Botulinum Toxin for Treatment of Primary Chronic Headache Disorders

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Executive Summary

Primary chronic headache disorders, including migraine, chronic tension, and cluster headache syndromes, affect a substantial portion of the general population, are difficult to classify and treat, and cause significant disability. Patients require medication to abort acute attacks; a wide variety of medications has been studied or used empirically for this purpose. Only the triptans have been developed specifically for the abortive treatment of migraine headaches. When patients have frequent attacks, prophylactic medication may also be prescribed. As with abortive medications, many different medications have been used for prevention; none is specific for the treatment of headaches. Because most abortive and prophylactic medications are only partially effective, or only work on some patients, and may have substantial adverse effects, some patients may benefit from better medications or from other types of therapy that may be used in addition to pharmacologic treatment.

Anecdotal reports of patients treated for cosmetic indications with botulinum toxin A (BTX-A) who have obtained relief from concomitant headache syndromes have stimulated interest in evaluating botulinum toxin therapy for prophylactic treatment of headaches. Botulinum toxin causes a reversible chemical denervation of muscle, and may also block the release of other neurotransmitters involved in the parasympathetic nervous system and the transmission of pain. This Assessment will evaluate whether or not the addition of botulinum toxin injections to patients' usual regimens of prophylactic and/or abortive drug therapy improves outcomes in patients with primary chronic headache syndromes who have significant disability due to headaches in spite of conventional pharmacologic treatment.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether the treatment of primary chronic headache disorders with botulinum toxin meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In December 1989, the U.S. Food and Drug Administration (FDA) approved a commercial preparation of botulinum toxin A (Botox®) for therapeutic use in patients with strabismus, certain movement disorders (blepharospasm) and VII nerve disorders (e.g., hemifacial spasm). On December 21, 2000, supplemental approval was granted for the indication of cervical dystonia. Finally, on April 12, 2002, supplemental approval was granted to include the indication of treatment of glabellar lines. Myobloc™ (BTX-B), was approved on December 8, 2000, for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain. Treatment of primary chronic headache represents an off-label indication.

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2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Included studies for this Assessment were required to be randomized, injection placebo-controlled, double-blinded trials published as a primary study in a peer-reviewed journal. Due to a well-documented and substantial placebo effect in trials of both abortive and preventive pharmacologic therapy for the treatment of primary headache disorders, uncontrolled and unblinded trials were excluded.

All reported trials of BTX injections for the treatment of primary headache syndromes have used commercial preparations of botulinum toxin type A. No evidence exists for the use of toxin types B through G.

The evidence was judged insufficient to meet the second TEC criterion for any of the indications evaluated.

BTX for Headache Prophylaxis

Migraine. Since the 2002 TEC Assessment, 1 new study meeting selection criteria has appeared. Published in 2004 (n=60), this trial randomized patients to saline placebo, low-dose BTX-A, or high-dose BTX-A. No significant differences were reported at 3 months for any of 7 pain-related outcomes. The low dose of BTX-A had a lower rate of accompanying symptoms (photophobia, phonophobia, nausea and vomiting), compared with the placebo and high-dose groups. A study from 2000 (n=123) provided mixed results for the use of BTX for migraine prophylaxis. This moderately sized trial reported only short-term outcomes, and questions remain regarding the variability of effect at different time points, as well as variability of dose and injection site. Isolated findings of statistical significance favoring BTX-A in these 2 studies could be explained by chance alone and evidence is judged insufficient for conclusions.

Tension Headaches. The 2002 TEC Assessment reviewed 4 trials providing data for 125 patients. Only 1 of these studies gave data suggesting better outcome for BTX-A over placebo. Four additional studies with data for 223 patients have appeared subsequently. Taking previously available and recent studies together, among 5 of 8 studies which identified a primary outcome, none found statistically significant differences favoring BTX-A over placebo for that outcome. In 2 studies, the primary outcome was area under the headache curve (AUC), computed as the sum of the product of headache duration and severity across days. The primary outcome was headache severity in 2 studies and headache frequency in 1 study.

Two of the 8 studies had fair quality ratings, while the other 6 were rated as poor. Neither of the two better-rated studies found significant differences between placebo and BTX-A groups. The largest study (n=107) found no differences between groups on 6 outcomes. The second study rated as fair in quality found no significant differences on 5 outcomes. Three of the 6 studies rated as poor in quality found inconsistent significant results. In 1 of these studies, there did not appear to be a statistically significant result on the primary outcome or 4 other outcomes, while 3 global rating scales significantly favored the BTX-A group. Groups differed greatly on the baseline mean frequency of headaches and the authors did not mention adjustment for confounding in the data analysis. Two other poor-quality studies finding selected significant differences between groups did not evaluate comparability of groups on any baseline characteristics or specify that analyses used adjustment techniques, so it is unclear whether findings were influenced by confounding.

The failure of 2 better-quality studies to find between-group differences calls into question the weakly positive findings of 3 poor quality studies. Overall, the evidence is not sufficient to support conclusions about the effects of BTX-A on tension headaches.

Cluster Headaches. Other than case reports, no studies of BTX-A treatment for the prevention of cluster headaches have been reported. Thus, no evidence of adequate quality exists to evaluate the effect of BTX-A injections on cluster headache.

BTX for Treatment of Acute Headaches

There were no studies meeting inclusion criteria that tested BTX for the treatment of acute headache attacks. Thus, the evidence is insufficient to determine whether or not BTX-A is an effective treatment for acute migraine episodes.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The available evidence does not permit conclusions regarding the prophylactic or abortive effect of BTX-A or any other botulinum toxin type on chronic primary headache syndromes.

