Association of British Neurologists

6 March 2012

Ms Kate Moore
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
Level 1A, City Tower
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Manchester
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By email only to: Kate.Moore@nice.org.uk

Dear Ms Moore,

RE: **Migraine (chronic) - botulinum toxin type A – comments from the ABN**

Please see below for comments from the Headache and Pain section of the Association of British Neurologists.

Yours sincerely,

[redacted]

[redacted]

pp [redacted]
[redacted] ABN Headache & Pain Section
Association of British Neurologists

[redacted]
Association of British Neurologists

Copy to: [redacted] Royal College of Physicians

Comments from ABN Pain & Headache Section re: Botulinum Toxin type A for the prevention of Headache in adults with Chronic Migraine

There appears to be a minor erroneous reference to "adverse reactions" in section 2.2 about the technology. The ABN suspects this should read "licensed indications" not adverse reactions".

Q 1 Has all the relevant evidence been taken in to account?

The ABN Pain Section agrees that the main clinical trial evidence for Botulinum toxin type A in chronic migraine has been evaluated i.e. PREMPT 1 and 2 trial programme sponsored by Allergan. We are not aware of other placebo controlled data although are aware of recently published comparator trials compared to Topiramate.

The ABN notes that the NICE appraisal committee recognised that chronic migraine is a debilitating condition seriously affecting quality of life. The ABN is keen to ensure that all evidence based treatments are appropriately available to appropriate patients and their doctors, given the current reliance on open label consensus therapies for this disorder.

The ABN headache and pain section noted that the following areas of evidence were not potentially taken into account:

1. The relative clinical effectiveness and cost effectiveness of advocated alternatives

Although the appraisal consultation document suggests expert consensus treatment with 3 prior agents prior to receipt of Botulinum toxin type A the fact that there is poor quality clinical trial evidence, let alone cost effectiveness evidence, for most alternative oral drug therapies advocated for the treatment of chronic migraine appears does not appear to have been considered by the appraisal document.

The only other drug with an evidence base from a positive double-blind randomised trial is Topiramate. This data is based on 2 small studies (total patient population = 387). The treatment dropout rate due to tolerability and significant side effects, let alone recurrent NHS services usage due to tolerability issues, is not insignificant with this treatment. (Data available from studies of Topiramate).

None of the other agents suggested have adequate methodically sound clinical trial evidence for the treatment of chronic migraine and any prior consensus is based on open label studies often with heterogeneous population, shorter follow-up and less robust assessment criteria than the PREMPT studies.

2. Evidence for differential effects within the studied chronic migraine trial population to better assess cost effectiveness relating to outcome:

The ABN agrees that although the "absolute mean effectiveness" of Botulinum toxin type A versus placebo for a population of sufferers may not be very large but for specific patients the benefit in reducing migraine related impairment may be much greater.

- It would have been useful to see the relative % frequency reduction in both headache assessment parameters in addition to quality of life data between both treatment/placebo groups e.g. splitting the data into 10% responder groups e.g. 20%, 30%, 40%, 50% etc. so as to help calculate cost effectiveness or alternatively into 25%, 50% & 75% responder groups?

The Appraisal committee state in their consultation documents that they are not aware of any relevant differential effectiveness subgroups but the ABN was unable to find data in the released documentation relating to point 2 outlined above.

In summary, in contrast to advocated alternative therapies in chronic migraine Botulinum toxin type A appears to show some evidence of benefit in contrast to lack of evidence for other drugs advocated for treatment of this disorder. This is potentially an important consideration if one seeks evidence based rather than simply consensus based clinical care.

Q 2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The ABN agrees that there is an absence of data on the use of the positive stopping rule. The ABN suggests that this is also the case for many other therapies used in clinical practice. The ABN suggests that if the appraisal were positive that its approval might be subject to an on-going condition that a positive stopping rule be audited to facilitate future assessment.

The ABN notes the comment from the appraisal recommendation that the PREMPT studies had a limited follow-up duration of 1 year. The ABN accepts this is potentially an important point but also wishes to point out that the PREMPT studies are the highest quality and longest ever follow-up studies performed in this condition. The study was performed according to the universally accepted International Headache society trial standards at the time of study inception so although the uncertainties may be valid, the reason for adopting these standards seem reasonable in the absence of retrospective knowledge.

The ABN would like to highlight areas of potentially missed NHS utility costs for the current care pathway that bear strong consideration in any health economic model over and above comparator potential approval of Botulinum toxin type A for chronic migraine.

Chronic migraine patients more often need secondary care outpatient consultations and its associated consultation related tariff costs for the following reasons:

- Lack of widespread GP familiarity with how to diagnose and treat chronic daily headache disorders.
- Frequent work or daily activity related impairment resulting from chronic migraine and associated symptoms
- The prescription of non-licensed, non-evidenced based drug therapies suggested to primary care physicians for this disorder who are unprepared or unfamiliar with using these drugs.
- The lack of adherence to advocated oral medications due to tolerability issues and thus frequent repeat consultation and/or wasted prescription costs

Chronic migraine patients treated with oral medications have “unseen” and difficult to **calculate iatrogenic morbidity costs:**

- Obesity as a side effect of consensus suggested therapies eg tricyclic antidepressants, beta-blockers
- Psychiatric morbidity, oral and depot contraceptive drug interaction and teratogenicity for Topiramate therapy

The ABN notes and welcomes a review of the model used to assess cost effectiveness and utility costs and looks forward to seeing if it is any better than the one originally proposed.

The ABN would additionally highlight previous comments (see question 1 above) in relation to evidence interpretation.

Q 3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The ABN is keen to ensure cost effective use of evidence based therapies. The ABN notes that Botulinum toxin type A has received a license in the UK, Europe and USA based on its differential efficacy over placebo.

The ABN is disappointed that NICE “are not minded to recommend” Botulinum toxin type A for the treatment of appropriately assessed and diagnosed patients with chronic migraine as it will:

1. Deprive sufferers of a new potentially effective and well tolerated therapy (especially compared with currently advocated oral evidenced based therapies).

2. Unintentionally lead to the withdrawal of already NHS initiated and commissioned therapies in some areas and/or if these already PCT approved treatment pathways continue, produce a situation of difficult to challenge problematic inequality to chronic migraine Botulinum toxin type A treatment provision.

Q 4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief.

Migraine affects the female adult population 3 times as more males and has its highest incidence in the teenage years and early twenties and its highest prevalence between the ages of 30-50 years. Chronic Migraine is more prevalent in females.

Whilst it is noted that any recommendation is not targeted to discriminate against women the decision will have a 3 times greater effect on women when compared with men eg a negative recommendation would indirectly increasing their risk of exposure to drugs with teratogenicity and/or contraceptive drug interaction. A positive decision does not take away this risk buts allows an informed discussion to occur to avoid unnecessary clinical risk.

Q 5 Are there any equality related issues that need special consideration and are not covered in the appraisal consultation document?

See comments discussed in Question 4 above.

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