BMJ Neurology Open

Adverse and serious adverse events incidence of pharmacological interventions for managing chronic and episodic migraine in adults: a systematic review

Seyran Naghdi ,[1] Martin Underwood,[1,2] Anna Brown,[3] Manjit Matharu,[4] Callum Duncan ,[5] Natasha Davies,[3] Aiva Aksentyte,[3] Hema Mistry [1,2]

To cite: Naghdi S, Underwood M, Brown A, *et al*. Adverse and serious adverse events incidence of pharmacological interventions for managing chronic and episodic migraine in adults: a systematic review. *BMJ Neurology Open* 2024;**6**:e000616. doi:10.1136/bmjno-2023-000616

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjno-2023-000616).

Received 17 December 2023
Accepted 01 April 2024

For numbered affiliations see end of article.

Correspondence to
Dr Hema Mistry;
Hema.Mistry@warwick.ac.uk

ABSTRACT

Background Migraine is the second most common prevalent disorder worldwide and is a top cause of disability with a substantial economic burden. Many preventive migraine medications have notable side effects that affect different body organs.

Method We systematically searched for published randomised controlled trials (RCTs) using terms for migraine/headache and preventive medications. Using eligibility criteria, two reviewers independently assessed the articles. Cochrane risk-of-bias tool was applied to assess the quality of the studies. Data were classified by system organ class (SOC).

Results Thirty-two RCTs with 21 780 participants met the eligibility criteria for the incidence of adverse events (AEs). Additionally, 33 RCTs with 22 615 participants were included to synthesise the incidence of serious AEs (SAEs). The percentage of attributed AEs and SAEs to each SOC for 10 preventive drugs with different dosing regimens was calculated. Amitriptyline and topiramate had a higher incidence of nervous system disorders; Topiramate was also associated with a higher incidence of psychiatric disorders. All drugs showed a certain incidence of infections and infestations, with Onabotulinumtoxin A (BTA) having the lowest rate. BTA had a higher incidence of musculoskeletal disorders than the other drugs. Calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) such as fremanezumab and galcanezumab were linked to more general disorders and administration site conditions than other drugs.

Conclusion Notably, the observed harm to SOCs varies among these preventive drugs. We suggest conducting head-to-head RCTs to evaluate the safety profile of oral medications, BTA, and CGRP MAbs in episodic and/or chronic migraine populations.

PROSPERO registration number CRD42021265993.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current landscape of migraine management involves preventive medications with notable side effects, contributing to challenges in adherence and treatment discontinuation. While previous reviews have explored the safety of migraine medications, there remains a gap in understanding how these pharmacological treatments affect specific organs in the body.

WHAT THIS STUDY ADDS

⇒ This study contributes by systematically evaluating adverse events and serious adverse events associated with 10 preventive migraine medications. Notably, it identifies varying safety profiles, with amitriptyline and topiramate showing higher adverse event incidence particularly in the nervous system, while newer treatments exhibit limited adverse events, emphasising the need for head-to-head trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further head-to-head randomised controlled trials to evaluate the safety profile of oral medications, Onabotulinumtoxin A and calcitonin gene-related peptide monoclonal antibodies in episodic and/or chronic migraine populations is encouraged.

BACKGROUND

Migraine ranks as the second most prevalent disabling condition worldwide, and it is the top cause of years lived with disability among individuals aged 15–49 years.[1] Migraine is a recurrent condition characterised by headaches lasting from 4 hours to 72 hours. These headaches are described as pulsating, typically unilateral, and can be moderate to severe in intensity. Migraine symptoms include nausea and/or vomiting, sensitivity to light and/or sound and can be aggravated from routine physical activity.[2] Migraine can significantly impact the patient's work–life, social and leisure activities as well as their physical and emotional well-being. This, in turn, can result in a considerable burden on

patients and their families and also an increase in healthcare expenditure.[3] The frequency of migraine episodes determines its classification: up to 14 migraine days per month is classified as 'episodic', while a headache occurring on 15 or more days per month, with at least 8 days meeting migraine criteria, is classified as 'chronic'.[4]

Currently, various migraine preventive therapies are recommended for individuals who experience four or more migraine attacks per month, have overused or failed on acute medication or suffer from significant migraine-related impairment in daily functioning or quality of life.[5] Many preventive migraine medications have notable side effects, including fatigue, memory problems, mental confusion, weight gain and sexual dysfunction. Poor adherence and persistence with preventive treatments for migraine are common, and adverse events frequently lead to treatment discontinuation.[5]

The published literature reveals a complex view regarding patient preferences and side effects related to migraine preventive drugs. Among the side effects, depression, memory loss and weight gain are the least accepted.[6] Women show a greater aversion to weight gain.[6] A 2019 choice experiment demonstrated that avoiding a 10% increase in weight was more desired by participants than avoiding issues with memory and reasoning.[5] Thus, it is important to have a picture of the side effects of each of these preventive drugs.