5. The improvement must be attainable outside the investigational settings.

It has not yet been demonstrated whether botulinum toxin improves health outcomes in the investigational setting. Therefore, it cannot be demonstrated whether improvement is attainable outside the investigational setting.

Based on the above, botulinum toxin therapy for primary chronic headache disorders does not meet the TEC criteria.

Contents

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Assessment Objective

Primary chronic headache disorders, including migraine, chronic tension, and cluster headache syndromes, affect a substantial portion of the general population, are difficult to classify and treat, and cause significant disability. Patients require medication to abort acute attacks; a wide variety of medications has been studied or used empirically for this purpose. Only the triptans have been developed specifically for the abortive treatment of migraine headaches. When patients have frequent attacks, prophylactic medication may also be prescribed. As with abortive medications, many different medications have been used for prevention; none is specific for the treatment of headaches. Because most abortive and prophylactic medications are only partially effective, or only work on some patients, and may have substantial adverse effects, some patients may benefit from better medications or from other types of therapy that may be used in addition to pharmacologic treatment.

Anecdotal reports of patients treated for cosmetic indications with botulinum toxin A (BTX-A) who have obtained relief from concomitant headache syndromes have stimulated interest in evaluating botulinum toxin therapy for prophylactic treatment of headaches. Botulinum toxin causes a reversible chemical denervation of muscle, and may also block the release of other neurotransmitters involved in the parasympathetic nervous system and the transmission of pain. This Assessment will evaluate whether or not the addition of botulinum toxin injections to patients' usual regimens of prophylactic and/or abortive drug therapy improves outcomes in patients with primary chronic headache syndromes who have significant disability due to headaches in spite of conventional pharmacologic treatment.

Background

This Assessment presents a brief introduction to classification and treatment of primary chronic headache disorders and botulinum toxin A. A more extensive review of background issues is available in the previous TEC Assessment (2002).

Primary Chronic Headache Disorders

Headache is a common symptom and occasional instances are routinely and adequately treated with over-the-counter analgesics. Primary chronic headache disorders, the focus of this Assessment, include migraine, cluster, and tension headache, are often associated with disability, and may be difficult to treat. This introduction will focus on migraine and tension headache.

Migraine. Guidelines for diagnosis and classification of migraine have been published by the International Headache Society (1988) and require a thorough history to rule out secondary causes. Characteristics of migraines include a unilateral and pulsatile presentation of moderate to severe intensity, aggravated by physical activity, and accompanied by nausea/vomiting, photophobia, and phonophobia. Migraine attacks vary in frequency, duration, severity, and reported symptoms. The prevalence of migraine is 17% in women and 6% in men, according to a summary of large surveys of prevalence (Bandolier Library 2002a). Migraine is associated with a substantial amount of time lost from work, school, daily activities, and social interactions (Bandolier Library 2002b).

The American Academy of Neurology (AAN), in conjunction with several other professional organizations constituting the U.S. Headache Consortium, published evidence-based guidelines for treatment of migraine headache, developed from a series of Technical Reviews on migraine sponsored by the Agency for Healthcare Research and Quality (American Academy of Neurology 2000). Agents supported by evidence include ergot alkaloids and derivatives, butalbital-containing agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and combination analgesics, opiate analgesics, and triptans. Evidence is lacking to support a specific algorithmic approach and there is a lack of head-to-head clinical trials comparing the relative efficacy and cost/benefit outcomes among agents.

Patients with frequent migraines causing significant disability may need to consider prophylactic therapy in addition to abortive therapy. Classes of prophylactic agents include anticonvulsants, beta-blockers, calcium-channel blockers, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants. Many acute and prophylactic agents have

significant adverse effects and/or are contraindicated in some patients; management must be individualized to the patient and treatment carefully monitored.

Tension-type Headache. The International Headache Society (1988) defines primary tension-type headache (TTH) as a constant bilateral cranial pressure of mild to moderate intensity that is not accompanied by other symptoms and is not related to structural or systemic illness. TTH can be episodic or chronic; by definition, chronic TTH occurs at least 15 days per month for at least 6 months. While episodic TTH experience is common, being reported by a majority of the general population, chronic TTH or CDH affects 2–3% of the population (Lavados and Tenhamm 1998; Jensen 1999; Schwartz et al. 1998).

Treatment strategies for TTH are largely empiric. Acute episodes may be readily treated with over-the-counter analgesics. If these are ineffective, prescription NSAIDs or muscle relaxants may be employed (Jensen and Olesen 2000). Sumatriptan has been evaluated in TTH with mixed results, but may be effective for some patients (Solomon 2002). Butalbital combinations may also be effective but have the potential for overuse and rebound pain. For chronic TTH patients who also require prophylactic medication, tricyclic antidepressants are most widely used. Although often prescribed, SSRIs appear to have limited efficacy for prophylaxis (Solomon 2002; Jensen and Olesen 2000). NSAIDs may be used but have not been validated for prophylaxis in clinical trials.

