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Botulinum toxin type A for the treatment of migraine

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Migraine is a common and debilitating disorder that often requires prophylactic therapy, particularly for those migraine patients who meet the diagnostic criteria for chronic daily headache (chronic migraine). Existing prophylactic treatments for migraine are inadequate for many patients due to their modest efficacy and/or systemic side effects. Alternative treatment strategies are needed, particularly in those with chronic migraine. Botulinum toxin type A is a locally injected protein complex that has been investigated as a treatment for episodic migraine and chronic daily headache. A systematic series of controlled trials has led to the identification of a subset of migraineurs with chronic daily headache who obtain demonstrated benefits of botulinum toxin type A over placebo that is maintained with repeated treatments.

Keywords: botulinum toxin, chronic daily headache, chronic migraine, transformed migraine

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1. Introduction

Migraine is a debilitating primary headache disorder that includes episodic and chronic variants, with the latter also classified as a subtype of chronic daily headache (CDH) according to the proposed classification by Silberstein and Lipton [1]. The International Headache Society recently added to its classification (ICHD-II) a definition for chronic migraine, which includes ≥ 15 days of migraine headache, without medication overuse. Bigal *et al.* [2] recently tested three alternate definitions [2]; in this review, the second proposed definition was used – the presence of headaches on ≥ 15 days per month, of which most days (≥ 50%) are migraine or probable migraine days. Approximately 18% of women and 7% of men are afflicted by migraine [3], and it has been estimated that 1.4 – 2.4% of the general population suffer from chronic (or transformed) migraine [4,5]. Chronic migraine represents one of the most frequent diagnoses seen in tertiary centres, accounting for almost 90% of adults with CDH seen, most of whom (60%) may overuse symptomatic headache medications [6].

Migraine is associated with substantial disability, as demonstrated by a large epidemiological survey in which 91% of individuals with migraine reported functional impairment and 53% reported that severe headaches substantially interfered with daily activities or required bed rest [3]. According to several reports, patients with CDH or chronic migraine have greater disability [7] and a reduced perception of their quality of life [8] than episodic migraine patients, with the greatest reduction observed in analgesic overusers [9].

Although many patients with episodic migraine obtain adequate relief from acute oral medications, others obtain incomplete relief and/or are intolerant of acute medications [10]. Individuals with chronic migraine are particularly difficult to treat and are often considered refractory to conventional acute treatments. Many also overuse acute medications, which may contribute to their chronic headache disorder. According to the American Academy of Neurology, preventive treatment for migraine should be considered for individuals whose migraines substantially impact their lives and have not responded to acute care, or where migraines are frequent enough that treating them with acute medication risks development of drug-induced headache [10]. Therefore, some patients suffering from episodic

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migraines and most patients suffering from chronic migraines may benefit from a prophylactic treatment.

Oral migraine prophylactic medications include divalproex sodium, flunarizine, amitriptyline, topiramate, β-blockers, such as propanolol [11-14] and, in selected cases (e.g., menstrual migraine), NSAIDs [15]. Although some of these agents have demonstrated efficacy in the reduction of migraine episodes in patients suffering from episodic migraines, their efficacy and safety have not been established in patients suffering from chronic migraine, as most studies have systematically excluded patients with chronic migraine. Therefore, only a few small controlled trials have examined the efficacy of any oral prophylactic treatment in CDH or chronic migraine (topiramate [16], tizanidine [17], gabapentin [18] and fluoxetine [19]). In general, these medications have been associated with modest therapeutic benefits in controlled trials and systemic adverse events such as weight gain, asthenia, paresthesias, diarrhoea, vomiting and somnolence [11-13,16-20]. Given the disability associated with migraine, the costs of inadequate treatment (humanistic and economic) and the adverse event profile of existing migraine preventive medications, it is clear that better treatments are needed for migraine prophylaxis. This is particularly true for the group of patients with chronic migraines, for which no medications are currently approved by the US FDA and only a few controlled trials have been conducted to substantiate safety and efficacy.

2. Botulinum toxin type A: introduction and pharmacology

Botulinum toxin type A (BTX-A) is a focal therapeutic agent that has been examined for the prophylaxis of episodic migraine and CDH [21-23]. In the treatment of primary headache disorders, BTX-A is injected locally into specific muscles of the head, face and/or neck. BTX-A has been investigated and used clinically in the treatment of several ophthalmic and neurological conditions for > 20 years [24,25]. The effects of BTX-A on pain were first reported in 1985, when injections were found to significantly improve neck and shoulder pain associated with the movement disorder cervical dystonia [26]. Over the ensuing years, BTX-A has been used and studied for a variety of other conditions involving pain [27].