Although systematic reviews and meta-analyses have been conducted to assess the safety of head-to-head medications,[7–14] there is currently no evidence available to compare the safety profiles of pharmacological medications for migraine and determine which organs in the body are affected. This review aims to synthesise evidence on the incidence of adverse events (AEs) and serious AEs (SAEs) in people with chronic or episodic migraine.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews.[15] No ethical approval was required. We considered the following standard definitions for AEs and SAEs (table 1).

Search strategy

The search strategy was constructed in MEDLINE by an information specialist and checked by another information specialist for any errors before being translated to other bibliographic databases. No date or language limits were applied. The following databases were searched in September 2021: MEDLINE (Ovid), Embase (Ovid), Cochrane CENTRAL, Science Citation Index Expanded (Web of Science), Global Index Medicus, ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform.

A supplemental search was performed in February 2022 for three medicines which are currently used in the UK which were not included in the original search: riboflavin, magnesium & CoQ-10. An additional, pragmatic search was also conducted to identify recent systematic reviews of migraine preventive drugs. The reference lists of the outputs of this search, those of the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and American Headache Society guidelines were checked for relevant literature. Authors of key studies were contacted and forward and backward citation tracking was conducted on all included papers.

We reran all searches in November 2022 and in June 2023 to identify any new publications. Full details of all searches are provided in online supplemental appendix 1. We used EndNote V.X20[16] to manage references including the removal of duplicates.

Eligibility and study selection

We only included randomised controlled trials (RCTs) with more than 100 participants per arm and defined AEs and SAEs according to the standard definitions in table 1. Our focus was on adult participants aged 18 years or older with chronic or episodic migraine. We considered pharmacological medications available in the UK or expected to become available, and compared them with placebo, usual care or other preventative drugs. We excluded traditional Chinese medicines, non-UK herbal remedies, non-pharmacological interventions, dose–response trials and drugs not recommended by NICE or SIGN. We did not include data on discontinuation or withdrawal from trials.

Table 1 : Definitions of key terms

Adverse events (AEs)	An AE that is not a SAE, meaning that it does not result in death, is not life-threatening, does not require inpatient hospitalisation or extend a current hospital stay, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, and does not cause a congenital anomaly or birth defect; it also does not put the participant in danger and does not require medical or surgical intervention to prevent one of the results listed above.[17]
Serious adverse events (SAEs)	An adverse event that results in death, is life-threatening, requires inpatient hospitalisation or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalisation may be considered SAEs if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.[17]

Our outcomes of interest were AEs, treatment-related AEs (TAEs), SAEs and treatment-related SAEs (TSAEs).

Two reviewers (AB and SN) assessed title and abstract screening first, and then abstract and full text screening were conducted by a combination of four reviewers (MU, SN, AA and ND). Discrepancies were resolved through discussion by a third reviewer (CD or MM).

Data extraction and synthesis

Data from included studies were extracted by one reviewer (SN) using a predetermined data extraction form in Microsoft Excel and checked for accuracy and completeness by a second reviewer (SK). Information collected included study characteristics, participant demographics, treatment details and adverse event definitions as well as data on adverse events, TAEs, serious adverse events and TSAEs.

We applied the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0[17] to classify the adverse events and serious adverse events and calculated their proportion for each system organ class (SOC) and preventive drug.

Quality assessment

The Cochrane risk-of-bias tool for RCTs[18] was applied to assess the risk of bias by SN. To ensure the accuracy, 20% of studies was checked by SK.

RESULTS

Study selection

Out of 19 111 initial records after removal of duplicates, 18 777 were excluded during title and abstract screening. Three-hundred and thirty-four records were assessed for eligibility and 59 articles reporting data from 33 trials were included after full text assessment (see online supplemental appendix 2 for excluded studies).[19–57] Although many of these linked articles were cited, we only used the main trial paper for the main citation, as the other linked papers only reported some subgroup analyses, were either repetitive or combined the data. The PRISMA flow diagram summarises study selection results (figure 1).

