Supplementary Information: Consensus workshop

Chronic Migraine Workshop: Research recommendations for pharmacological prevention of chronic migraine

Pre-Meeting information

Background

Over recent years a number of new drugs, calcitonin gene-related peptide monoclonal antibodies (CGRP-MABs) have been introduced for the treatment of chronic migraine. Little is known about the effectiveness of these drugs when compared with each other, or with other drugs used to treat chronic migraine. These new drugs are very expensive. Other well-established, and cheaper drugs might be preferred for the treatment of chronic migraine if they were as effective as these new drugs. The evidence supporting the use of these older drugs for the treatment of chronic migraine is not of the same standard as the recent large, industry sponsored, trials of CGRP-MABs.

We have been funded by the National Institute for Health and Care Research (NIHR) to review the available research on drugs for the prevention of chronic migraine.

What we did

We have looked for randomised controlled trials of drugs for the prevention of migraine in people with chronic migraine that have published their findings about how these drugs affected the number of headache days, number of migraine days, and headache-related quality of life.

We have then done a 'network meta-analysis'. This is a technique to bring together results from multiple studies of different drugs, to get the best estimate of how effective each drug might be, and to help us decide which drug is the most likely to be cost-effective.

We looked for randomised controlled trials which report the side effects of drugs for migraine in people with episodic and chronic migraine.

We looked for previous studies of the cost-effectiveness of drugs for prevention of chronic migraine.

Finally, we developed a new economic model to estimate the comparative cost-effectiveness of drugs for the prevention of chronic migraine.

Our task for this meeting is to develop a clear and understandable set of research recommendations based on the findings of our systematic reviews and economic model. We expect the NIHR will then want to fund studies to address these recommendations. These recommendations might be for trials of drugs compared to placebos or comparing two different drugs. The focus of this exercise is just on

drug treatments for prevention of chronic migraine.

What we found

Below are the findings of each of the projects listed above. There will be an introductory session at the start of the day which goes through all of this, but it may be beneficial to read this beforehand.

Effectiveness review

Our focus for this review was on drugs that might be used **in the UK** for **prevention** of chronic migraine. To ensure the task was manageable, and to only include good quality research, we only included studies with at least 100 people in each arm of the study. We found 11 trials, with total 7,352 participants, reported in 51 individual publications. We did not find any trials of commonly used drugs such as Propranolol or Amitriptyline. **We had enough data on several CGRP MABs, Botox (BTA) and Topiramate** to analyse.
We found:

- CGRPs reduced headache/migraine days by an average 2.0 to 2.5 per month, some provided a worthwhile improvement on the 'HIT-6' measure of headache-related quality of life, and overall they were **consistently best choices** for headache days, migraine days, and headache-related quality of life
- BTA reduced headache/migraine days per month by just under two on average and had a worthwhile effect on the HIT-6 measure of headache-related quality of life. **BTA was less likely to be best choice than CGRP MABs** for headache days, migraine days & headache-related quality of life
- Topiramate reduced headache/migraine days by less than 1.5 fewer headache/migraine days per month on average. There was no convincing benefit on the MSQLQ measure of headache-related quality of life. **Topiramate was very unlikely to be the best choice** for headache days, migraine days & headache-related quality of life when compared to CGRP MABs or BTA.

Adverse events review

Again, we restricted ourselves to trials with at least 100 people per arm, but widened our inclusion criteria to include studies of both episodic and chronic migraine. We included 40 trials with 25,891 participants reported in 67 articles. Two additional drugs Amitriptyline and Atogepant were included in this review because there were articles which fit our criteria.
We found:

- There were **very few serious adverse events**, none of which were linked to the use of the drugs
- Non-serious adverse events were common.
- There were differences in the incidence of adverse events between the CGRP MABs with most people using Fremanezumab and one in four people using Galcanezumab reporting injection site issues. These were much less common in people using Eptinezumab or Erenumab.

- Most people using Topiramate or Amitriptyline had nervous system or gastrointestinal adverse events.
- Adverse events related to BTA were uncommon.

Cost-effectiveness model & review

For the cost-effectiveness model, we looked at the cost per quality-adjusted life year **(QALY)**. This is the theoretical cost of buying **one year in perfect health** when **all health care costs are taken into account – not just the cost of the drug**. To give you an idea, typically, the National Institute for Health and Care Excellence (NICE) supports medications costing less than £20,000 to £30,000 per QALY.