BTX-A is a protein complex synthesised by various strains of the bacteria *Clostridium botulinum*. The protein complex includes the neurotoxin molecule (150 kDa) along with non-toxin proteins that range in size [28]. BTX-A (BOTOX® Allergan, Inc.) contains the 900 kDa complex, which includes the neurotoxin molecule and associated haemagglutinin and non-haemagglutinin proteins [29]. The non-toxin proteins help stabilise the neurotoxin and protect it from degradation [30,31]; the size and structure of the large protein complex may also minimise migration of the neurotoxin away from its intended area of action.

BTX-A is a biological product and, as such, is manufactured and regulated differently from chemically synthesised pharmaceuticals. BTX-A must be isolated from the bacterial cultures, purified, stabilised and quantified *prior to* being marketed as a therapeutic agent [32]. Excipients are added, which affect the character of the final therapeutic agent [33]. Doses are quantified in biological units, with one unit equal to the LD_{50} in female Swiss-Webster mice. Another botulinum toxin type A product (Dysport®, Ipsen Ltd.) has been examined in several headache studies [34,35], although this product is not yet available for clinical use in the US. This product has a different formulation, is used at higher doses, and is not bioequivalent to the Allergan product regardless of the dose [36].

BTX-A is injected locally into muscles (or dermis, depending on the indication) and does not appreciably enter the systemic circulation at typical doses. Once injected, BTX-A binds to, and is internalised by, cholinergic neurons [37,38]. BTX-A then cleaves one of the proteins integral to synaptic neurotransmitter release [39]. Through this mechanism, BTX-A inhibits cholinergic neurotransmission at the neuromuscular junction and autonomic terminals [39].

However, the inhibition of acetylcholine release at the neuromuscular junction is unlikely to fully explain the effects of BTX-A in pain disorders, and thus a variety of other possible mechanisms have been proposed [27,40] and are being investigated. Several studies have found that BTX-A inhibits the release of nociceptive, inflammatory mediators, such as calcitonin gene-related peptide, glutamate and substance P, which may at least partly explain the reported effects of BTX-A in migraine and other pain conditions [41-45].

3. Clinical efficacy of botulinum toxin type A in migraine

The clinical efficacy of BTX-A for the prophylactic treatment of episodic and chronic migraine has been examined in a number of open-label and controlled studies. This review considers only controlled studies.

The evaluation of any treatment for migraine is beset by a number of challenges, including a typical and robust placebo response [21,46], the allowance of concomitant acute headache pain medications and, sometimes, prophylactic therapies, and compliance and reliability issues with headache diaries used to document efficacy. Furthermore, because very few trials have examined the prophylaxis of chronic migraine, there is neither an accepted optimal end point nor trial design in this area of research.

A further challenge with BTX-A is that effective injection sites and doses must be identified, which is not as straightforward in migraine as in some neuromuscular disorders, although even these can be complicated. The controlled studies described here represent a systematic attempt to identify a responsive patient population, effective injection sites and doses, optimal efficacy measures, a study design that minimises the effect of placebo response typically

expected in pain trials and a data-reporting method that encourages patient compliance.

In the following summaries of the individual controlled trials, only the BTX-A preparation manufactured by Allergan, Inc (BOTOX). Due to differences among BTX-A preparations in neurotoxin complex size and composition, serotype, manufacturing processes, excipients and unit testing methods, results with any single BoNT preparation cannot be automatically generalised to the others. In addition, for safety reasons, it is important to note that all doses included in this review apply only to BTX-A manufactured by Allergan, Inc. The statement of statistical significance refers to $p < 0.05$.

3.1 Episodic migraine

3.1.1 *Silberstein et al., 2000* [21]

In this randomised, double-blind study, patients (n = 123) with episodic migraine received a single treatment with BTX-A (25 or 75 U) or placebo into the muscles of the front and sides of the head, using a fixed sites approach. Eligible patients had between two and eight moderate to severe migraine episodes per month, responded to acute migraine therapy and, if taking prophylactic medications, were on stable doses prior to and during the trial. Patients documented headache-related characteristics in a paper diary and a global treatment efficacy assessment at monthly follow-up visits. The primary efficacy variable was change in frequency of moderate to severe migraine episodes. All but one patient completed the study.