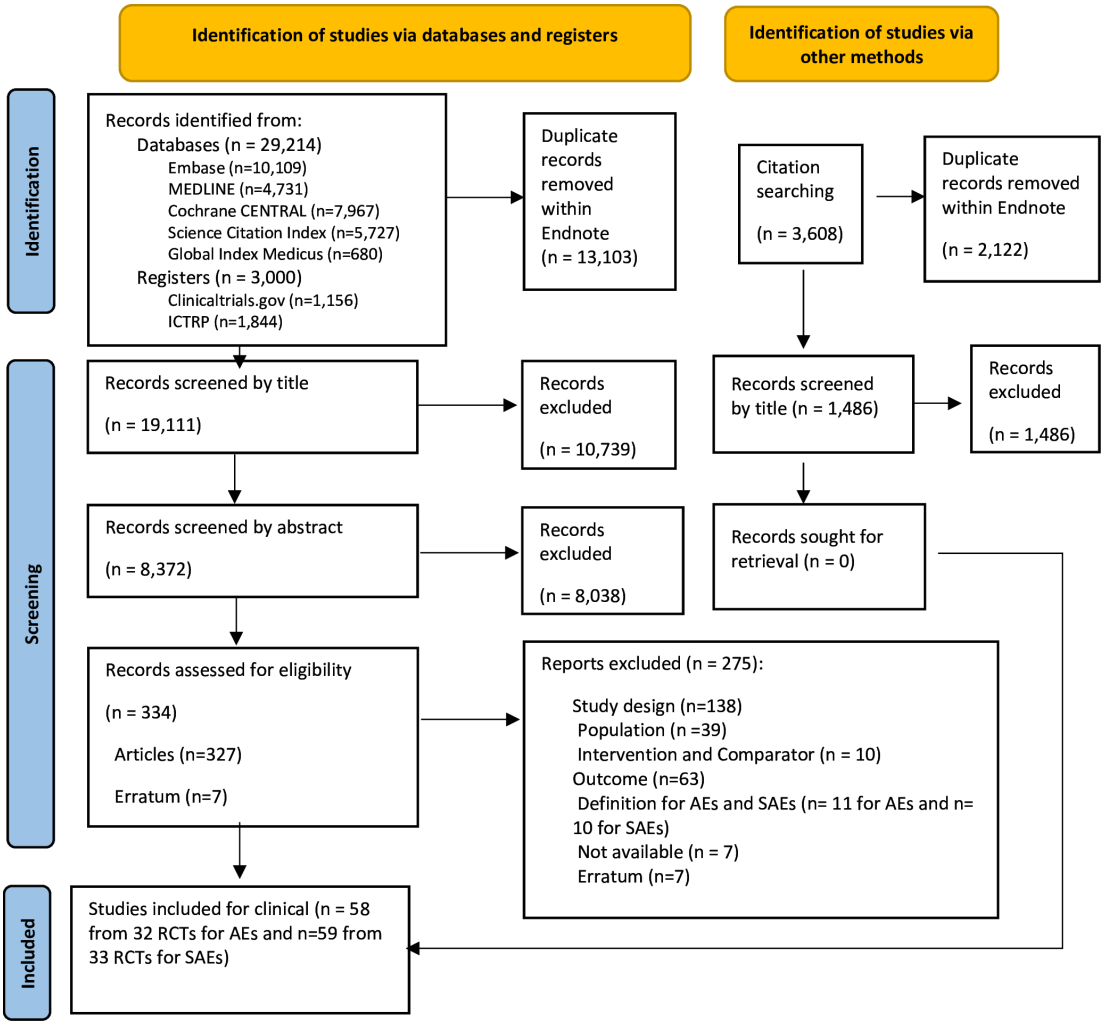


Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials; SAEs, serious adverse events.

Study characteristics

The patients in each of the included studies satisfied the diagnostic criteria of chronic or episodic migraine in accordance with the International Classification of Headache Disorders.[58] Nineteen RCTs included only participants with episodic migraine,[19 21 36–45 47–49 51–53 55] nine RCTs enrolled participants exclusively with chronic migraine,[20 22–26 29–31 35 57] and five RCTs had a mixed population of both chronic or episodic migraine participants.[34 46 50 54 56] All of the RCTs were conducted across multiple centres. The number of participants randomised across the 33 trials evaluating the safety of pharmacological treatment ranged from 217[39] to 1379[25] with a total of 22 615 participants. The mean age of trial participants ranged from 36[30] to 46[34] years; and the percentage of female participants ranged from 74%[53] to 91%.[54]