When we compared the drugs against placebo, we found:

- The **best value** drug was Topiramate that gave better health outcomes at a lower cost than placebo.
- When compared to placebo, BTA appeared **good value** at around £6,000 per QALY.
- Whilst at list price the CGRP-MABs were in the £20,000 to £30,000 range except for Eptinezumab 300mg at £73,000. Although we do know these are discounted by the manufacturers. If this discount were around 50% then all the CGRP MABs except Eptinezumab 300mg would cost **below NICE £20,000** threshold compared with placebo

When we compare these drugs against each other:

- If prepared to pay **less than £17,000 per QALY, Topiramate** is the best choice.
- But if **willing to pay more, BTA is the best choice** as it is more effective but at a higher cost.
- **None of the CGRP MABs represented good value** for money in this comparative analysis.

These findings are similar to those found in simpler analyses just looking at BTA vs placebo and CGRP MABs vs. placebo. **It is likely that CGRP MABs are likely to be cost-effective in people who have failed treatment with BTA.**

What do we want you to do at the workshop?

On the day we want to decide on:

1. The top five research recommendations for comparisons of preventive drugs for chronic migraine with placebo
2. The top five research recommendations for active drugs with each other.
3. Then we would like to rank these ten research recommendations in order of priority.

Summary

- CGRP MABs
  - Up to 2.0 – 2.5 fewer headache/migraine days per month
  - Some have a worthwhile effect on HIT-6
  - Consistently best choices for headache days, migraine days & headache-related quality of life
  - Generally few adverse events (except Fremanezumab)
  - Poor value for money at list price (OK if discount were 50%)
  - Very poor value for money compared to BTA/Topiramate (but may be good after failure of BTA)
- Botox (BTA)
  - Just under two fewer headache/migraine days per month
  - Worthwhile effect HIT-6 (a headache-related quality of life measure)
  - Less likely to be best choice for headache days, migraine days & headache-related quality of life
  - Few adverse events
  - Good value for money
- Topiramate
  - Less than 1.5 fewer headache/migraine days per month
  - No convincing benefit on MSQLQ (a headache-related quality of life measure)
  - Very unlikely to be best choice for headache days, migraine days & headache-related quality of life
  - Many adverse events
  - Very good value for money
- Amitriptyline
  - Many adverse events
- Atogepant
  - Few adverse events
- Other drugs
  - Not enough evidence

Crib sheet

Drug/group	Evidence level	Notes on safety	Notes on efficacy	Notes on feasibility/costs
Tricyclic anti-depressants (e.g. Amitriptyline, Nortriptyline)	Low quality/ insufficient	Common gastro and nervous system disorders	Not enough evidence	
SNRIs (e.g. Venlafaxine)	Low quality/ insufficient	Not enough evidence	Not enough evidence	
Valproic acid	Low quality/ insufficient	Teratogenic: Not advised for women of reproductive age	Not enough evidence	Usually not prescribed to women of reproductive age, which is the largest group affected by migraine
Beta blockers (e.g. Propranolol)	Low quality/ insufficient	Not enough evidence	Not enough evidence	
Flunarizine	Low quality/ insufficient	Not enough evidence	Not enough evidence	Not yet approved by NICE or Scottish Medical Consortium
Pizotifen	Low quality/ insufficient	Not enough evidence	Not enough evidence	Not yet approved anywhere
Angiotensin-based (e.g. Candesartan, Lisinopril)	Low quality/ insufficient	Not enough evidence	Not enough evidence	Approved by Scottish guidelines, not NICE
Gepants (e.g. Atogepant)	Low quality/ insufficient	Minor concerns	Not enough evidence	Not yet approved by NICE or Scottish Medical Consortium
Botox (BTA)	Good quality/ sufficient	Minor concerns	Probably better than Topiramate but not as good as MAbs	This drug is the best if the NHS is willing to pay >£17,000 per year of improved quality of life
Erenumab *(CGRP MAb)*	Good quality/ sufficient	Minor concerns	Most likely to be best choice	Poor value for money (better if 50% discounted for NHS) Very poor value for money compared to BTA/Topiramate (but may be good after failure of BTA)
Fremanezumab *(CGRP MAb)*	Good quality/ sufficient	Pain at injection site		
Galcanezumab *(CGRP MAb)*	Good quality/ sufficient	Minor concerns		
Eptinezumab *(CGRP MAb)*	Good quality/ sufficient	Minor concerns		
Topiramate	Good quality/ sufficient	Common gastro and nervous system disorders	Unlikely to be best choice	This drug is the best if the NHS is willing to pay £17,000 or less per year of improved quality of life