Compared with placebo, the 25-U dose of BTX-A showed a statistically significantly greater decrease in frequency of moderate to severe migraine episodes, frequency of migraine episodes of any severity, severity of migraine episodes, days with acute medication use and several other variables. The 75-U group did not show statistically significant differences from placebo on these variables. However, both BTX-A dose groups showed statistically significant benefits over placebo in global improvement of symptoms at day 60.

3.1.2 *Barrientos and Chana, 2003* [47]

This was a small (n = 30), randomised, double-blind study, in which patients with episodic migraine received a single treatment with BTX-A (50 U) or placebo into muscles of the front and back of the head and neck using a fixed-site approach. Patients who were overusing acute headache medications or prophylactic therapies were excluded. Patients documented headache-related characteristics in a paper diary and a global treatment efficacy assessment at the end of the study. The primary efficacy variables were number of migraine episodes per month, frequency of severe migraine episodes and duration of migraine episodes. All patients completed the study.

Compared with placebo, BTX-A showed a statistically significantly greater decrease in frequency of migraine episodes, frequency of severe migraine episodes, and acute medication use. At the end of the study, global efficacy evaluations completed by both investigators and patients indicated a statistically significant benefit for BTX-A over placebo.

3.1.3 *Evers et al., 2004* [48]

This was a small randomised, double-blind, placebo-controlled study of 60 patients with between two and eight migraines per month. Patients received a single treatment with either placebo, BTX-A 16 U injected into frontal muscles only or BTX-A 100 U injected into frontal and neck muscles, in order to examine the effects of different injection sites. Patients recorded migraine-related variables in a paper diary for 90 days following treatment and completed several questionnaires. The primary efficacy variable was the percentage of patients with a reduction in migraine frequency of ≥ 50% during month 3 post-treatment. All patients completed the study.

No statistically significant differences were noted between the BTX-A and placebo groups in the percentage of patients with a reduction in migraine frequency of ≥ 50% or most other migraine-related, headache disability or depression measures. The 16-U dose of BTX-A showed statistically significant improvement over placebo on migraine-associated symptoms (e.g., photophobia, nausea).

3.1.4 *Saper et al. (in press)* [49]

In this randomised, double-blind, study, patients (n = 232) with between four and eight moderate to severe migraine episodes per month received a single treatment with placebo or one of four BTX-A doses injected into different muscle regions: frontal (10 U), temporal (6 U), glabellar (9 U) or all three areas (total dose 25 U). Eligible patients responded to acute migraine therapy, and if taking prophylactic medications, were on stable doses. Patients documented headache-related characteristics in a paper diary and completed a number of questionnaires. In general, BTX-A was not statistically superior to placebo at improving migraine or quality of life, as assessed by a number of different measures.

3.1.5 *Elkind et al. (in press)* [50]

This series of three sequential, randomised, double-blind studies included patients (n = 418) with between four and eight moderate to severe migraine episodes per month. In the first study, patients were treated with placebo or BTX-A (7.5, 25 or 50 U) injected into muscles of the front and sides of the head using a fixed-sites-fixed-dose approach. In the second study, patients continued to receive, or were randomised to, two consecutive treatments with 25 or 50 U. In the third study, patients were randomised to placebo or continuation of 25 U or 50 U. Patients documented headache-related variables in a paper diary and completed several questionnaires. No consistent, statistically significant differences were observed for BTX-A over placebo on any efficacy variable; all groups including placebo showed sustained improvements on multiple headache-related variables. At

day 120 in the first study, all three BTX-A groups showed statistically significantly better global assessment scores than the placebo group.

3.1.6 *Aurora et al., 2005* [51]

This randomised, double-blind, placebo-controlled trial included 369 patients with at least four moderate to severe migraine episodes per month and 15 or fewer headache days per month. Patients were allowed to continue acute headache medications and stable doses of prophylactic medications. Patients received three treatments (90-day intervals) with placebo or 105 to 260 U of BTX-A (mean dose 190.5 U) injected into head and neck muscles using a modified follow-the-pain paradigm. Headache-related variables were recorded using an electronic diary. The primary efficacy outcome measure was change in the number of migraine episodes in the subgroup of patients who did not respond to placebo during an initial placebo injection phase. Most patients (285 out of 369) completed the study. Patients classified as placebo non-responders who were treated with BTX-A did not show statistically significant improvements over those treated with placebo on migraine frequency (primary efficacy variable) or ≥ 50% decrease in migraine frequency from baseline, although sustained improvements in migraine were observed in both the BTX-A and placebo groups.