Most of the trials utilised double-blinded designs except two trials that were classed as open-label.[35 55] Treatment duration varied across the trials; one trial had a 4-week treatment duration,[52] while 19 trials reported 12 weeks.[20–22 29–31 34 36 37 39 40 42 47–51 53 57] Additionally, one trial had a treatment duration of 22 weeks,[41] 11 trials reported a 24-week treatment duration,[21 25 26 35 38 43–46 54 56] and for one trial the treatment duration was 52 weeks.[55]

The included studies evaluated 20 different dosing regimens of nine drugs, including calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) (eptinezumab 100 mg and 300 mg, erenumab 70 mg and 140 mg, fremanezumab 225 mg and 675 mg and galcanezumab 120 mg, 150 mg and 240 mg), onabotulinumtoxin A (BTA) 7U, 25U, 50U, 155U and 195U, topiramate 100 mg, atogepant 10 mg, 30 mg and 60 mg, amitriptyline 25 mg to 100 mg and rimegepant 75 mg. Further details of included characteristics of these studies are presented in online supplemental table 1 and online supplemental appendix 3.

Adverse events

Thirty-two studies reported adverse events for 20 different dosing regimens of nine drugs with 21 780 participants.[19–57] The most reported adverse events belonged to Amitriptyline 25 mg to 100 mg and galcanezumab 150 mg with 89%[39 41] and 72.0%,[39] respectively. The lowest number of any adverse events are for erenumab 140 mg (33%).[31 43 46–48] Online supplemental table 2 summarises the pooled adverse events as reported in the 32 trials; we have highlighted in bold for each SOC the medication, which contributed to the largest percentage of AEs. For example, for gastrointestinal disorders, amitriptyline (25 mg to 100 mg) had the highest percentage of adverse events (59%); and for nervous system disorders, topiramate 100 mg was attributed with the highest percentage of AEs at 60%. Table 2 presents the most common adverse events for each medication. For example, participants in the amitriptyline (25 mg to 100 mg) group experienced dry mouth (36%), and participants in the topiramate 100 mg group suffered from paraesthesia (36%). Further details of adverse events for each individual study categorised according to SOC are presented in online supplemental appendix 4, online supplemental tables 2–17.

Serious adverse events

Serious adverse events were reported in 33 trials, evaluating 20 different dosing regimens of nine drugs with data from 22 615 participants.[19–57] One trial did not report the number of people with SAEs, but the results indicated no treatment-related SAEs.[49] Thus, SAEs from 32 trials with 21 643 participants were combined, and online supplemental table 3 shows the percentage of attributed SAEs for each SOC. In online supplemental table 3, we have highlighted in bold for each SOC the medication, which contributed to the largest percentage of SAEs. For example, for infections and infestations, topiramate 100 mg had the highest percentage of serious adverse events (1.13%); and for neoplasm-benign malignant and unspecified, BTA was attributed with the highest percentage of SAEs at 1.21%. Further information on the incidence of SAEs for each dosing regimen is found in online supplemental appendix 5, online supplemental tables 19 to 40.

Risk of bias assessment

Figure 2 and online supplemental table 1 provide a summary of the risk of bias results. In terms of overall risk of bias, two trials were rated as being at high risk of bias,[35 55] 16 trials at medium risk of bias[22 29 30 38 39 41 44–47 49–51 53 54 57] and 15 trials at low risk of bias.[19–21 25 26 31 34 36 37 40 42 43 48 52 56] Overall, there were no major concerns that the studies were not applicable to the research question for this review.

