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News from MIPCA

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Management of Chronic Migraine

Overview

This newsletter is concerned with the management of chronic migraine in the clinic. It contains a review of the latest clinical data on this difficult to treat condition and incorporates chronic migraine into MIPCA Headache Management Guidelines. We discuss the classification and epidemiology of chronic migraine, currently available treatments, an analysis of the Phase III studies on Botulinum Toxin Type A (BOTOX®: Allergan, Marlow, UK) for the treatment of chronic migraine and practical issues relating to the management of chronic migraine in clinical practice. From this work we have prepared a statement summarising our overall conclusions (Box 1).

Box 1.	*MIPCA Statement on Chronic Migraine*
1	Chronic migraine is now recognised by the International Headache Society and defined in their classification of headache document. A sufferer has a minimum of 15 headache days per month of which a minimum of 8 days exhibit migraine features.
2	The World Health Organization has ranked migraine in the 20 most disabling illnesses but it is still under-recognised, under-diagnosed and under-treated.
3	It is accepted that there are a number of treatments used in chronic migraine which are effective but not licensed. In July 2010 Botulinum Toxin Type A (BOTOX®) was licensed for chronic migraine in the UK by the Medicine and Healthcare Products Regulatory Agency (MHRA), after consideration of data that included the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies. BOTOX® currently remains the only licensed drug for the condition and should be available to NHS patients. At present the National Institute for Clinical Excellence (NICE) is performing a review and it is regrettable that there is likely to be very little NHS availability of BOTOX®, at least until the NICE decision is known.
4	Chronic migraine affects approximately 2.5% of the population who will seek advice from various sources: Internet, General Practitioner, Physical Therapist, etc. If these initial efforts fail to allow the patient to regain control, it is suggested that specialist intervention is optimal.
5	We suggest that for a healthcare professional to offer BOTOX® for chronic migraine the minimum training requirement is to understand the impact of the condition and its differential diagnosis and management, as well as to have undertaken the specific 'BOTOX® in chronic migraine' training.

Classification and Diagnosis of Chronic Migraine

- The currently used definition of chronic migraine is ≥15 headache days per month of which ≥8 days exhibit migraine features.[1]
- Patients with chronic migraine may or may not have concomitant medication overuse headache (MOH). This does not coincide with the latest International Headache Society (IHS) classification for chronic migraine, which excludes MOH.[1] However, field testing showed that the inclusion of MOH in the definition correlated closely with the pattern of headaches in chronic migraine patients attending the clinic.[2]
- There is an algorithm for the diagnosis of chronic headache subtypes[3], from an initial diagnosis of chronic primary headache (≥15 headache days per month[4]). This is shown in Figure 1 and is simple to use and well suited to everyday clinical use.