3.1.7 *Relja et al., 2005* [52]

This randomised, double-blind, placebo-controlled study included 322 patients with at least three moderate to severe migraine episodes per month who were not taking concomitant migraine prophylactic medications. Patients received three consecutive treatments at 90-day intervals with placebo or BTX-A (75, 150 or 225 U) into fixed sites in the frontal and posterior regions of the head. There were no statistically significant among-group differences observed in the number of migraines or other migraine-related variables.

3.2 Chronic migraine and chronic daily headache

3.2.1 *Ondo et al., 2004* [53]

This study included 60 patients who were randomised to a single double-blind treatment with BTX-A (200 U) or placebo. A total of 46 had chronic tension-type headache based on the 1994 criteria of Silberstein *et al.* [54] and 14 had chronic migraine. The study included those taking concurrent prophylactic medications (40 out of 60) and medication overusers (34 out of 60). Injections were generally administered using a follow-the-pain approach, which included sites in the muscles of the front and back of the head and, for almost 50% of the patients (16 out of 40), the masseter muscles. Patients recorded headache-related variables in a paper diary and completed global efficacy ratings and several psychological scales. The primary efficacy variable was number of headache-free days over the 90-day post-injection period. All but two patients completed the double-blind trial.

Results specific to chronic migraine were not analysed separately; therefore, it should be noted that the results reported apply to all enrolled patients, which include only a small number of chronic migraine patients. Compared with placebo, BTX-A tended to improve headache-free days over the 90-day period ($p = 0.07$), and statistically significantly improved headache-free days from days 60 to 90. Both patient- and investigator-rated global impression of efficacy scores were significantly better statistically in the BTX-A group than the placebo group. No significant differences were found between groups in number of abortive medications used, palpation scores, the Beck Depression Inventory or the Psychosocial Adjustment to Illness Scale.

3.2.2 *Mathew et al., 2005* [22]

In this large randomised, double-blind, 11-month study, patients with CDH (n = 355) received three consecutive and identical treatments with BTX-A or placebo injected at 90-day intervals into seven muscle areas of the face, head and neck. The total dose was in the range of 105 – 260 U. Eligible patients had > 15 headache days per month and were on stable migraine prophylactic medication regimens. Prior to randomisation, all patients received a single placebo treatment and were classified as placebo responders or non-responders; patients were then randomised to receive BTX-A or placebo. Patients recorded headache-related variables daily via an electronic telephone diary, which were assessed every 30 days throughout the study. The primary efficacy variable was change in the frequency of headache-free days for the placebo non-responder group. Most patients (273 out of 355) completed the trial.

At baseline, there were no significant differences between treatment groups in demographic characteristics, except that there was a trend for more patients treated with BTX-A overusing acute headache medications (53 versus 42% placebo; $p = 0.052$) when the newly proposed 2004 ICHD-II definition for medication overuse [55] was retrospectively applied to the data set. All patients reported at least one migraine or probable migraine headache during the baseline period and, thus, all were considered migraineurs with CDH (or chronic migraine). Most patients (279 out of 355) were classified as placebo non-responders and approximately one third were taking concomitant migraine prophylactic medications (BTX-A: 56 out of 173; placebo: 71 out of 182; $p = 0.192$).

Among placebo nonresponders, BTX-A did not produce statistically significantly greater improvement than placebo in headache-free days at any time point (primary efficacy variable). However, a statistically significant between-group difference was noted for the secondary efficacy measure. A significantly higher percentage of BTX-A patients had a decrease from baseline of 50% or greater in the frequency of headache days at day 180 (32.7 versus 15.0%, $p = 0.027$). In addition, the mean change from baseline in the frequency of headache episodes was significantly greater for the BTX-A group compared with placebo at most time points (day 180: -6.1 for the BTX-A patients versus -3.1 for the

placebo patients [p = 0.013]). Furthermore, as trends for both placebo responder and placebo non-responder strata were generally equivalent, these groups were pooled for the rest of the preplanned analyses.

In the pooled analysis, BTX-A patients had a statistically greater percentage of patients with a decrease from baseline of ≥ 50% in the frequency of headache days at days 180 and 210. In addition, a greater improvement in the frequency of headache episodes compared with placebo was noted at multiple time points throughout the study, as well as a greater percentage of patients with a decrease from baseline of ≥ 50% headache episodes at days 180 and 210. However, BTX-A did not significantly reduce acute medication use compared with placebo.