Health Outcomes for Chronic Headache Prevention Therapy. A technical review of drug treatment for migraine prevention (Gray et al. 1999), supported by the Agency for Healthcare Research and Quality, stated, "The goals of migraine preventive therapy are to: 1) reduce attack frequency, severity, and duration; 2) improve responsiveness to treatment of acute attacks; and 3) improve function and reduce disability." The report identified preferred efficacy outcomes in order as follows: 1) headache index (a composite score of headache frequency, severity, and/or duration); 2) headache frequency; 3) headache duration. Data are obtained directly from the patient, who has recorded information in a daily headache diary. Outcomes are analyzed 8–12 weeks post-treatment. Additionally, at least 2 tools have been developed to assess the impact of migraine in terms of daily activities and pain intensity (Dowson 2001).

Quality of Evidence. Clinical trials of therapies for headache disorders pose problems because of unavoidable elements of subjectivity in establishing a diagnosis and in patient assessments of symptom relief. In addition, trials of headache therapy have shown a high and variable placebo response. Responses in the placebo arms of trials of acute migraine therapy are usually in the range of 15–45% (Tfelt-Hansen et al. 2000; Lipton 2000). There is also evidence of a significant placebo effect (20–40% or higher) in trials of prophylactic migraine therapy (Tfelt-Hansen et al. 2000). Thus, there is a need for comparative, placebo-controlled, double-blinded trials for testing the efficacy of migraine therapy. Trials that compare medications should also include a placebo arm for accurate interpretation of efficacy. Either parallel groups or crossover trial designs are acceptable. Trials should be powered to take the placebo effect into account, and to allow the detection of clinically meaningful differences. Randomization is essential, given the variability seen among patients with a given headache syndrome. Even with randomization, treatment groups should be compared in terms of their baseline characteristics to ensure that groups are similar at baseline, or take significant differences into account in analyzing trial outcomes. Other, less-rigorous trial designs, including single-arm studies, can be hypothesis-generating but are considered insufficient for establishing new treatment.

Botulinum Toxin

Anecdotal reports of patients treated for cosmetic indications with BTX-A who obtained relief from concomitant headache syndromes stimulated interest in evaluating botulinum toxin therapy for prophylactic treatment of headaches. The BTX-A molecule is produced by growing a high toxin-producing strain of *Clostridium botulinum* in culture and purifying the toxin from the culture medium. The standard unit (U) for measuring toxin potency is derived from a mouse assay, in which one unit of botulinum toxin is defined as the amount that kills 50% of a group of 18–20 Swiss-Webster mice (the LD_{50}) (Schantz and Johnson 1990). It is important to note that dose standardization differs between commercially available preparations, and may differ among lots of the same product (Blitzer

and Sulica 2001). One nanogram of the British product (Dysport®, produced by Ipsen, Ltd., not approved in the U.S.) contains 40 mouse units, while 1 nanogram of the American product (Botox®, produced by Allergan, Inc.) contains only 2.5 mouse units (Jankovic 1994; Quinn and Hallett 1989). Botox® is available only in single-use 100-U vials as a frozen precipitate, which must be stored frozen and reconstituted with saline at the time of injection.

When injected into muscle, BTX-A causes a temporary chemodenervation. This is a result of: the toxin binding to presynaptic cholinergic-nerve terminals; transport across the cell membrane into the cell interior; and the toxin cleaving a presynaptic plasma membrane (Jankovic 1994; Blasi et al. 1993). In this manner, presynaptic release of acetylcholine at cholinergic nerve terminals is inhibited, resulting in reversible paralysis of the muscle. The mechanisms of BTX-A effect on pain are currently unclear.

Adverse Events. There have been no reports of anaphylaxis or deaths directly resulting from BTX-A overdose in over 23 years of use (Blitzer and Sulica 2001; Huang et al. 2000). Antibody is available for acute treatment of a massive overdose. No evidence suggests permanent muscle degeneration or atrophy after several high-dose injections over an extended period of time for dystonic or spastic disorders (Klein 2001). Three cases of generalized muscular weakness following BTX-A injection for dystonia have been reported (Bhatia et al. 1999) indicating a need to treat cautiously. In rare case reports, patients injected in the anterior neck have developed aspiration pneumonia after the finding of dysphagia and have died (Botox® package insert). However, major adverse events in association with BTX-A injections remain rare.

FDA Status. In December 1989, the U.S. Food and Drug Administration approved a commercial preparation of BTX-A (Botox®) for therapeutic use in patients with strabismus, certain movement disorders (blepharospasm) and VII cranial nerve disorders (e.g., hemifacial spasm). On December 21, 2000, supplemental approval was granted for the indication of cervical dystonia. Finally, on April 12, 2002, supplemental approval was granted to include the indication of treatment of glabellar lines. Myobloc™ (BTX-B) was approved on December 8, 2000, for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain. Treatment of primary chronic headache represents an off-label indication.

Methods

Search Methods

The MEDLINE database was searched from through September 2002 through October 2004, in two different ways: 1) using Medical Subject Headings (MeSH®) "Botulinum Toxin" AND "Headache Disorders"; and 2) using textwords (myobloc or neurobloc or botulinum or botox) AND (migraine* OR headache*). In addition, reference lists of pertinent review articles and clinical trial publications were searched for relevant citations. Allergan, Inc., the manufacturer of Botox®, was contacted and forwarded relevant references.

Study Selection

Included studies were required to be randomized, injection placebo-controlled, double-blinded trials published as a full-length individual study report in a peer-reviewed journal. Either parallel-group or crossover designs were considered acceptable. Non-randomized comparative trials and case reports were excluded from this Assessment.

Rating Study Quality

This systematic review applies the general approach to grading evidence developed by the U.S. Preventive Services Task Force (Harris et al. 2001). Below are the study design criteria and rating definitions developed by this group.

