The cost effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK

Batty AJ, Hansen RN, Bloudek LM, Varon SF, Hayward EJ, Pennington BW, Lipton RB, Sullivan SD

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
This study evaluated the cost-effectiveness of botulinum neurotoxin type A (onabotulinumtoxinA) to prevent headache in adults with chronic migraine. The authors concluded that onabotulinumtoxinA was cost-effective for the UK NHS, with important benefits for patients poorly served by existing treatments. Reporting was generally clear, but the study had significant limitations. The probabilistic sensitivity analysis was vaguely defined, but the primary limitation was the omission of topiramate as an explicit comparator. This omission casts doubt on the validity of all the analyses.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the cost-effectiveness of botulinum neurotoxin type A (onabotulinumtoxinA) for the prevention of headaches in adults with chronic migraine.

Interventions
OnabotulinumtoxinA was compared with placebo. With onabotulinumtoxinA injections, if a patient’s headache days in 28 days did not reduce by 30% in the first 24 weeks, then treatment was stopped (negative rule). Patients for whom treatment was successful tried to stop treatment after one year (positive rule); 24% of these patients successfully stopped for one year.

Placebo was an injection of saline solution. All patients were allowed to continue their previous analgesic and tryptamine-based drug (triptan) use as necessary.

Location/setting
UK/secondary care.

Methods
Analytical approach:
A two-year Markov model, with 12-week cycles, was developed to analyse the licensed population of all chronic migraine patients. Patients who had received one or more oral prophylactic treatments, and patients who had received three or more oral prophylactic treatments were also analysed. The health states were on or off treatment; three frequencies of headache, classified as episodic migraine; and three frequencies, classified as chronic migraine. The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
The main effectiveness data were the probabilities of transition between each health state every 12 weeks. These data were from two randomised controlled trials, within the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) programme. They were multicentre trials of 1,384 patients in total. Each was a 24-week, randomised, double-blind, parallel-group, placebo-controlled trial, followed by 32 weeks of open-label treatment. The transition probability, for the first cycle, was directly from the data for onabotulinumtoxinA and placebo. For placebo, there was only one further cycle, so these data were used for all the remaining cycles. For onabotulinumtoxinA, the data for the subsequent four cycles were combined and used for all the remaining cycles.
Monetary benefit and utility valuations:
All patients in the PREEMPT trials completed the Migraine Specific Quality of Life Questionnaire (MSQ). These scores were mapped to the EQ-5D, using a published algorithm, to produce utility values for the different migraine states.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs) gained. Benefits were discounted at a rate of 3.5% per year.

Cost data:
OnabotulinumtoxinA use and the care for patients with migraines were analysed. This included general practitioner (GP) visits, emergency department visits, hospitalisations and triptan costs. Resource use was from UK patients in the International Burden of Migraine Study. The unit costs were NHS reference costs. The cost of triptans was from the NHS Prescriptions Cost Analysis. Patients received 155 to 195 units of onabotulinumtoxinA, in each 12-week cycle, in the PREEMPT trials. Consultant time was assumed. The costs were in 2010 GBP (£UK £), discounted at 3.5% annually.

Analysis of uncertainty:
Probabilistic sensitivity analysis was conducted to evaluate uncertainty in the cost-effectiveness estimate by varying each model parameter simultaneously. Scenario analyses were conducted on the administration cost, stopping rules (positive and negative), the time horizon, and utility scores.

Results
For the licensed population, the average cost per patient was £1,680 for the placebo group and £3,077 for the onabotulinumtoxinA group. The QALYs gained were 1.2 with placebo and 1.3 with onabotulinumtoxinA.

The incremental cost-effectiveness ratio (ICER), for onabotulinumtoxinA was £15,028 per QALY gained. The likelihood that onabotulinumtoxinA was cost-effective at a willingness-to-pay threshold of £20,000 was 96%.

In the scenario analyses, the most uncertainty was in the utility values. If the same utility values were applied to both treatment arms for each health state, the ICER increased to £29,157 per QALY gained.

