Preventive drug treatments for adults with chronic migraine: a systematic review with economic modelling

Hema Mistry,[1,2*] Seyran Naghdi,[1] Anna Brown,[3] Sophie Rees,[4] Jason Madan,[1] Amy Grove,[3] Saval Khanal,[3] Callum Duncan,[5] Manjit Matharu,[6] Andrew Cooklin,[1] Aiva Aksentyte,[1] Natasha Davies[1] and Martin Underwood[1,2]

[1]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[2]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK
[3]Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK
[4]Bristol Clinical Trials Unit, University of Bristol, Bristol, UK
[5]Department of Neurology, NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK
[6]Headache and Facial Pain Group, University College London (UCL) Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK

[*]Corresponding author Hema.Mistry@warwick.ac.uk

Published October 2024
DOI: 10.3310/AYWA5297

Scientific summary

Preventive drug treatments for adults with chronic migraine: a systematic review with economic modelling

Health Technology Assessment 2024; Vol. 28: No. 63
DOI: 10.3310/AYWA5297

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Chronic migraine is a profoundly disabling condition and affects 2–4% of the world's adult population. It is defined as headaches on 15 days or more a month with features of migraine on at least 8 of those days. Since 2020, expensive calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) have become established as specific treatments for people with chronic migraine who have failed to improve with other medications. Little is known about the effectiveness of these drugs when compared with each other, or with other well-established, cheaper, oral drugs used to treat chronic migraine. Therefore, it is timely to compare the clinical effectiveness and cost-effectiveness of these medications to treat chronic migraine. We set out to address the following research question:

What is the clinical effectiveness and cost-effectiveness of prophylactic drug treatments for people with chronic migraine?

Objectives

Our overall aim is to produce evidence needed for people with chronic migraines and their doctors to make more informed decisions about prophylactic medications for chronic migraine.

Our objectives were:

- What is the comparative effectiveness of prophylactic drugs for chronic migraine?
- What are the comparative incidences of adverse events (AEs) of prophylactic drugs used for migraine?
- What is known about the cost-effectiveness of prophylactic drugs for chronic migraine?
- Which prophylactic drugs for the management of chronic migraine are the most cost-effective?
- Based on our findings, what should the research recommendations be?

Methods

Systematic reviews of trial evidence on:

1. The clinical effectiveness of prophylactic medications for chronic migraine; analyses included headache days, migraine days and headache-related quality of life: migraine- specific quality of life (MSQ); headache impact test-6 (HIT-6). Only randomised controlled trials (RCTs) with at least 100 people per arm were included. We report the comparative effectiveness using a network meta-analysis (NMA) for these different outcomes to see which drug was the most 'effective'.
2. To identify the comparative incidence of AEs of prophylactic drugs used for chronic or episodic migraine. RCTs with at least 100 people per arm were included.
3. The cost-effectiveness studies of prophylactic drugs used for treatment of chronic migraine.

We developed an economic model comparing the cost-effectiveness of prophylactic drugs for chronic migraine for the adult population from a National Health Service (NHS) and personal social services (PSS) perspective. The base-case analysis used a 2-year time horizon, with a starting age of 30 years for the patient cohort. Health states in the model were based on effectiveness data [reduction in the mean difference (MD) in monthly headache days (MHDs)] from the NMA. Costs are in 2021–2 prices and

utilities were estimated based on EuroQol-5 Dimensions, five-level version (EQ-5D-5L) scores from the CHESS trial using the Hernandez-Alava crosswalk algorithm. Cost-effectiveness was measured in terms of an incremental cost per quality-adjusted life-year (QALY) gained [Institute for Clinical and Economic Review (ICER)]. Probabilistic sensitivity analysis (PSA) was undertaken to account for uncertainty in model parameters. Uncertainty around the cost-effectiveness of the various medications showing which is the preferred strategy is presented using a cost-effectiveness acceptability frontier (CEAF).

At the end of the project, we held a consensus workshop bringing together people with chronic migraine and clinicians and other health professionals who are experts in chronic migraine. We presented the findings from our reviews, NMA, the economic model and some potential recommendations. We then split into groups (mixed with health professionals and participants) and asked them to discuss our suggested research recommendations, identify any other recommendations, and rank these recommendations in terms of priority. We then had another breakaway session, where all participants with chronic migraine met and all health professionals met. Finally, everyone was bought back together to discuss their rankings as a wider group and to reach a consensus using anonymous polling.