DISCUSSION

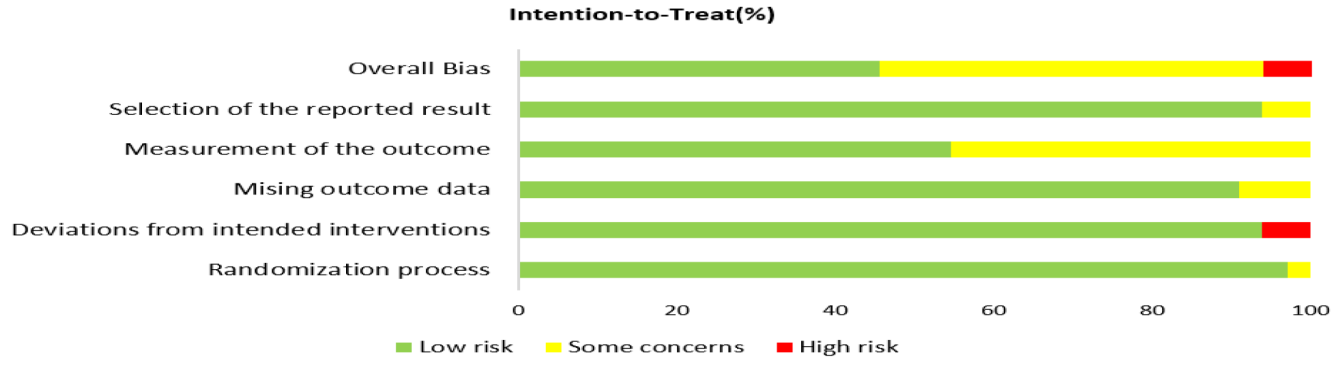
Overview and key findings

We systematically reviewed and narratively synthesised the incidence of adverse and serious adverse events from 33 clinical trials involving 22 615 participants with chronic or episodic migraine.[19–57] Our findings suggest that all the pharmacological interventions reviewed were well tolerated, although the incidence of adverse events varied among the drugs. For instance, amitriptyline and topiramate had a higher incidence of adverse events in nervous system disorders, while rimegepant did not cause such disorders in any of the trials. Topiramate was associated with a higher incidence of psychiatric disorders. All drugs caused some infections and infestations, with erenumab and eptinezumab having the highest rates and BTA having the lowest rates. BTA had a higher incidence of musculoskeletal and connective tissue disorders compared with other medications. Amitriptyline and topiramate were associated with more gastrointestinal disorders in participants, while fremanezumab and Galcanezumab were linked to more general disorders and administration site conditions than other drugs.

Table 2 Most common adverse events for each medication (%)

Medications	Doses	Participants (N)	Most common adverse events (%)
Amitriptyline[41]	25 mg to 100 mg	169	Dry mouth (36), somnolence (18), dizziness (11), dyspepsia and constipation (8) and nausea (7).
Atogepant[36 55]	10 mg	221	Constipation (8), nausea (5) and upper respiratory tract infection (4).
	30 mg	228	Constipation (7), upper respiratory tract infection (6) and nausea (4).
	60 mg	774	Nasopharyngitis (4), influenza, upper respiratory tract infection and urinary tract infection (3) and constipation (2).
BTA[25 35]	155 U	907	Neck pain (6), muscular weakness, cognitive disorder (4) and migraine, headache and dizziness (2).
Eptinezumab[26 30 38 52 54]	100 mg	1238	Nasopharyngitis and upper respiratory tract infection (4) and dizziness, nausea, fatigue (2).
Eptinezumab[26 30 38 54]	300 mg	989	Nasopharyngitis (7), upper respiratory tract infection (6) and nausea (3)
Erenumab[37]	21 mg	105	Nasopharyngitis (5), influenza (4), headache (3) and upper respiratory tract infection (2).
Erenumab[37]	7 mg	108	Nasopharyngitis (9), migraine (4) and upper respiratory tract infection and influenza (2).
Erenumab[31 37 40 43 48 56 57]	70 mg	1637	Nasopharyngitis (6), upper respiratory tract infection and constipation (4) and injection site pain (2).
Erenumab[31 43 46–48]	140 mg	1238	Constipation (6), nasopharyngitis and fatigue (4), upper respiratory tract infection (2).
Fremanezumab[19 20 22 34 42]	Monthly	1263	Injection site induration (18), injection site pain (17), injection site erythema (15), injection site reaction (7), nasopharyngitis (6).
	Quarterly	1251	Injection site pain (20), injection site erythema and injection site induration (14), nasopharyngitis (8), injection site reaction (7).
Galcanezumab[21 29 44 45 50 53]	120 mg	1313	Injection site pain (8), nasopharyngitis (6), injection site erythema (4), injection site reaction and injection site pruritus (3).
Galcanezumab[21 29 44 45]	240 mg	844	Injection site pain (11), injection site erythema (7), injection site reaction and injection site pruritus (5), nasopharyngitis (4).
Galcanezumab (LY2951742)[39]	150 mg	107	Injection site pain and upper respiratory tract infection (17), back pain (7), abdominal pain and arthralgia (6), injection site erythema, dizziness, rash, and hypertension (5).
Rimegepant[51]	75 mg	370	Nasopharyngitis (4), nausea (3), upper respiratory tract infection and urinary tract infection (2).
Topiramate[35 41 46]	100 mg	707	Paraesthesia (36), difficulty with concentration, dizziness and fatigue (12), nausea (9), hypoesthesia and dry mouth (5), depression, somnolence and vertigo (3)

BTA, Onabotulinumtoxin A.