Study Design Criteria

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care, patient characteristics) were distributed equally among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders, intention-to-treat analysis

To conclude that a study achieved initial assembly of comparable groups, it had to use an adequate randomization method and had to have equal distribution of confounders. Adequate randomization was defined as either central randomization or use of opaque envelopes (concealment). For the purposes of this review, equal distribution of confounders was defined as a minimal difference (less than 20%) in mean values between groups on age, disease duration and either headache severity or headache frequency. Low loss to follow-up and maintenance of comparable groups was defined as loss less than 20% of the initial sample and no differential loss to follow-up between groups. Analysis of results was considered appropriate if the investigators adjusted for confounders and analyzed by intention-to-treat, which was defined as analyzing all randomized patients or no more than 5% loss of the initial sample.

Definitions of Ratings

Good. Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for randomized, controlled trials (RCTs), intention to treat analysis is used.

Fair. Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor. Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Medical Advisory Panel Review

Current Assessment. This TEC Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on October 26, 2004. In order to maintain the timeliness of the scientific information in the Assessment, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Previous Assessment. The MAP reviewed use of botulinum toxin for primary chronic headache in October 2002, concluding the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria were not met. The MAP also previously reviewed the effects of treatment with botulinum-A toxin on the health outcomes of patients with chronic limb spasticity in February 1996. The Panel found that botulinum-A toxin therapy for children with cerebral palsy in whom dynamic joint deformity secondary to spasticity or athetosis produces pain and/or interferes with function met the TEC criteria. Botulinum-A toxin therapy for ambulatory and nonambulatory patients with chronic limb spasticity, in whom dynamic joint deformity produces pain and/or interferes significantly with supportive care and quality of life (sitting, balance, hygiene, pain control) also met the TEC criteria. Botulinum-A toxin therapy for other patients with chronic limb spasticity did not meet the TEC criteria. Botulinum-A toxin therapy for treatment of primary headache syndromes was not reviewed at that time.

Formulation of the Assessment

Patient Indications

Patients are those with a history of IHS-defined primary chronic headaches and significant disability despite conventional pharmacologic treatment. Patients with primary chronic headache syndromes are defined as those with:

- migraine headache with or without aura;
- chronic or episodic tension-type headache; or
- cluster headache.

Technologies to be Compared

Standard abortive and/or preventive medication treatment versus standard abortive and/or preventive medication treatment plus BTX injections.

Health Outcomes

This Assessment will examine outcomes related to headache frequency, severity and duration; disability, such as days missed at work/school; and adverse events related to BTX injection therapy.

Specific Assessment Questions

1. Does the addition of BTX injections to patients' usual regimen of preventive and/or abortive drug therapy prevent headaches in patients with primary chronic headache syndromes who are refractory to conventional pharmaceutical treatment?

2. Do BTX injections abort acute headache attacks in patients with primary chronic headache syndromes who are refractory to conventional pharmaceutical treatment?

Review of Evidence

1. Does the addition of BTX injections to patients' usual regimen of preventive and/or abortive drug therapy prevent headaches in patients with primary chronic headache syndromes who are refractory to conventional pharmaceutical treatment?

All reported trials of BTX injections for the treatment of primary headache syndromes have used commercial preparations of botulinum toxin type A. No evidence exists for the use of toxin types B through G. Thus, this review of evidence will only consider BTX-A.

Migraine Headaches

The literature search identified 1 new trial on the use of BTX-A for migraines appearing since the 2002 TEC Assessment (Evers et al. 2004). Previously, a single study met selection criteria (Silberstein et al. 2000). These 2 studies are summarized in Tables 1A, 2A, and 3.

Evers and colleagues (2004) selected 60 patients who had migraines with or without typical aura and experienced 2–8 headaches per month during the previous 3 months. They were randomized to 3 interventions: the first received saline placebo injections to the frontal and neck muscles; the second received a total of 16 U BTX-A to the frontal muscles and placebo to the neck muscles; or 100 U total to the frontal and neck muscles. The overall quality of this study is good and it is the only study on the use of botulinum toxin for headache that clearly used an appropriate concealed randomization technique. The primary outcome was a 50% or greater reduction in the frequency of migraine, which did not differ significantly between groups at the 3 month follow-up examination. Between-group differences were not statistically significant on these outcomes: attack frequency; number of days with migraine; number of days with moderate-severe migraine; number of acute antimigraine drugs; Beck Depression Inventory score; and Headache Disability Inventory score. The only efficacy outcome that achieved significance was the sum of accompanying symptoms, including photophobia, phonophobia, nausea, and vomiting. The 16-U group had significantly better findings that both the placebo group and the 100-U group, which did not differ. Adverse events were minor and transient, but the total was significantly higher in the 100-U group, compared with the placebo group.

The Silberstein et al. (2000) study is a randomized double-blind trial in which a placebo group (n=41) receiving injection vehicle only (0 U BTX-A) was compared with a group that received 25 U BTX-A (n=42) and another that received 75 U BTX-A (n=40). Table 1A gives details about study design, methods and efficacy outcomes. Table 2A shows data on adverse events and Table 3 provides information about study quality. The overall quality rating of this study is fair. The article's chief shortcoming is that the description of the randomization method lacks enough detail to assess its adequacy. Groups were shown to be comparable at baseline on 10 demographic and headache characteristics, while a significant difference between groups was found on the time since onset of migraines. Analysis of covariance was performed to adjust for baseline differences and the authors stated that intent-to-treat analyses were conducted. Measurements were made at 1 month, 2 months and 3 months and appeared to equal, reliable and valid. Interventions were clearly described and comparable: a standard injection protocol was followed for all patients in which a fixed number of injections were made in the frontalis, temporalis and glabellar muscles.