Results

The clinical effectiveness review focused on prophylactic medications which might be used in the UK for the prevention of chronic migraine. We found 11 RCTs reported across 51 individual publications, involving 7352 adult participants with chronic migraine, which showed that all pharmacological treatments for all outcomes of interest were beneficial in preventing migraine when compared to placebo. There were no trials of sufficient quality of the commonly used drugs, such as amitriptyline, candesartan, flunarizine or propranolol. Overall, the CGRP MAbs reduced headache/migraine days by 2.0 to 2.5 days per month. The most effective medication in reducing MHDs was eptinezumab 300 mg which reduced MHDs by 2.46 [95% credible interval (CrI) 3.24 to −1.67] days. The most effective medication in reducing monthly migraine days (MMDs) was fremanezumab monthly which reduced MMDs by 2.76 (95% CrI −3.36 to −2.15) days. Botox (BTA) reduced MHDs by 1.87 (95% CrI −2.55 to −1.18) days per month and MMDs by 1.96 (95% CrI −2.69 to −1.24) days per month. Topiramate was the least effective, prescribable drug and only reduced headache/migraine days by less than 1.5 fewer headache/migraine days per month. The NMA results showed that eptinezumab 300 mg had the highest probability ranking to reduce MHDs and MMDs – Surface Under the Cumulative Ranking Area (SUCRA) was 0.88 and 0.77, respectively.

The CGRP MAbs provided a worthwhile improvement on the HIT-6 measure of headache-related quality of life (eptinezumab 300 mg reducing the HIT-6 by a score of 3.22 points); BTA had a worthwhile effect on the HIT-6 measure, reducing the HIT-6 score by 2.10 points; and there was no convincing benefit of topiramate on the MSQ measure. Galcanezumab 120 mg provided the best improvement in quality of life for the preventative role dimension of migraine-specific quality of life (MSQ-PR) (MD 6.97, 95% CrI 3.79 to 10.24, SUCRA 0.88), but for two other dimensions of the MSQ, erenumab 140 mg was superior to other treatments: for migraine-specific quality of life-restrictive role (MSQ-RR) – MD: 7.28, 95% CrI: 3.05 to 11.65, SUCRA 0.75, and for migraine- specific quality of life-emotional function (MSQ-EF) – MD: 8.89, 95% CrI: 3.20 to 14.55, SUCRA 0.79.

The results from the quality assessment using the revised Cochrane risk-of-bias (RoB 2) tool for RCTs found that approximately 46% of the included RCTs in this review had low RoB and 36% of the RCTs had some concerns of bias.

The incidence of AEs and serious adverse events (SAEs) review used evidence from 40 RCTs reported across 67 articles, which investigated pharmacological interventions to manage chronic or episodic migraine. These trials included 25,891 participants and 3 additional drugs were included – amitriptyline, atogepant and rimegepant. There were very few SAEs – none of which were linked to the use of these

drugs. Non-SAEs were common, and results suggested that all the pharmacological medications included in this review were found to be tolerable. There were differences in the incidence of AEs between the CGRP MAbs, with most people using fremanezumab and one in four people using galcanezumab reporting injection site issues. These issues were much less common in people using eptinezumab or erenumab. Most people using topiramate or amitriptyline had nervous system or gastrointestinal side effects; topiramate was also linked to a higher prevalence of psychiatric disorders; and AEs related to BTA were uncommon.

The cost-effectiveness review identified nine peer-reviewed journal articles and seven published reports of chronic migraine prophylactic medications in the adult population. All articles were model-based evaluations, and none were trial-based economic evaluations. We found that although these newer drugs (BTA and CGRP MAbs) were more costly than the oral preventatives, they were however deemed cost-effective. Generally, the articles were classed as high quality when appraised by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting tool.

We developed a Markov (state-transition) model to assess the cost-effectiveness of different pharmacological medications to treat or prevent chronic migraine in the adult population. Our base-case deterministic results showed when comparing each of the medications separately against placebo, topiramate dominated placebo (cheaper and more effective); and each of the other medications, when compared separately, were more expensive than placebo; however, they generated more QALYs than placebo. The best value medication when compared with placebo was BTA, with the cost per QALY around £25,000.

When comparing all medications together, the deterministic results showed that topiramate was the least costly option and had slightly more QALY gains than placebo, whereas eptinezumab 300 mg was the more costly option but generated the most QALY gains. Most medications were eliminated due to dominance. The ICER between BTA and topiramate and the ICER between eptinezumab 300 mg and BTA were not within plausible cost-effectiveness thresholds. Probabilistic results were similar to deterministic results. The CEAF showed that when comparing all medications topiramate was the most cost-effective medication if the decision maker is willing to pay up to £50,000 per QALY. None of the CGRP MAbs represented good value for money in this comparative analysis.