A Summary of risk of bias assessment

Study ID	D1	D2	D3	D4	D5	Overall
Sakai, 2021	+	+	+	+	+	+
Silberstein, 2017	+	+	!	+	+	!
Dodick, 2010	+	+	+	+	+	+
Lipton, 2020	+	+	+	+	+	+
Detke, 2018	+	+	!	+	+	!
Dodick, 2019	+	+	+	!	+	!
Tepper, 2017	+	+	+	+	+	+
Ferrari, 2019	+	+	+	+	+	+
Rothrock, 2019	!	-	+	!	+	-
Ailani, 2021	+	+	+	+	+	+
Sun, 2016	+	+	+	+	+	+
Ashina, 2020	+	+	!	+	+	!
Dodick, 2014	+	+	+	!	+	!
Dodick, 2018	+	+	+	+	+	+
Dodick, 2009	+	+	+	!	!	!
Dodick, 2018	+	+	+	+	+	+
Goadsby, 2017	+	+	+	+	+	+
Sakai, 2021	+	+	+	+	+	+
Stauffer, 2018	+	+	+	!	+	!
Skljarevski, 2018	+	+	+	!	+	!
Reuter, 2018	+	+	+	!	+	!
Reuter, 2022	+	+	+	!	+	!
Wang, 2021	+	+	+	+	+	+
Mulleners, 2020	+	+	+	!	+	!
Elkind, 2006	+	+	+	!	!	!
Croop, 2021	+	+	+	!	+	!
Winner, 2021	+	+	+	+	+	+
Bo Hu, 2022	+	+	+	!	+	!
Ashina, 2022	+	+	+	!	+	!
Sakai, 2020	+	+	+	+	+	+
Takeshima, 2021	+	+	+	+	+	+
Yu, 2022	+	+	+	!	+	!
Ashina, 2023	+	-	+	!	+	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

B Traffic lights for the risk of bias for each included study

Figure 2 Risk of bias assessment result.

It should be noted that the number of included trials for each drug are different. Safety profiles for erenumab, topiramate and galcanezumab were investigated more extensively than other medications. Additionally, almost half of the included trials were potentially biased (medium or high risk), which should be taken into consideration when interpreting the results. Many of these trials raised concerns due to their outcome assessors being aware of the interventions received by study participants. It remained unclear whether the assessment of outcomes had been influenced by knowledge of whether interventions were received or not.

RCTs are not typically powered to show adverse events. Even in this systematic review, there is likely to be insufficient statistical power to identify differences in the incidence of uncommon adverse events. These are best identified in observational studies.

Our review found that placebo-related adverse events were more frequent than those observed in patients who were receiving various doses of erenumab, rimegepant, topiramate and eptinezumab. Reported AE percentages for placebo were similar to those for atogepant, while they were lower for the other medications.

Generalisibilty and other studies

Some trials have exclusively investigated the safety profiles of certain medications in patients with either episodic or chronic migraine, while others have included a mix of both. Despite these differences, the incidence of AEs and SAEs appears to be generally consistent across all types of migraine, suggesting that the type of migraine is not a critical determinant of the safety profiles of these medications.

In our comparisons with other studies, we have identified some evidence that support our findings, while others do not align with the conclusions we have drawn about the adverse events and standard adverse events in this review. We have compared our findings with the other studies for each drug separately:

- Topiramate: overall, three trials[35 41 46] reported that topiramate was poorly tolerated, with the most common AEs related to the nervous system and gastrointestinal disorders. The results of a meta-analysis showed that the safety profile favoured the CGRP MAbs, with a higher likelihood of benefit compared with harm when compared with topiramate.[59]
- BTA: the results of three trials[25 35] indicated that BTA is well tolerated with the most common adverse events limited to musculoskeletal and connective tissue disorders. Furthermore, a pairwise meta-analysis revealed that the total AEs for BTA were higher than placebo, with a relative risk ratio of 1.22 (95% CI 1.07 to 1.14).[7] This is consistent with our findings.
- Eptinezumab: all doses of eptinezumab were generally well tolerated and acceptable in the three trials[38 52 54] it was reported. Eptinezumab at 100 mg dose exhibited a smaller proportion of AEs, which may be attributed to the short treatment duration of 4 weeks in one study.[52] Results of a meta-analysis showed that CGRP MAbs safety profiles were not significantly different from placebo (OR 1.17, 95% CI 0.91 to 1.51).[8] The most common AEs for all doses were related to infections and infestations[8] which is in line with our results.
- Erenumab: two meta-analyses yielded results consistent with our review, indicating no significant differences in the occurrence of AEs and SAEs between the erenumab and placebo.[9 10] According to our findings from nine trials,[31 37 40 43 46–48 56 57] the lowest incidence of AEs occurred in patients taking 140 mg of erenumab. Patients who were prescribed 70 mg of erenumab reported a higher incidence of infection and infestation, which was consistent with another review.[8]
- Fremanezumab: five trials reported the incidence of adverse events, which was reported to be lower in the monthly groups compared with the quarterly groups.[19 20 22 34 42] Statistical analysis of a meta-analysis showed that the fremanezumab group is more likely to suffer from adverse events related to the trial regimen rather than placebo (RR=1.21, 95% CI 1.09 to 1.34, p=0.0005).[60] However, the most common adverse event remained as injection-site reactions, which is in line with our results.[60]
- Galcanezumab: seven trials found that the incidence of adverse events was lower for the 12-week treatment period[29 39 50 53] compared with the 24-week period.[21 44 45] General disorders and administration site conditions, followed by infection and infestations, were the most frequent AEs for all doses. While Hou *et al* presented upper respiratory infections and viral infections (infection and infestations) as the most common AEs,[8] this was not consistent with our finding, perhaps due to the fact they only reported safety data on galcanezumab from one trial.
- Rimegepant: the results for rimegepant 75 mg from one small trial showed similar tolerability to placebo, and there were no unexpected or serious safety issues noted.[51 61] In line with our findings, Gao *et al* demonstrated that rimegepant 75 mg was safe for treating episodic migraine.[11]
- Atogepant: the AEs for all doses from two studies were approximately the same and well tolerable,[36 55] which is supported by results of another systematic review.[12] Infection was more common in all doses.
- Amitriptyline 25 mg to 100 mg: the results of a small trial indicated poor tolerability, with gastrointestinal disorders being the most commonly experienced adverse events, followed by nervous system disorders.[41] We could not find any evidence for the safety profile of Amitriptyline that had been synthesised through systematic review or meta-analysis.

Strengths and limitations

The main strength of our review is the analysis of adequately powered studies of the wide range of medications, as most systematic reviews in the literature focus

on only one or a few drugs. We included the CGRP MAbs namely fremanezumab, eptinezumab, galcanezumab and erenumab, along with BTA, topiramate, amitriptyline, atogepant and rimegepant. This diversity provides a comprehensive overview of medication safety, enabling decision-makers to compare treatments and obtain a more accurate reflection of clinical practice. We used a comprehensive search strategy across a wide range of electronic databases, without imposing any restrictions on date or language.

It is important to mention additional limitations of some included trials in this review. Specifically, atogepant and rimegepant have product licenses but are not yet approved by NICE. However, Scottish Medicine Consortium in 2023 approved atogepant for chronic and episodic migraine and rimegepant for episodic migraine. The BTA trial for episodic migraine patients used non-standard doses, while the standard dose for chronic migraine patients is 155U. Additionally, the 150 mg dose of galcanezumab, which is not commonly used, had a noticeably higher adverse events profile.

Excluding studies with fewer than 100 participants per arm and also excluding studies without reporting AEs and SAEs according to the standard definition have limited our analyses to more recently investigated treatments where the trial methodology is more precise, at the risk that we might exclude pertinent data from smaller, usually older, trials. Because of this, we were unable to identify any eligible studies of adequate quality for other commonly used oral drugs used in the management of migraine, such as candesartan, flunarizine and Propranolol.

Furthermore, the results must be viewed cautiously due to limitations. It is important to note that differences in the definition and measurement of side effects may have influenced reporting. To manage this variability, we opted to include trials adhering to the standard definition AEs and SAEs, enabling categorisation within the SOC. However, we acknowledge that variations in the measurement and reporting of side effects exist among the included trials, and this aspect remains unclear in some original papers. Also, we used CTCAE V.5.0 to classify AEs and SAEs, but some events in the studies were not classified in the CTCAE. To address this, our clinical experts determined the appropriate category for those events, such as categorising panic attacks as a psychiatric disorder (further details in online supplemental table 18 and 41, online supplemental appendix 4 and 5).

Other systematic reviews we compared with ours noted limitations in the RCTs and recommended further head-to-head RCTs to obtain more robust results for AEs. Similarly, we suggest conducting additional head-to-head RCTs to evaluate the safety profile of oral medications, BTA and CGRP MAbs in episodic and/or chronic migraine populations.