Table 1A. BTX-A Prophylaxis for Migraine, Efficacy Outcomes

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response				
Evers et al. 2004 (Double-blind RCT)	Patients with migraine with or without typical aura, by IHS criteria, 18–65 yo, average frequency 2–8 per mo in last 3 mo, duration > 1 yr, onset before 40 yo, other headache types < 10 days/mo; not pregnant/ lactating, other migraine, dystonia, neuromuscular disease, substance addiction, drug-induced headache, drugs affecting neuromuscular junction, drug treatment changes in last 3 mo	60	Saline placebo injection both muscle site groups BTX-A injection in frontal muscles, placebo injection in neck muscles BTX-A injection in frontal muscles and neck muscles	0 U, 16 U 100 U	Frontalis, temporalis, sterno-cleidomastoideus, trapezius, splenius capitis, semispinalis	3 mo	**Outcome**	**Group**	**1 mo.**	**2 mo.**	**3 mo.**
							≥50% decrease migraine freq.	0 U			25%
								16 U			30%
								100 U			30%
							Attack frequency	0 U	3.5	3.4	3.2
								16 U	3.0	2.8	2.5
								100 U	3.5	3.4	3.2
							No. of days with migraine	0 U	5.8	5.5	5.0
								16 U	5.9	5.7	5.0
								100 U	5.6	6.2	5.0
							No. days with mod-sev migraine	0 U	4.8	4.8	4.0
								16 U	3.8	4.0	3.3
								100 U	4.1	4.5	3.7
							No. acute antimigraine drugs	0 U	5.8	5.4	5.2
								16 U	4.9	5.2	4.0
								100 U	5.2	6.1	4.7
							Sum accompanying symptoms	0 U	2.9	3.0	2.9
								16 U	2.5	2.4	2.2*
								100 U	3.4	3.2	3.0
							Beck Depre ssion Inventory	0 U			7.8
								16 U			8.4
								100 U			7.1
							Headache Disability Inventory	0 U			53.5
								16 U			53.5
								100 U			41.0

* $p<0.05$

Table 1A. BTX-A Prophylaxis for Migraine, Efficacy Outcomes (cont'd)

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response				
Silberstein et al. 2000 (Double-blind RCT)	Patients recruited from 12 U.S. headache centers; history of 2–8 but <15 IHS-defined migraines during previous 3 mo.; mean of 4.0–4.8 migraines/mo. by treatment arm; pain reported as moderate to severe	123	Control: Injection vehicle" (n=41) Treatment: Botox®, prophylaxis at 2 doses (n=42, n=40)	0 U, 25 U, 75 U	Frontalis, temporalis, and glabellar (corrugator and procerus) muscles	3 mo.	**Outcome**	**Group**	**1 mo.**	**2 mo.**	**3 mo.**
							Change freq. mod-sev migraines	0 U	-.079	-0.37	-0.98
								25 U	-1.2	-1.57*	-1.88*
								75 U	-.72	-1.0	-1.05
							Change in maximum severity	0 U	-0.04	-0.1	-0.29
								25 U	-0.4*	-0.55*	-0.69
								75 U	-0.13	-0.33	-0.29
							% with decrease > 2 migraines	0 U	26	34	34
								25 U	46	46	62*
								75 U	27	31	42
							Change in days med acute use/mo.	0 U		-0.76	
								25 U		-2.45*	
								75 U			
							Global Assessment score	0 U		0.46	
								25 U		1.19*	
								75 U		1.25*	

* $p<0.05$

Table 1B. BTX-A Prophylaxis for Tension Headache, Efficacy Outcomes

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response			
Schulte-Mattler et al. 2004 (Double-blind RCT)	Patients with chronic tension-type headache by IHS criteria, at least partially resistant to adequate therapy; among exclusions: no migraine, analgesics or benzodiazepines >10 days/mo,	107	Control: saline injection placebo (n=54) Treatment: Dysport® for prophylaxis (n=53)	0 U, 500 U	Frontalis, temporalis, steno-cleidomastoid, auricularis, occipitalis, splenius capitis, semispinalis capitis, trapezius	10 wk.	**Change in outcome, 0–12 wk** Area under headache curve Days with headache per 6 wk. Days with intake of analgesics Muscle tenderness score Beck Depression Inventory Sleep duration	**0 U** -4 -3.0 +0.4 0 +1 -0.2	**500 U** -8 -5.1 +0.5 -1 0 -0.1	
Padberg et al. 2004 (Double-blind RCT)	Patients with chronic tension-type headache by IHS criteria, exclusions: <18, pregnant, neuromuscular disorders, previous use other INDs <30 days, previous use BTX-A	40	Control: saline injection placebo (n=21) Treatment: Botox® for prophylaxis (n=19`)	0 U, 1 U/kg (≤100 U)	Selected individually by experienced clinical neurophysiologist in muscles with clinically increased muscle tone or muscle tenderness (occipitofrontalis, masseter, steroncleido-mastoideus, splenius capitis, trapezius and semispinalis, ≤10–20 U/muscle	3 mo.	**Change in outcome, 0-3 mo.** Improved VAS headache severity Improved headache days Improved % headache hrs/day Improved % sx treatment days Improved # analgesics per day	**0 U** 7.1 5 0.93 3.7 0.10	**1 U/kg** 10.6 12 2.3 5.6 0.12	**Between-group Δ, 95% CI** -3.5 (-20, 13) -7% (-20, 4) -1.4 (-3.9, 1.1) -1.9 (-11, 7) -0.01 (-0.25, 0.22)