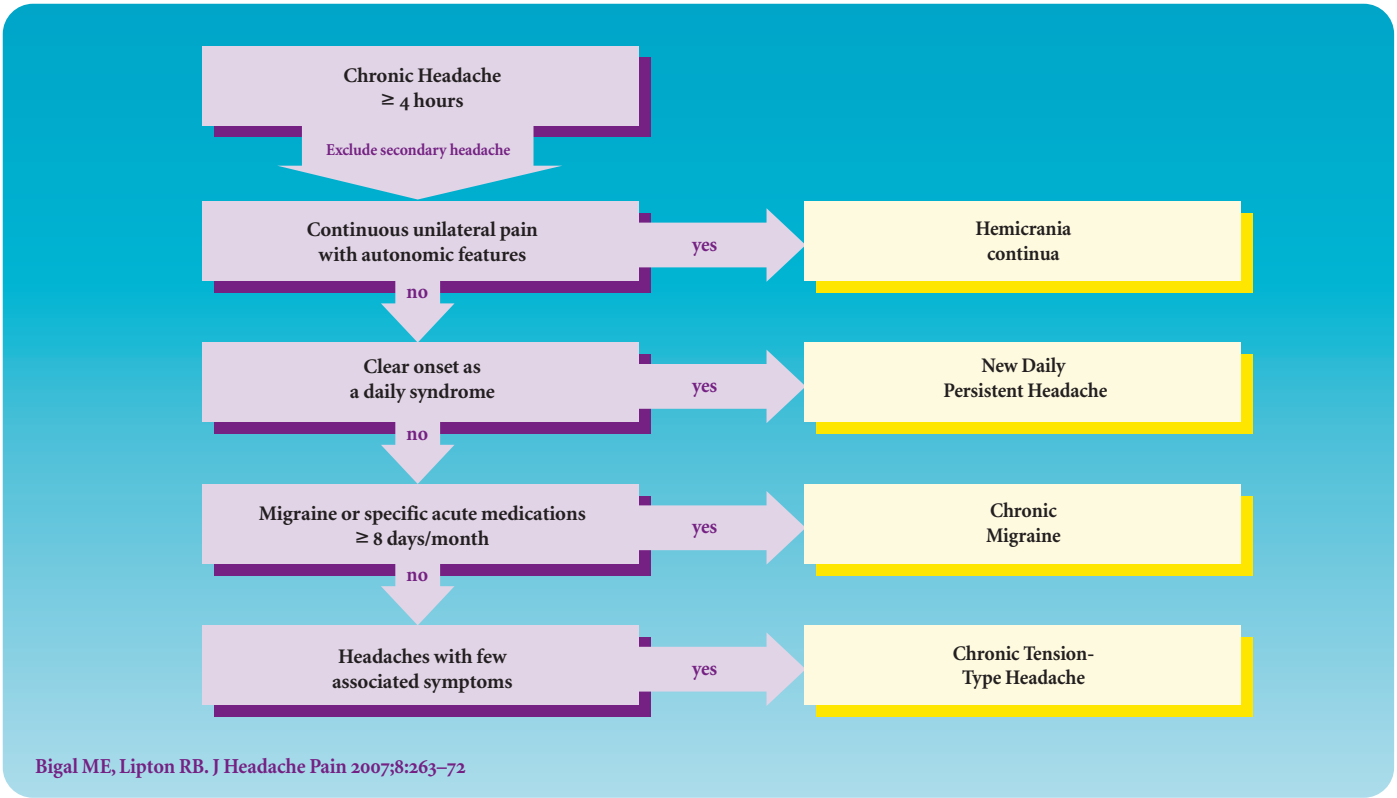


Figure 1. Differential diagnosis of chronic migraine.[3]

Epidemiology of Chronic Migraine

- Population-based studies show that the prevalence of chronic primary headache lasting ≥4h is about 4%.[5] Chronic migraine prevalence varies from about 1.5–2.5%[6,7], while MOH affects about 1.5% of adults.[8]
- However, chronic migraine is the most common headache seen in specialty clinics. In one US study, over 60% of patients had chronic migraine with MOH, while a further 25% had chronic migraine without MOH (Figure 2).[9]
- Patients with chronic migraine are severely affected by the condition. Compared with episodic migraine, chronic migraine patients have significantly worse disability, pain intensity and health-related quality of life (HRQoL), greater anxiety and depression and higher utilisation of healthcare resources.[10,11]
- Risk factors for developing chronic migraine include high disability, increasing headache frequency, medication overuse, allodynia (central sensitisation), obesity and sleep disturbance and snoring (e.g. sleep apnoea).[12]