While assessing the incidence of AEs and SAEs from these drugs is important and gives important new insights, there is a wider literature related to known adverse effects of these drugs when used in the general population. For example, the SAEs of sodium valproate (teratogenicity and developmental delay) when used in women of childbearing potential are well documented. To a lesser extent, there are similar concerns about teratogenicity and developmental delay, and effects on the efficacy of hormonal contraceptives, in topiramate and so it should be used with caution in women of childbearing age. These effects are unlikely to be captured in RCTs.

CONCLUSION

To the best of our knowledge, our study is the most comprehensive review of the safety profile of preventive medications for adults with chronic or episodic migraine classified by SOC. Only a minimal number of SAEs were observed, with no treatment-related SAEs to the drugs were reported. Minor adverse events were prevalent, and the findings indicated that amitriptyline and topiramate are associated with a higher frequency of adverse events, especially in the context of nervous system disorders and exhibit lower overall tolerance levels. Conversely, emerging treatments such as BTA, CGRP MAbs and the gepants demonstrate a reduced incidence of adverse events and enhanced tolerance. Notably, the observed harm to SOCs differs among these drugs. It should be noted that the trial numbers are poor with amitriptyline, better with Topiramate and good for the others.

Disparities in the occurrence of adverse events were identified among the CGRP MAbs. The majority of fremanezumab users and one out of four galcanezumab users reported problems at the injection site, a concern far less frequently noted among eptinezumab or erenumab users. Nervous system or gastrointestinal side effects such as paraesthesia and dry mouth were commonly experienced by those taking topiramate or amitriptyline. Notably, topiramate showed a higher association with psychiatric disorders, particularly depression, while adverse events linked to BTA were uncommon. We suggest conducting additional head-to-head RCTs to evaluate the safety profile of oral medications, BTA and CGRP MAbs in episodic and/or chronic migraine populations.

Author affiliations
[1]Warwick Clinical Trials Unit, University of Warwick, Warwick Medical School, Coventry, UK
[2]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
[3]Warwick Medical School, University of Warwick, Coventry, UK
[4]Headache Group, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK
[5]Department of Neurology, Aberdeen Royal Infirmary, Aberdeen, UK

Acknowledgements We would like to thank Dr Saval Khanal, who helped check the extracted data.

Contributors AB, CD, MM, HM and MU developed the study design; AB developed and ran the literature searches; AA, ND, SN and MU screened the literature; SN extracted data from the articles. SN led the data analysis, with support from HM and

MU. HM and SN wrote the first draft of the manuscript, which all authors revised. All authors reviewed and agreed with the final version. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication. HM is guarantor.

Funding This study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme—project reference NIHR132803.

Competing interests Martin Underwood is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research and is a co-investigator on grants funded by the Australian NHMRC and Norwegian MRC. He was an NIHR Senior Investigator until March 2021. He is a director and shareholder of Clinvivo Ltd which provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd, funded by the European Social Fund, related to return-to-work initiatives. He receives some salary support from University Hospitals Coventry and Warwickshire. He is a co-investigator on two current and one completed NIHR-funded studies that have, or have had, additional support from Stryker Ltd. Callum Duncan is chair of Scottish Intercollegiate Guideline Network (SIGN) 155 and has provided advice on the use of Botox, CGRP monoclonal antibodies and CGRP antagonists to the Scottish Medicines Consortium and on Eptinezumab to NICE. He was the Secretary for the British Association for the Study of Headache 2015-2022 and is a Board member of Anglo Dutch Migraine Association. Manjit Matharu is the President of the medical advisory board of the CSF Leak Association. He has received consulting fees from AbbVie, TEVA, Lundbeck, Eli Lilly, Salvia, and Pfizer. He has received payment for the development of educational presentations from AbbVie, Pfizer and Eli Lilly and support for attending a meeting from Pfizer. He is on the advisory board for AbbVie, TEVA, Lunbeck, Eli Lilly, Salvia, and Pfizer. He has the following patent issued WO2018051103A1: System and method for diagnosing and treating headaches. He has stock options with Tesla, Adobe, Nvidia, META and Microsoft. He has received grants from Abbott, Medtronic and Ehlers Danlos Society.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Seyran Naghdi http://orcid.org/0000-0001-5504-7189
Callum Duncan http://orcid.org/0000-0002-4516-9024
Hema Mistry http://orcid.org/0000-0002-5023-1160

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