눈근육 경련 및 마비, 시각 장애를 동반한 편두통 또는 뇌저성 편두통 병력이 있는 환자 12) 말초혈관 질환 환자 13) 허혈성 장 질환, 염증성 장 질환 환자 14) 활동성 소화성 궤양, 활동성 장출혈 환자 15) 뇌혈관 출혈, 기타 출혈 질환 또는 심한 혈액이상 환자 16) 중등증 또는 중증 간장애 환자 17) 중증 신장애 환자 18) 고칼륨혈증 환자 19) 임부 또는 임신하고 있을 가능성이 있는 여성, 수유부 20) 18세 미만의 소아 및 청소년 21) 에르고타민 및 그 유도체 함유제제(methysergide 포함) 또는 다른 트립탄, 5-HT1 수용체 효능제를 복용하는 환자 22) MAO 억제제를 투여 중이거나 투여 중단 후 2주 이내의 환자, 선택성 5-HT 재흡수 억제제, 클로미프라민 또는 리튬을 투여 받고 있는 환자 **[제조자]** Halo Pharmaceutical Incorporated, 미국, 30 North Jefferson Road, Whippany, New Jersey 07981, USA **[소분제조자]** 에스케이케미칼(주) 충청북도 청주시 흥덕구 산단로 149 **[판매자]** 에스케이케미칼(주) 경기도 성남시 분당구 판교로 310
2023.10.30 개정
※처방하시기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는 '식품의약품안전처 의약품안전나라 (https://nedrug.mfds.go.kr/index)'에서 확인할 수 있습니다.

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전문의약품

[유효성분] 1프리필드시린지/1오토인젝터(1.5 밀리리터) 중 프레마네주맙(별규) 225밀리그램 **[효능효과]** 성인에서의 편두통의 예방 **[용법용량]** 이 약은 1회 225mg을 1개월 간격 또는 1회 675mg(225mg 3회 연속)을 3개월 간격으로 피하 주사한다. 투여간격을 변경할 경우 다음 예정일부터 새로운 투여 일정으로 투여한다. 이 약의 투여를 잊은 경우 가능한 한 빨리 투여한다. 이후 최종 투여 일자를 기준으로 이 약의 투여 일정을 정할 수 있다. **[수입자]** ㈜한독테바, 서울시 강남구 테헤란로 132 **자세한 품목허가 사항은 식품의약품안전처 의약품통합정보시스템 (http://nedrug.mfds.go.kr) 또는 제품의 첨부문서를 확인하여 주시기 바랍니다.** ☎소비자 상담전화(02-527-5506)

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