Table 1B. BTX-A Prophylaxis for Tension Headache, Efficacy Outcomes (cont'd)

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response				
Relja and Telarovic 2004 (Double-blind RCT)	Patients with chronic tension-type headache by IHS criteria, resistant to standard medication including tricyclic antidepressants	16	Control: saline injection placebo (n=8) Treatment: botulinum A toxin for prophylaxis (n=8)	0 U, 40-95 U	Most affected pericranial muscle	2 mo.	**Outcome** Mean tenderness (% of 0 wk.) Severity at 8 wk. % Severe % Moderate % Mild % None	**Group** 0 U 40–95 U 0 U 56 37 7 0	**2 wk** 105 37* 40–95 U* 0 25 37 37	**4 wk.** 107 50*	**8 wk.** 110 77*
Ondo et al. 2004 (Double-blind RCT)	Headaches > 15 days/mo, 14 (24%) had chronic migraine and 46 (76%) had chronic tension-type headache by Silberstein's criteria	60	Control: saline injection placebo (n=30) Treatment: Botox® for prophylaxis (n=30)	0 U, 200 U	At physician discretion, employed "follow the pain" strategy	3 mo.	**Outcome** Days with headache # abortive medications Global impression, patient* Global impression, physician* Change in headache, patient* Presentation of statistical test results unclear. "Compared with placebo, headache-free days improved in the BTX group from week 8 to 12 ($p<0.05$, t-test), but tended to improve strongly only over the entire period of weeks 0–12, 33 ± 23 vs. 24 ± 16 ($p=0.07$) fewer headache days, the primary efficacy point (Fig.2)."	**Group** 0 U 200 U 0 U 200 U	**0–4 wk.** 26 23	**4–8 wk.** 25 22	**8–12 wk.** 24 20 135 106

* $p<0.05$

Table 1B. BTX-A Prophylaxis for Tension Headache, Efficacy Outcomes (cont'd)

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response
Schmitt et al. 2001 (Double-blind RCT)	Patients with IHS-defined chronic tension headache, recruited by newspaper notice	59	Control: saline injection placebo (n=29) Treatment: Botox® for prophylaxis (n=30)	0 U, 20 U, in 4 injections	2 injections bilaterally in frontal muscles + 2 injections bilaterally in temporal superficial muscles	2 mo.	**Outcome** / **Group** / **0 mo.** / **1 mo.** / **2 mo.** Mean pain severity on WHYMPI / 0 U / 2.99 / 2.69 / 2.63 20 U / 3.28 / 2.77 / 2.88 Significant improvement for 20 U group in 2 of 19 other WHYMPI variables: affective distress, angry mood No significant difference in %responders, headache frequency, intake of analgesic drugs, activity level
Rollnik et al. 2001 (Double-blind RCT)	Patients with IHS-defined chronic tension headache	8	Control: saline injection placebo (n=4) Treatment: Dysport for prophylaxis (n=4)	0 U, 500 U	Several bilateral injections into the pericranial and neck muscles	3 mo.	**Outcome** / **Group** / **0 mo.** / **1.5 mo.** / **3 mo.** Cumulative pain intensity / 0 U / 1194 / 1135 / 895 500 U / 1223 / 851 / 825 Acute headache prevalence at 1.5 and 3 mo. not significantly different
Rollnik et al. 2000/2002 (Double-blind RCT)	Patients with IHS-defined episodic or chronic tension headache	21	Control: Saline injection placebo (n=10) Treatment: Dysport™ for prophylaxis (n=11)	0 U, 200 U	Several bilateral injections into the pericranial muscles: temporalis, sternocleido-mastoid, auricularis, occipitalis, splenius capitis, semispinalis capitis, trapezius	3 mo.	Pain intensity by visual analog scale decreased similarly for both treatment and control arms; there were no significant differences between arms in this or in headache frequency, duration, or in use of analgesics

Table 1B. BTX-A Prophylaxis for Tension Headache, Efficacy Outcomes (cont'd)

Study (Study type)	Patient Population	n	Intervention	BTX-A Total Dose	Injection Site(s)	Follow-up	Response		
Smuts et al. 1999 (Double-blind RCT)	Patients with IHS-defined chronic tension headache and a history of failed prophylactic drug treatment, ≤1 migraine attack per month in previous 6 mo. (38%); 41 patients enrolled; dropouts not reported by study arm	37	Control: saline injection placebo (n=15) Treatment: Botox® for prophylaxis (n=22)	0 U, 100 U	Several bilateral injections into temporal and cervical muscles using EMG guidance	3 mo.	**Outcome** Change in headache severity score % with > 25% improvement Increase in # headache-free days Change in chronic pain index	**Group** 0 U 100 U 0 U 100 U 0 U 100 U 0 U 100 U	**3 mo.** -0.05 -1.0* 13 60 no change -1* no change -1

*p<0.05

Abbreviations/Definitions

EMG	electromyelogram
IHS	International Headache Society criteria for migraine with or without aura (HIS 1988)
mo.	month
RCT	randomized controlled trial
sx	symptoms
WHYMPI	West Haven-Yale Multidimensional Pain Inventory
wk	week
yo	years old