For patients who had received one or more prior treatment, the ICER was £14,273 per QALY gained. For patients who had received three or more prior treatments, the ICER was £17,212 per QALY gained.

Authors’ conclusions
The authors concluded that onabotulinumtoxinA reduced the frequency of headaches and was cost-effective for the UK NHS, with important benefits for patients who were poorly served by existing treatments.

CRD commentary
Interventions:
The authors indicated that they excluded some relevant comparators because they could not identify relevant effectiveness data for them. There was a trial of topiramate for chronic migraine, in 2007, that used migraine-free days as an outcome (see ‘Other publications of related interest’). No dietary or lifestyle interventions were assessed. It is clear that topiramate is a relevant comparator as first-line treatment for chronic migraine patients. As we don’t know what drugs were previously taken by the cohort, it is not clear that any relevant medication, including topiramate, should be excluded for second or third-line treatment. The authors stated that placebo represented standard care, and acknowledged that this was an issue with their study.

Effectiveness/benefits:
The authors stated that a systematic literature search was conducted to identify the relevant data. This search was not described, so it is unclear if any relevant comparators were missed, and other relevant clinical trials may have existed. At least two trials had the same population, interventions or comparators, outcomes, and designs as the two PREEMPT trials, but were omitted (for example, see ‘Other publications of related interest’). An indirect comparison, using data from these trials, would have been appropriate. The methods and reporting were limited. Few details of the clinical
trials were given, but they were referenced. The reliability of the mapping algorithm from the MSQ to the EQ-5D was not reported, though the reference was provided. The outcomes for multiple cycles of onabotulinumtoxinA therapy were averaged; it was unclear if this was appropriate. The impact of assuming that patients on placebo will continue at the same rate of improvement beyond 24 weeks is unclear. The model assumed that 24% of patients successfully ceased treatment in the second year, based on 24% of patients reporting that they remained largely headache free for at least six months. It was unclear if this assumption was justified.

Costs:
The cost analysis was sufficiently reported. The estimates were from sources that were relevant to the study population. There was no indication that a review of the literature was conducted to identify the resource use and cost estimates for the treatment of migraine.

Analysis and results:
The results were well reported and the analyses were generally well reported. Insufficient information was provided on the probabilistic sensitivity analysis methods to assess their conduct.

Omitting topiramate from the licensed population analysis was inappropriate and misleading as topiramate is licensed for the population referenced in the PREEMPT trial. Due to the omission of topiramate, the cost-effectiveness of onabotulinumtoxinA may be not be accurately estimated in the licensed population analysis. The authors expected that the two stopping rules (negative and positive) would be central to the cost-effectiveness estimate for onabotulinumtoxinA, but removing them had little impact on cost-effectiveness. National Institute for Health and Care Excellence (NICE) guidance from 2012 recommends that onabotulinumtoxinA should only be used in patients with chronic migraine for whom three other treatments have failed. None of the subgroup analyses explicitly include topiramate as a previous treatment. Therefore, the validity of the subgroup analyses is unclear.

Concluding remarks:
Reporting was generally clear, but the study had significant limitations. The probabilistic sensitivity analysis was vaguely defined, but the primary limitation was the omission of topiramate as a comparator. This omission casts doubt on the validity of all the analyses.

Funding
Supported by Allergan, Inc, manufacturer of BOTOX.

Bibliographic details

PubMedID
23647483

DOI
10.3111/13696998.2013.802694

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Botulinum Toxins, Type A /adverse effects /economics /therapeutic use; Chronic Disease; Clinical Trials, Phase III as Topic; Cost-Benefit Analysis; Data Interpretation, Statistical; Great Britain; Humans; Markov Chains; Migraine Disorders /drug therapy /economics /prevention & control; Quality-Adjusted Life Years; State Medicine /economics

**AccessionNumber**
22013019520

**Date bibliographic record published**
17/06/2013

**Date abstract record published**
01/05/2014