Extensive sensitivity analyses showed that when MHDs is used as an outcome measure, the results were generally in line with the base-case results. The main exception was when using MMDs as an outcome measure instead of MHDs, fremanezumab monthly generated more QALY gains than eptinezumab 300 mg; the ICERs between the plausible options, once any dominated options were removed, were not within plausible cost-effectiveness thresholds.

Our consensus workshop brought together 8 participants with chronic migraine and 11 health professionals with expertise in chronic migraine to set research priorities for preventive drugs for chronic migraine. Each of the small groups found that the need for trials of cheaper, oral medications, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs) when compared with placebo were ranked highly; and for trials comparing the medications with each other, the CGRP MAbs and BTA separately or in combination with each other were ranked highly.

The final (anonymised) rankings showed that the top three research priorities versus placebo were: (1) candesartan, (2) flunarizine and (3) melatonin; and for medications compared with each other were: (1) CGRP MAbs and BTA versus CGRP MAbs, (2) CGRP MAbs versus BTA and (3) a multi-arm trial of CGRPs MAbs receptor (erenumab) versus CGRP MAbs ligand (eptinezumab, fremanezumab and galcanezumab).

In terms of priority, a consensus was established regarding the three most recommended medication comparisons for treating chronic migraine: (1) CGRP MAbs and BTA versus CGRP MAbs, (2) candesartan compared to placebo and (3) flunarizine in comparison to placebo.

Discussion and conclusions

Of the treatments included in the NMA, the CGRP MAbs overall were consistently the best choices for headache days, migraine days and headache-related quality of life. BTA was less likely than CGRP MAbs to be the best choice for headache days, migraine days and headache-related quality of life. Topiramate was very unlikely to be the best choice for headache days, migraine days and headache-related quality of life when compared to CGRP MAbs or BTA. The economic model found that topiramate was the best value drug if you are prepared to pay up to £50,000 per QALY. It is likely that CGRP MAbs are likely to be cost-effective in people who have failed treatment with BTA. At the workshop, general consensus was agreed on the top three choices of medication for chronic migraine.

Topiramate was the only established oral drug for which we were able to include data. It is disappointing that we did not find a sufficient quality evidence base to support the use of drugs, such as amitriptyline, candesartan, flunarizine and propranolol that are recommended by National Institute for Health and Care Excellence (NICE) and/or Scottish Intercollegiate Guidelines Network (SIGN). Our consensus meeting identified the need for trials comparing candesartan and flunarizine with placebo as the top priorities for placebo-controlled trials. Only for topiramate can we make any observations for how this may compare with CGRP MAbs. The CGRP MAbs appear to be clinically superior, but even so topiramate, in spite of its high incidence of AEs, represents the best value for money. Within the current care pathway, it is unlikely that CGRP MAbs will be recommended ahead of topiramate without a very substantial reduction on price. What is perhaps a more critical decision point is whether BTA or CGRP MAbs might be preferred as the first choice after failure of oral medication. Our findings support continuing with the current care pathway since our CEAF found that only topiramate met an acceptable threshold. Data from our health economics review, however, do support the use of CGRP MAbs after failure of BTA for chronic migraine.

Our consensus group identified the direct comparison of BTA and CGRP MAbs as a key research question. They also identified the question of whether these drug effects might be additive. The effect sizes, in terms of mean monthly migraine/headache days for each of these drugs, are at best modest, the largest being 2.76 days for fremanezumab monthly dose. As these drugs work through different pathways, it might be that more substantial effects are possible. Adding together the effects of BTA and a CGRP MAb, assuming no negative interaction, might have a mean effect size of 4–5 days that would be transformative for many people with chronic migraine. Our consensus group identified the comparative, and additive, effects of BTA and CGRP MAbs as high priority research questions.

In conclusion, we have summarised the existing clinical and cost-effectiveness data on preventive drugs for chronic migraine and identified which directions future research on these drugs might take. We did not find convincing evidence that the CGRP MAbs are more clinically effective and cost-effective compared to topiramate or BTA.

Study registration

This study is registered as PROSPERO CRD42021265990, CRD42021265993 and CRD42021265995.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: NIHR132803) and is published in full in *Health Technology Assessment*; Vol. 28, No. 63. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number NIHR132803. The contractual start date was in September 2021. The draft manuscript began editorial review in May 2023 and was accepted for publication in November 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).