Table 2A. BTX-A Prophylaxis for Migraine, Adverse Events

Study (Study type)	Adverse Events
Evers et al. 2004 (Double-blind RCT)	No serious adverse events Incidence of all adverse events lower for 0-U group (7), compared with 100-U group (13); 16 U had 9 adverse events. Types: neck pain (0 U – 5, 16 U – 1, 100 U – 3); ptosis (0 U – 0, 16 U – 4, 100 U – 2); weakness of frontal muscles (0 U – 1, 16 U – 2, 100 U – 2); weakness of neck muscles (0 U – 0, 16 U – 0, 100 U – 4); frontal paraesthesia (0 U – 1, 16 U – 2, 100 U – 0); impaired mobility of cervical spine (0 U – 0, 16 U – 0, 100 U – 2)
Silberstein et al. 2000 (Double-blind RCT)	No serious adverse events Incidence of all adverse events ~same for vehicle and 0.25 U BTX-A groups but higher incidence in 75 U BTX-A group vs. vehicle (50% vs. 24%). All events transient and included blepharoptosis, diplopia, and injection site weakness.

Table 2B. BTX-A Prophylaxis for Tension Headache, Adverse Events

Study (Study type)	Adverse Events
Schulte-Mattler et al. 2004 (Double-blind RCT)	9 patients (all received BTX). 7 had transient weakness of the eyelids, neck or both (accompanied by pain in 1 patient). 1 patient had transient neck pain and 1 patient had pain in the left temporomandibular joint.
Padberg et al. 2004 (Double-blind RCT)	21 patients reported minor adverse events, 13 in the placebo group and 8 in the BTX group. The main complaint was short-lasting pain at the injection site.
Relja and Telarovic 2004 (Double-blind RCT)	No serious adverse events reported during study.
Ondo et al. 2004 (Double-blind RCT)	Only a patient with eyelid ptosis was thought to have a definite BTX-related adverse event. Overall, 33 adverse events were reported in the BTX group and 39 in the placebo group.
Schmitt et al. 2001 (Double-blind RCT)	No significant difference in the occurrence of adverse events; most frequent included pain at the injection site and an increase in headache
Rollnik et al. 2001 (Double-blind RCT)	Not reported
Rollnik et al. 2000/2002 (Double-blind RCT)	Not reported
Smuts et al. 1999 (Double-blind RCT)	No serious adverse events

Table 3. Study Quality Ratings

Study	Initial Assembly of Comparable Groups	No Differential Loss to F/U or Low Loss to Follow-up,	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Evers et al. 2004	Yes	Yes	Yes	Yes	Yes	Good
Silberstein et al. 2000	Partial	Yes	Yes	Yes	Yes	Fair
Schulte-Mattler et al. 2004	Partial	Yes	Yes	Yes	Yes	Fair
Padberg et al. 2004	Partial	Yes	Yes	Yes	Yes	Fair
Relja and Telarovic 2004	No	?	Yes	No	No	Poor
Ondo et al. 2004	No	Yes	Yes	Yes	No	Poor
Schmitt et al. 2001	No	Yes	Yes	Yes	No	Poor
Rollnik et al. 2001	No	?	Yes	Yes	No	Poor
Rollnik et al. 2000/2002	No	?	Yes	Yes	No	Poor
Smuts et al. 1999	No	Yes	Yes	Yes	No	Poor

For components of study quality, see Appendix

On the primary health outcome, change in the frequency of moderate to severe migraines, a placebo effect of 22% was observed in the group receiving 0 U of BTX-A. The group that received 25 U BTX-A had significantly greater improvement than placebo at 2 months and 3 months, while the 75 U group did not differ from placebo at any point in follow-up. Several secondary outcomes showed significant advantages for the 25 U group over placebo at selected follow-up intervals: change in maximum pain severity at 1 month and 2 months; percent with a decrease of 2 or more migraines at 3 months; change in days of acute medication use per month at 2 months; and Global Assessment Scale at 2 months. The 75 U BTX-A group performed significantly better than the placebo group only for one comparison: the Global Assessment Scale at 2 months.

Although not a large trial, design and analysis appear to be of adequate quality. Some results are suggestive of a significant effect for 25 U Botox®, but overall the data do not present a consistent picture. Significant differences between treatment arms occurred only at some time points, and at different time points for different outcome measures. The significance levels were marginal; p-values for decrease in migraines, percentage of patients with a decrease in migraine frequency of at least 2, and decrease in the maximum migraine severity were 0.042, 0.046, and 0.029, respectively. It is also surprising that the 75 U Botox® treatment group showed so little effect; even if there was no dose-response effect, one might expect a plateau effect where the 75 U dose was at least as effective as 25 U.

Migraine Summary. Two randomized trials on migraines provide only weak evidence on the effectiveness of botulinum toxin. A trial published in 2004 found no significant effect of botulinum toxin for pain-related outcomes and a low dose relieved non-pain symptoms more than placebo. Another moderately sized trial from 2000 reported only short-term outcomes, and questions remain regarding the variability of effect at different time points, as well as variability of dose and injection site. Both studies found only isolated significant differences that may have been due to chance alone. In each case, the advantage favored a low dose over a higher dose of botulinum toxin, which contrasts with the expected result of a dose-response relationship. Currently, the available evidence is judged insufficient for conclusions.

