

Complicated decisions on new migraine-prevention therapies



The development and introduction of monoclonal antibodies for migraine prevention that target calcitonin gene-related peptide (CGRP) or the CGRP receptor is one of the most important advances in migraine therapy in decades. For many neurologists, it came as a surprise, therefore, that on Jan 10, 2019, the UK National Institute for Health and Care Excellence (NICE) published draft guidance in which it does not recommend the use of one of these drugs, erenumab. As erenumab is the first of these drugs to be evaluated by NICE, this guidance sets a precedent that anti-CGRP therapies will not be available on the NHS for patients with migraine any time soon.

Migraine is one of the most prevalent and disabling neurological diseases worldwide, so these new migraine-specific therapies are a welcome development. They work by interfering with the signalling of CGRP, a neuropeptide expressed in the cranial sensory nerves. Four monoclonal antibodies that act on the CGRP pathway have been developed for migraine prevention. In 2018, erenumab was approved for the prevention of episodic migraine and chronic migraine by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and fremanezumab and galcanezumab were approved by the FDA for chronic migraine prevention. These drugs are administered monthly by subcutaneous injection. Eptinezumab, which is delivered intravenously every 3 months, is yet to start the approval process.

Standard of care options for migraine prevention in the UK are currently oral medications originally developed for other conditions, such as epilepsy. These oral drugs are poorly tolerated and have low adherence rates. NICE recommends botulinum A toxin (botox) for patients with chronic migraine who have failed oral preventive treatments and therefore botox is the relevant trial comparator for CGRP therapies. Trial evidence for erenumab shows that reductions in monthly migraine days are -1.9 migraine days/month in patients with episodic migraine (across three trials) and -2.5 migraine days/month for chronic migraine (in one trial). However, some specialists argue that the proportion of patients who have a reduction in migraine days of 50% or more, which was significantly more with erenumab than placebo (38% vs 15%), is more clinically meaningful. The trials of botox and erenumab used different primary

endpoints (mean headache days vs migraine days, respectively). However, in each trial, researchers also collected the data for the other endpoint, thus, these comparisons should be feasible and should eventually be reported. Additionally, botox has a good safety profile. Erenumab also has a favourable side effect profile so far and adherence for this treatment seems high. However, long-term safety data for CGRP therapies are not available, which is another reason why NICE has been cautious in its recommendations.

Botox is far cheaper than erenumab (£386.50 per month vs £379.00 every 3 months). NICE was considering approval of erenumab for patients with migraine on more than 4 days per month, which would result in a huge number of eligible patients. An estimated 11 million people in the UK have migraine; the percentage of people that have attacks on more than 4 days per month is hard to estimate, but the proportion decreases as the number of days increases. Despite the undeniable burden of disease, erenumab is therefore unlikely to be considered a cost-effective option for NHS patients with low-frequency episodic migraine (<10 days/month) due to the large patient population. Fewer patients have chronic migraine (≥ 15 days/month), but the number of eligible patients would still be relatively high because oral preventives fail to reduce migraines in many patients.

There are patients with chronic migraine, however, in whom botox does not reduce the number of migraine attacks. The results of a subgroup analysis of a trial of erenumab in patients with chronic migraine that had failed other preventive treatments, including those who took botox, suggested efficacy in reducing monthly migraine days. Furthermore, patients with high-frequency episodic migraine (10–14 days/month), for whom disability is arguably similar to that of patients with chronic migraine, do not have further treatment options after oral treatments fail, because botox is not indicated for these patients.

NICE has acted correctly in not recommending erenumab on these specific terms. But, if the cost of erenumab is reduced and the eligible patient population is refined, then NICE should recommend its use. The many patients who have experienced failures in treatment and continue to have frequent and severe migraines need further options. ■ *The Lancet Neurology*



For the 2018 developments for headache see [Round Up](#) *Lancet Neurol* 2019; **18**: 5–6

For NICE's guidelines see <https://www.nice.org.uk/guidance/gid-ta10302/documents/appraisal-consultation-document>

For the global burden of migraine see [Articles](#) *Lancet Neurol* 2018; **17**: 954–76

For more on adherence to oral treatments for migraine see *Cephalalgia* 2015; **35**: 478–88

For more on NICE's recommendation for botox see <https://www.nice.org.uk/guidance/ta260/documents/nice-recommends-botox-for-preventing-headaches-in-adults-who-have-chronic-migraine>

For more on the trial evidence for erenumab see *J Headache Pain* 2019; published online January 16. <https://doi.org/10.1186/s10194-018-0955-y>

For the trial on chronic migraine see [Articles](#) *Lancet Neurol* 2017; **16**: 425–34

For the subgroup analysis of patients who fail preventive treatments see *Cephalalgia* 2018; **38**: 1611–21

For the study on high frequency episodic migraine see *Cephalalgia* 2016; **37**: 104–13