3.2.2.1 Subanalysis: no concurrent prophylactic medications [23]

Most trials in migraine prophylaxis excluded patients taking prophylactic medications because of their potential to confound the results. Dodick *et al.* [23] reported the results of a subgroup analysis from the trial just described that only included patients not taking concomitant headache prophylactic medications. Of the 355 patients included in the primary analysis, 228 (64%) were not taking concurrent prophylactic headache medication at time of enrolment or during the trial.

At day 180, the BTX-A group showed a statistically significant greater reduction than the placebo group in headache-free days (primary efficacy variable). BTX-A produced statistically significant greater reductions than placebo in the frequency of headache episodes at multiple time points, and at every time point throughout the study, the mean decrease with BTX-A was greater than that of placebo (**Figure 1**). Compared with placebo, BTX-A was also associated with a statistically significantly greater percentage of patients with a decrease of ≥ 30% and ≥ 50% in the frequency of headache episodes at multiple time points. In addition, BTX-A was associated with statistically significantly greater reductions, compared with placebo, in the number of days with acute medication use at multiple time points.

3.2.2.2 Subanalysis: no concurrent prophylactic medications, overusing acute medications [56]

Saper *et al.* [56] reported the results of another subgroup analysis from the Mathew *et al.* 2005 trial [22] that included patients not receiving concomitant prophylaxis and overusing acute pain medications according to the recently published IHS definition (≥ 15 days and ≥ 2 days/week). Of the 355 patients included in the primary analysis, 107 patients were not using concomitant prophylactic medications and overusing acute pain medications. For this subpopulation, the decrease from baseline in the frequency of headaches was statistically significantly greater for BTX-A at every time point except one (**Table 1**).

3.2.2.3 Subanalysis: frequency of headaches with duration of at least 4 h [57]

Aurora and colleagues reported the results of a subgroup analysis from the trial by Mathew *et al.* [22] that examined the effects of BTX-A versus placebo on the frequency of headaches with durations of 4 h or more. Such headaches are especially incapacitating. During the pretreatment baseline period, most of the headaches reported by patients were ≥ 4 h in duration (71.1 and 72.4% in the BTX-A and placebo groups, respectively), with mean frequencies of 9.6 and 9.2 per month in the BTX-A and placebo groups, respectively. At all follow-up time points, BTX-A produced statistically significantly greater reductions than placebo in headaches of ≥ 4-h duration, with between-group differences of 1.3 – 2.7 headaches per month (**Figure 2**).

3.2.3 Silberstein et al., 2005 [58]

In this randomised, double-blind study, patients (n = 702) with CDH received three consecutive treatments with BTX-A or placebo injected at 90-day intervals into seven muscle areas of the face, head and neck. Patients were randomised to placebo or one of three fixed doses of BTX-A: 75 U, 150 U, or 225 U. Similarly to the trial previously described and reported by Mathew *et al.* [22], eligible patients had > 15 headache days per month and, if they were taking concomitant migraine prophylactic medication, were on stable regimens. Prior to randomisation, all patients received a single placebo treatment and were classified as placebo responders or non-responders; patients were then randomised within these groups. Patients recorded headache-related variables daily via an electronic telephone diary, which was assessed every 30 days throughout the study. The primary efficacy variable was change in the frequency of headache-free days for the placebo nonresponder group. Most patients (511 out of 702) completed the trial.

No statistically significant differences in demographic and other baseline characteristics were found among the four treatment groups. Close to 80% of the patients who had their headache types classified met the criteria for chronic (or transformed) migraine (375 out of 485), followed by chronic tension-type headache (89 out of 485) and new daily persistent headache (16 out of 485). Of the patients, ~ 50% (348 out of 702) were taking concurrent prophylactic headache medications. Approximately 42% of patients in all treatment groups were overusing acute headache pain medications (≥ 15 days and ≥ 2 days/week). However, all but five patients reported at least one migraine or probable migraine during the baseline period, suggesting that all may have been migraineurs, despite the investigator-assigned diagnosis.

Among placebo non-responders, BTX-A did not produce statistically significantly greater improvements than placebo in headache-free days (primary efficacy variable) or any other efficacy variable, although all groups including placebo experienced improvements from baseline. Because no statistically significant differences were noted between placebo responders and non-responders, the two strata were pooled for the rest of the analyses.