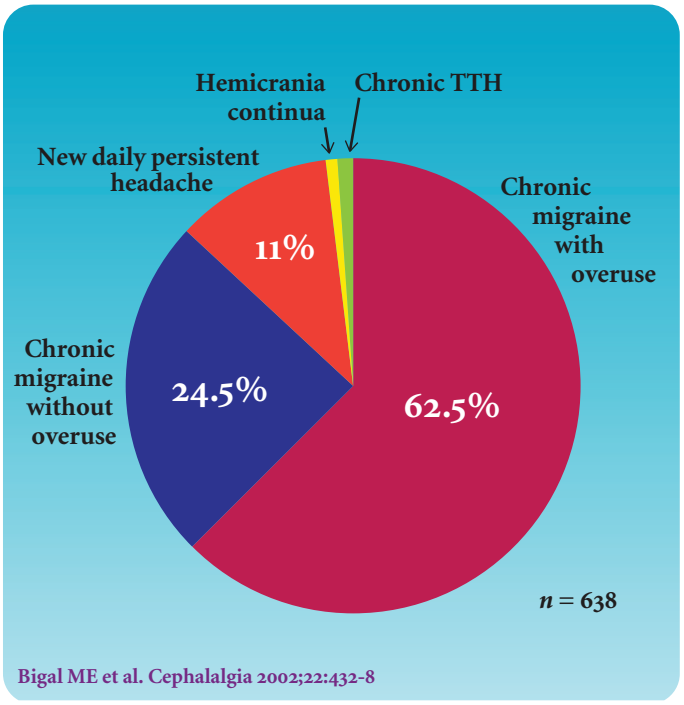


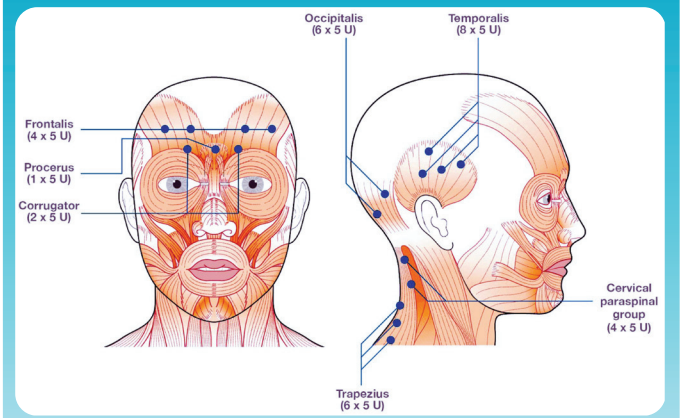
Figure 2. Prevalence of chronic headache types in the clinic.[9]

Treatments for Chronic Migraine

- Until recently there has been no licensed treatment for chronic migraine. Trials have been conducted with conventional migraine preventive drugs, but most have been small and/or uncontrolled.
- The best quality evidence comes from studies with topiramate. Topiramate was superior to placebo in two placebo-controlled studies (one large, one small), but was associated with frequent adverse events.[13–15]
- Preliminary studies with amitriptyline,[16] sodium valproate,[17,18] pregabalin,[19] zonisamide,[20] and tizanidine[21] have also shown promise, although the data require substantiation in larger studies.

- In a Phase II multicentre, randomised, placebo-controlled study, 355 chronic headache patients were treated for up to 11 months. Treatment with BOTOX® resulted in a mean of 6.7 more headache-free days per month compared with 5.2 for placebo (not significant). However, the difference was significant for patients not using other preventive medications (10.0 vs 6.7 days, p<0.05).[22,23]
- Phase III PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) studies.[24-26]
- Two multicentre, randomised (1:1 BOTOX®: placebo), placebo-controlled studies were conducted in 1384 patients with chronic migraine, treated for 24 weeks in a double-blind phase, followed by a 32-week open-label phase.[24-26]
- A fixed-site, fixed-dose injection paradigm was used (Figure 3) for treatment, given every 12 weeks.[27]

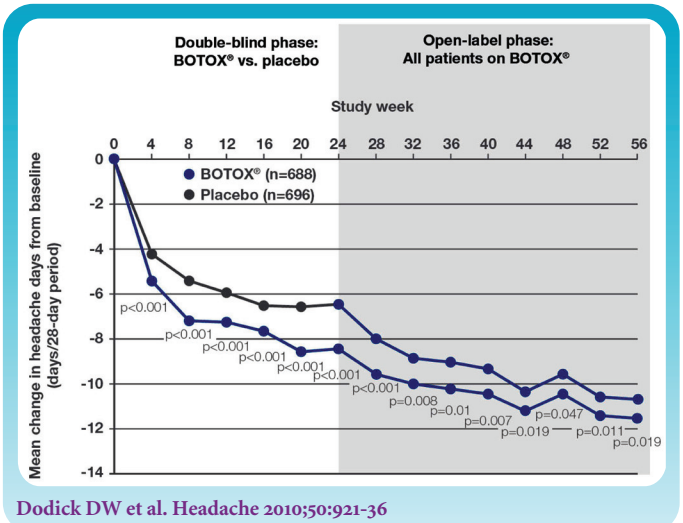
A total of 31 injections across seven specific head and neck muscles, with a minimum dose of 155 U of BOTOX® injected per patient



Blumenfeld A et al. Headache 2010;50:1406-18

Figure 3. The fixed-site, fixed-dose injection paradigm used in PREEMPT.[27]

- Data from the two studies were pooled to provide greater power for statistical analysis. The primary efficacy analysis was amended from the original protocol in one study to the frequency of headache days.[26]
- For the primary efficacy analysis, patients treated with BOTOX® averaged 8.2 fewer headache days/month at Week 24 compared with 6.2 with placebo (p<0.001, Figure 4).[26]



Dodick DW et al. Headache 2010;50:921-36

Figure 4. PREEMPT pooled analysis: mean change from baseline in frequency of headache days (primary endpoint).[26]

- BOTOX® was significantly superior to placebo for all secondary efficacy endpoints at Week 24, including measures of disability (HIT-6 Questionnaire, Figure 5). An HRQoL measure (MSQ Questionnaire) was significantly superior for BOTOX® at Week 56 (end of the open-label phase).[26]