In the pooled population of placebo responders and non-responders, BTX-A was statistically significantly superior to placebo at reducing the frequency of headache episodes and

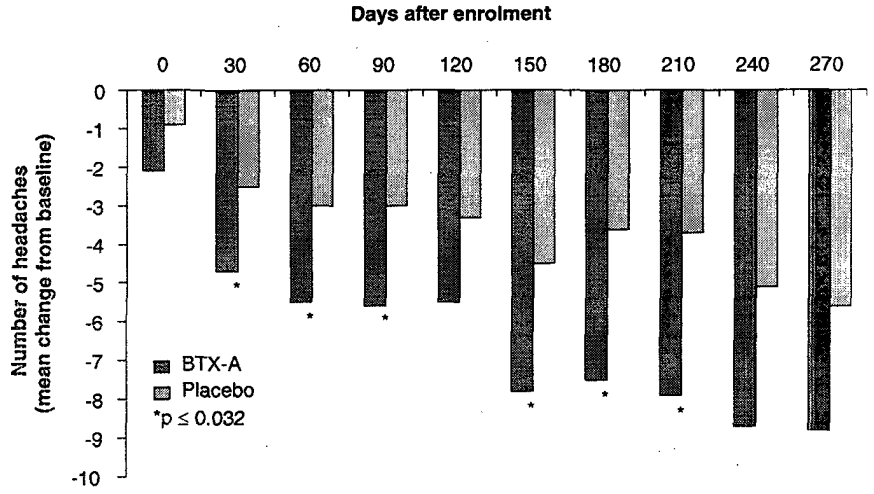

Figure 1. Frequency of headaches per 30-day period in patients not taking concomitant prophylactic therapies. Data represent a subanalysis from a large randomised, double-blind study of patients with CDH who received three consecutive treatments with BTX-A or placebo [22]. Data shown as mean change from baseline (BTX-A n = 117, placebo n = 111). The baseline period (day -60 to day -30) preceded the placebo run-in period (day -30 to 0). Numbers of headaches during the 30-day baseline period were not significantly different between groups (BTX-A: 14.1, placebo 12.9; p = 0.205). Standard deviations were 4.16 – 8.19.
Information from [23].
BTX-A: Botulinum toxin type A; CDH: Chronic daily headache.

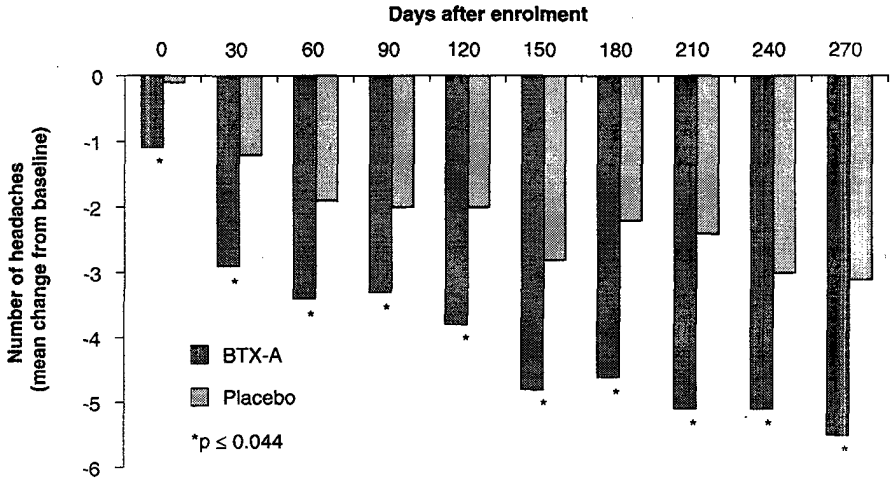

Figure 2. Frequency of headaches with duration of ≥ 4 h per 30-day period [56]. Data represent a subanalysis from a large randomised, double-blind study of patients with CDH who received three consecutive treatments with BTX-A (n = 173) or placebo (n = 182) [22]. Data shown as mean change from baseline. The baseline period (day -60 to -30) preceded the placebo run-in period (day -30 to day 0). Numbers of headaches during the 30-day baseline period were not significantly different between groups (BTX-A: 9.6, placebo 9.2; p = 0.186). Standard deviations were 3.56 – 6.19.
Information from [56].
BTX-A: Botulinum toxin type A; CDH: Chronic daily headache.

Table 1. Frequency of headaches for chronic daily headache patients not taking concomitant prophylactic therapy and overusing acute headache pain medication.

	BTX-A n = 91	Placebo n = 77	p-Value*
Baseline	15.2 (8.2)	14.9 (8.9)	0.592
Day 30	-4.5 (6.1)	-2.5 (4.9)	0.020
Day 60	-5.6 (5.9)	-2.6 (5.2)	0.001
Day 90	-5.2 (6.4)	-3.7 (5.6)	0.168
Day 120	-6.2 (6.4)	-3.6 (5.2)	0.044
Day 150	-8.2 (6.6)	-4.3 (6.3)	0.018
Day 180	-8.1 (6.3)	-3.6 (6.4)	0.003
Day 210	-9.3 (7.3)	-3.9 (6.2)	0.003
Day 240	-10.1 (8.1)	-4.5 (6.1)	0.007
Day 270	-9.5 (8.0)	-4.9 (6.4)	0.017

*Between treatment comparison from a Wilcoxon rank sum test.
Information from [56]. Data shown as mean (standard deviation) at baseline and change from baseline. BTX-A treatments were administered at baseline, day 90 and day 180.

number of migraine or probable migraine episodes at multiple time points, after adjusting for baseline differences. BTX-A also statistically significantly reduced the percentage of patients using acute headache medications at day 30 and overusing acute headache medications at day 210. Although these variables were not statistically significantly different between groups at other time points, the percentages of patients were consistently numerically lower with BTX-A than placebo at all time points past day 150.

4. Safety and tolerability of botulinum toxin type A in migraine

4.1 Episodic migraine studies

Across all of the early exploratory episodic migraine studies [21,47-50], BTX-A was found to be well tolerated, with no or a low discontinuation rate due to adverse events. The most frequently reported treatment-related adverse events in these studies were muscle weakness, skin tightness, blepharoptosis, diplopia and injection-site pain. Adverse events were transient and generally mild-to-moderate in severity, and no clinically relevant differences in laboratory variables or vital signs were observed in the studies where they were assessed. Adverse events seem to be dose-related [21,48,50].

In the later Phase II studies of episodic migraine in which higher doses of 75 – 260 U were used [51,52], there were statistically significantly more treatment-related adverse events in the BTX-A groups compared with placebo. However, BTX-A was also well tolerated in these studies, with approximately 2% of patients discontinuing due to adverse events. The most frequently reported treatment-related adverse events were neck pain and rigidity, arm pain, muscle weakness and blepharoptosis. Adverse events were transient and generally mild-to-moderate in severity, and no clinically relevant differences were observed in laboratory variables or vital signs.

4.2 Chronic migraine or CDH studies

In the chronic migraine or CDH studies, BTX-A was found to be well tolerated, with no or a low discontinuation rate due to adverse events. In these studies, in which doses of 75 – 260 U were used, BTX-A was associated with significantly more treatment-related adverse events than placebo [22,58]. The most frequently reported treatment-related adverse events included neck pain and rigidity, arm pain, muscle weakness, skin tightness, injection-site pain, hypertonia and blepharoptosis. The percentages of patients who discontinued due to adverse events were 2.3 [22] and 3.8% [58]. In the study by Silberstein *et al.* [58], 34 patients experienced 39 serious adverse events, all considered by the investigator to be unrelated to treatment. In the Mathew study [22], 13 patients experienced 16 serious adverse events, with only one deemed by the investigator to be possibly related to treatment (placebo). One patient treated with placebo died during this study due to an existing cardiovascular disorder.

5. Regulatory status of botulinum toxin type A

BTX-A is classified as a biological compound and is regulated by the Center for Biologicals Evaluation and Research (CEBR).

In the US, BTX-A (BOTOX) is approved by the FDA for treatment of the movement disorder cervical dystonia, to decrease the severity of abnormal head position and associated neck pain. It is also approved for the treatment of severe primary axillary hyperhidrosis that is refractory to topical agents, benign essential blepharospasm and strabismus, as well as the temporary improvement of glabellar lines.

BTX-A is not approved in the US for the treatment of migraine or any other primary headache disorder. As just described, Allergan, Inc. has completed a number of exploratory trials designed to investigate the use of BTX-A for the treatment of various types of headache and levels of headache severity. Based on the Phase II findings in patients with CDH, Allergan has reached an agreement with the FDA to initiate a large Phase III clinical trial programme to investigate the safety and efficacy of BTX-A as a prophylactic therapy in a subset of migraine patients with CDH.

6. Conclusion

In the controlled trials that have examined BTX-A for the treatment of episodic migraine, statistically significant improvements over placebo have not been observed in a consistent manner. However, these trials are complicated by a substantial placebo effect that may be physically caused or cued by the injection procedure: a novel and salient cue that is

absent in oral medication trials. Furthermore, in contrast to the episodic migraine trials of oral medications, the BTX-A trials permitted concomitant use of other prophylactic headache medications, which further complicate interpretation of the results. BTX-A was well tolerated in all studies.