Endpoint, Mean Change From Baseline	*BOTOX® (n=688)*	*Placebo (n=696)*	*p Value*
Frequency of HA days	-8.4	-6.6	<0.001
Frequency of migraine days	-8.2	-6.2	<0.001
Frequency of moderate/severe HA days	-7.7	-5.8	<0.001
Total cumulative HA hours on HA days	-119.7	-80.5	<0.001
% Patients with severe (≥60) HIT-6 score	67.6	78.2	<0.001
Total HIT-6 score	-4.8	-2.4	<0.001
Frequency of HA episodes	-5.2	-4.9	0.009
Frequency of migraine episodes	-4.9	-4.5	0.004
Frequency of acute HA pain medication intake (all categories)	-10.1	-9.4	0.247
Frequency of triptan use	-3.2	-2.1	<0.001

Figure 5. Pooled efficacy of BOTOX® at Week 24 (primary time point).[26]

- Data for the MOH+ subgroup of patients (65%) were very similar to those for the whole patient population.[26]
- BOTOX® was generally well tolerated in repeated use. Most treatment-related adverse events in the BOTOX® group were related to pain and weakness at the injection site and to known side effects of the drug.[26]
- In conclusion, the pooled results from PREEMPT showed that BOTOX® was an effective and well tolerated preventive treatment for chronic migraine, with significant improvements in multiple headache symptoms, disability and HRQoL.
- Based on these data, the MHRA licensed BOTOX® for chronic migraine in the UK in July 2010, and it currently remains the only licensed drug for the condition.

Current situation in the UK

- It is now more than 1 year since the UK launch of BOTOX® for chronic migraine. To date, there has been very little take up by the NHS, with resistance from some PCTs. The situation has not been helped by negative comments in Drugs and Therapeutic Bulletin[28] and from the Scottish Committee on Medicines.[29]

Criticism of the PREEMPT studies

- The PREEMPT studies were large, controlled and well-designed. The population of patients, almost all of whom suffered only from migraine attacks and the majority of whom had MOH, were similar to the patient population typically seen in specialist clinics.[9] BOTOX® exhibited consistent efficacy across multiple endpoints, and was well tolerated.

- However, the PREEMPT studies have been criticised for several reasons. First, the dose used (155–195 U) was higher than that used previously in clinical practice (100 U). In the first study, the primary endpoint (frequency of headache episodes) did not show a significant difference between BOTOX® and placebo. The primary endpoint was subsequently altered in the second study to the frequency of headache days. Second, the placebo response was high, although this feature is reported commonly in studies of preventive medications for chronic migraine.[30] However, some critics have interpreted the data as indicating that the efficacy of BOTOX® was due to the effect of the injection, rather than the active drug, or that blinding in the studies was not maintained efficiently. Third, at present, there is also no persuasive cost-efficacy data for BOTOX®.

Latest clinical research

- A prospective, open-label, longitudinal study was conducted in a naturalistic clinical practice setting. Patients (n=24) with cervical dystonia associated with chronic headache and a history of migraine were given three sets of BOTOX® injections (30-100U) over a 16–24 week period and monitored for 3 months after the final injection. The change in disability (MIDAS score) from baseline to end of study was the primary endpoint.[31] By the end of the study, patients treated with BOTOX® had significant improvements in MIDAS score, headache frequency and in the number of headache medications used (Figure 6), as well as in HRQoL (SF-36 score).

Endpoint	*Baseline value*	*End of study value*	*p-value*
MIDAS score	47.1	26.7	<0.01
Days with headache/month	21.6	15.3	<0.01
Headache severity*	2	1.9	NS
No. medications used/month	38.4	20	<0.05
Effectiveness of medications used**	3.1	3.4	NS

* 3 = severe; 2 = moderate; 1 = mild; 0 = none
** 5 = excellent; 4 = good; 3 = reasonable; 2 = poor; 1 = very poor
Dowson AJ et al. Drugs RD 2008;9:147-58

Figure 6. Efficacy results from the clinical practice study.[31]

- Several small studies have been conducted comparing BOTOX® with other preventive medications in patients with chronic migraine. BOTOX® was as effective as anti-epileptic drugs (topiramate and divalproex sodium), but was tolerated better.[32-34] In another study, BOTOX® was as effective as amitriptyline.[35] However, further large studies are required to elucidate the clinical profile of BOTOX® and other migraine preventive drugs.