More consistent benefits of BTX-A were observed in the controlled trials of chronic migraine or CDH, particularly when excluding the confounding factor of concomitant prophylactic therapy. Although statistically significant improvements over placebo were not observed with BTX-A on the primary efficacy variables in the overall trials, secondary outcomes showed significant improvements at multiple time points. There are hints from these trials that benefits of BTX-A may accrue with repeated treatment. This is accompanied by a leveling off of the placebo effect after the third treatment [23,57]. BTX-A was also well tolerated in these studies.

Interestingly, in the two CDH studies, 36 and 50% of patients were using prophylactic medications but were still reporting > 15 headache days per month. This is a testament to the relative lack of efficacy of the concomitant prophylactics in a substantial number of patients with CDHs and underscores the need for better treatments.

7. Expert opinion

BTX-A has certainly added to the armamentarium of agents for prophylaxis in migraine. The Phase II exploratory studies have definitely provided a strong signal of efficacy in the CDH population in which most of the patients had chronic migraine. The Mathew *et al.* [22] study demonstrated a significant reduction compared with placebo in the frequency of headache episodes, accompanied by a reduction in acute medication use. However, a reduction in headache days, which was the primary efficacy measure, was observed in both the BTX-A and placebo groups, with no statistically significant difference between the two. Primary efficacy measures were difficult to assign, as this was the first large study in this population. Most clinicians would probably agree that the reduction in the frequency of headache episodes is just as clinically meaningful and could have easily been chosen as primary efficacy measure. Moreover, a subanalysis of those patients who were not taking concomitant prophylaxis (identified as a confounding factor) demonstrated a significant reduction in both headache days and headache episodes. A subanalysis conducted for those patients overusing medications according to the International Headache Society classification for medication overuse also showed a significant reduction in the frequency of headaches.

The possibility of conducting blinded studies with BTX-A has been debated. Because of the visible cosmetic effect of BTX-A, some have questioned whether the study subjects could identify the active treatment, which, in the context of a pain trial, could exacerbate or trigger a response. Although this may intuitively seem reasonable, analyses of the Mathew *et al.* [22] trial showed that patients were not more capable of guessing their treatment than those in other headache prophylaxis trials, and that the patients who guessed correctly did respond differently to treatment than those who guessed incorrectly. For instance, as the percentage of patients correctly guessing their treatment decreased over time, the separation between BTX-A and placebo increased over time, suggesting a poor correlation between the ability to guess and response to treatment. Furthermore, both the cohort of patients who guessed their first treatment of the blinded phase correctly and those who guessed incorrectly exhibited statistically significant reductions in the frequency of headache episodes at multiple time points, always favouring BTX-A over placebo.

In any double-blind, placebo-controlled trial with a 1:1 randomisation, patients have a 50% chance of correctly guessing their treatments purely by chance. In the presence of noticeable efficacy and/or side effects, this percentage is likely to increase to 60 or 70%. In the Mathew *et al.* trial, 70, 65 and 60% of the patients in the various groups guessed correctly at each injection cycle during the double-blind phase, which is very likely aligned with other trials examining prophylactic headache treatments. This emphasises the challenge of performing a real 'double-blind study', unless neither the treatment effect nor side effects can be observed by patients and investigators.

These issues notwithstanding, the exploratory studies met the main goals of Phase II trials, which were to establish the safety of the compound and identify a responsive population. These studies demonstrated that adverse effects were few and mainly consisted of local neck pain and, in general, the drug and injections were well tolerated. Migraine patients with CDH exhibited a strong response to treatment with statistically significant reductions compared with placebo in the frequency of headache episodes and several other clinically meaningful variables. These results are particularly meaningful because CDH patients have been systematically excluded from previous clinical trials of prophylaxis of migraine and only a few small trials have attempted to investigate this population, with significant limitations. Patients overusing acute pain medications also seemed to be particularly responsive to BTX-A. This also deserves some attention, as this population has been one of the most difficult to treat in the headache clinics.

Phase III studies are underway to confirm these findings. It seems likely that a placebo response will be identified in these trials, as it was in the Phase II studies, and that the trials will need to demonstrate an effect of BTX-A beyond that of placebo. The results of these trials will hopefully provide guidance related to patient and dose selection in clinical practice and may serve as the basis for pharmacoeconomic comparisons.

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