- Greater occipital nerve stimulation (GONS) with surgically-implanted devices and/or injections to block transmission (GONI) are seen by some specialists as promising treatments for chronic headaches. Very recently, a randomised, double-blind, placebo-controlled, Grade A clinical study has been completed, assessing the efficacy and safety of an implantable device used for GONS (St. Jude Medical, Bourne End, Bucks, UK).[36] Results have not been fully published to date, but show that, although statistical significance for the primary endpoint was not achieved, patients treated with GONS had significantly greater benefits on a range of efficacy measures compared with those receiving placebo. The device was well tolerated by patients. Based on these data, the device was approved for chronic migraine in the UK by the MHRA in September 2011. To date, there is little evidence to support a role for GONI in chronic migraine treatment, although it is used by some specialists.

Issues relating to the use of BOTOX in clinical practice

- To date BOTOX® has the best quality evidence of efficacy, and is the only licensed drug for chronic migraine.

- BOTOX® is expensive; a course of treatment costs £250, plus operator costs (up to £1000). Other drugs are much cheaper. Cost-efficacy data are therefore required for BOTOX®, and NICE are currently conducting a Technology Appraisal of BOTOX® in chronic migraine.

Remaining questions

- Which patients are most suited for BOTOX® treatment?

- Can superior efficacy be obtained with BOTOX® in combination with another preventive drug (e.g. topiramate)?

- Does BOTOX® work on the neck? The drug is licensed for cervical dystonia in the UK and one open-label study showed BOTOX® to be effective in treating chronic migraine associated with cervical dystonia.[31]

MIPCA Guidelines for Managing Chronic Migraine

- Diagnosis: headache diaries should be used to help diagnose chronic headache (headaches on ≥15 days per month) and chronic migraine (chronic headache with ≥8 days exhibiting migraine features, with or without MOH). The diagnosis can be confirmed using the algorithm shown in Figure 1.[3]

- Goals of treatment: to reduce migraine frequency and its negative effect on functioning, and to limit the use of acute medications. The optimal way to accomplish this is to introduce effective preventive medications.[37]

- Initial management: this is dependent on whether the migraine is of chronic, intermediate or episodic frequency (Figure 7).

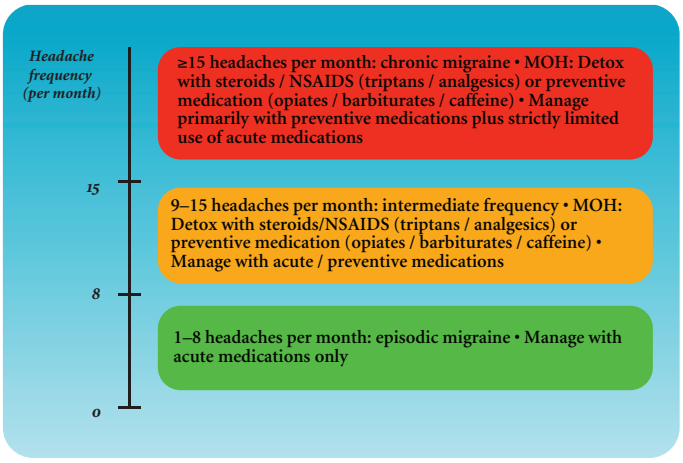


Figure 7. Strategies for managing migraine of different frequencies in the clinic.

- Choice of initial preventive treatment: this should be tailored to the individual patient, determined on the efficacy and adverse event profiles and the likely costs involved (Figure 8). It should be noted that BOTOX® is the only drug licensed for chronic migraine in the UK and so far has the best clinical evidence for efficacy and safety. There is also evidence that its use leads to reduced consumption of acute medications.[26,31]

Medication	*Efficacy*	*Adverse events*	*Quality of clinical evidence*	*Cost*
BOTOX®	**	**	A	*
Topiramate	**	*	B/C	**
Divalproex	**	*	B/C	**
Amitriptyline	**	*	B/C	**

** = more favourable
* = less favourable

Figure 8. Factors to be taken into account in the choice of initial preventive medication for chronic migraine.

- Several methods can be used to assess the efficacy of preventive medications, including the decrease in headache frequency and/or severity and the increased response to acute treatment. A global assessment tool is also desirable, but is not currently available for migraine prevention.

- Follow up: this should be mandatory, with regular patient visits scheduled. Headache diaries are invaluable in monitoring the patient's pattern of headaches, and their response to treatment (in terms of efficacy, tolerability and compliance). Alternative medications should be considered where the current medications show lack of efficacy and/or an unacceptable tolerability profile.

- The current license for BOTOX® has no restrictions. However, we suggest that training is required, with a minimum requirement of:
  - Understanding the classification and diagnosis, epidemiology, burden of illness and management options associated with chronic migraine
  - Gaining an understanding of the PREEMPT study data for BOTOX®
  - Have training in the use of BOTOX®: the injection protocol, adverse events and follow-up procedures.

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