Tension Headaches

The 2002 TEC Assessment identified 4 studies that met selection criteria (Schmitt et al. 2001; Rollnik et al. 2001; Rollnik et al. 2000/2002; Smuts et al. 1999), with sample sizes between 8 and 59 patients. Data suggestive of better outcome for BTX-A over placebo was found in only 1 study and the review concluded that evidence was insufficient to support conclusions. Four additional studies have appeared since completion of the previous Assessment (Schulte-Mattler et al. 2004; Relja and Telarovic, 2004; Ondo et al. 2004; Padberg et al. 2004).

All 8 studies were double-blind, randomized, placebo-controlled trials. Both older and more recent studies are included in the evidence tables. Table 1B summarizes study design, methods and efficacy outcomes. Table 2B shows data on adverse events. Table 3 gives study quality ratings. Two of the 8 studies have fair quality ratings, while the other 6 were rated as poor. Neither of the two better-rated studies found significant differences between placebo and BTX-A groups; one of these is the largest study (n=107). Three of the 6 poor quality studies found inconsistent significant results, 2 of which made no comparisons of baseline characteristics and one of which had a large difference between groups on an important variable (headache frequency) that was not adjusted for in the statistical analysis.

Of the 8 total studies meeting selection criteria, the recent trial by Schulte-Mattler et al. (2004) included the largest patient sample and was among 2 studies rated highest in quality. These authors enrolled 107 patients with chronic tension-type headaches that were at least partially resistant to adequate therapy. The placebo control group (n=54) had saline injections and the treatment group (n=53) received 500 U Dysport® according to a standardized protocol, without EMG guidance. The primary outcome measure was area under the headache curve (AUC), calculated as the sum of the product of headache duration and severity across days. At baseline, groups were comparable in these characteristics: age, gender, headache duration, muscle tenderness, Beck Depression Inventory scores, headache frequency and AUC. The overall study quality rating was fair. All study quality dimensions were rated as adequate, with the exception of initial assembly of comparable groups, which was partially satisfied because, while specified baseline characteristics were comparable, details on

the randomization method were missing that would allow assessment of its adequacy. After 12 weeks, there were no statistically differences in the degree of change between groups in the primary outcome, AUC, or in any of these outcomes: days with headache per 6 weeks; days with intake of analgesics; muscle tenderness score; Beck Depression Inventory score; or sleep duration.

The other study rated as fair was by Padberg et al. (2004). This trial compared saline placebo (n=21) with 1 U/kg Botox® (maximum 100 U, n=19). Patients with chronic tension-type headache were injected at sites selected by an experienced clinical neurophysiologist in muscles with increased muscle tone or tenderness. Groups were comparable on age, gender, headache severity, headache duration, medication days, number of analgesics per day and tenderness. No details about the randomization method were provided. No patients were lost to follow-up. The primary health outcome was change in visual analog scale headache severity. There was no statistically significant difference in degree of improvement between groups on this outcome, or any of the following measures: number of headache days; percent headache hours per day; percent medication days; and number of analgesics per day.

The study by Relja and Telarovic (2004) had an overall rating of poor. These investigators selected patients with chronic tension-type headache who were resistant to standard medication, including tricyclic antidepressants. Injections to the most affected pericranial muscle contained either saline placebo (n=8) or 40–95 U BTX-A (n=8). The article did not present any comparison of baseline patient characteristics and did not specify the randomization method, so group comparability is unclear. The paper also did not document whether any loss of data occurred among randomized patients. No primary outcome was identified, but statistically significant differences favoring the treatment group were observed for 2 outcomes: change in mean tenderness at 2 weeks, 4 weeks, and 8 weeks; and distribution of headache severity ratings at 8 weeks.

While all other studies included only patients with chronic tension headache, Ondo et al. (2004) selected a mix of patients with migraine (24% of the sample) and those with tension headache (76%). An investigator selected sites using a "follow the pain" strategy, injecting patients with either saline placebo (n=30) or 200 U Botox® (n=30). After a 12-week double-blind period, patients in both groups were allowed to choose open-label Botox® injections. While no details were given on the randomization method, groups were comparable on age, gender, headache type, palpation score, Beck Depression Inventory score, Psychosocial Adjustment to Illness Scale score, number of failed and current medications, narcotic overuse, and dose by site distribution. The placebo group had a much higher mean number of days with headache (25.8) than the treatment group (4.8) during the 4-week run-in period and the article mentions no use of statistical adjustment for this baseline difference in the analysis of results.

Ondo et al. (2004) identified headache frequency, or headache-free days, as the primary outcome. Results were presented in a confusing manner. A figure was included plotting days with headache across time for both groups, but it did not note a test of statistical significance. The text of the article confusingly stated: "Compared with placebo, headache-free days improved in the BTX group from week 8 to 12 ($p<0.05$, t-test), but tended to improve strongly only over the entire period of weeks 0–12, 33 ± 23 vs. 24 ± 16 ($p=0.07$) fewer headache days, the primary efficacy point (Fig. 2)." It appears that the change from 0 to 12 weeks was not statistically significant. Statistically significant advantages favoring the BTX group were found for 3 outcomes rated with 6 categories: patient global impression, physician global impression, and patient change in headache. No significant differences were observed for number of abortive medications needed, palpation scores, Beck Depression Inventory score, Psychosocial Adjustment to Illness Scale score.

Schmitt et al. (2001) randomized 59 patients with chronic tension headache to 20 U Botox® (n=30) or saline injection placebo (n=29) in 4 standardized injection sites (frontal and temporal muscles). While groups appeared comparable on treatment duration, monthly intake of analgesics, percent taking 30 or more units of analgesics per month, there was a 30% difference between groups in the mean disease duration. There was no mention of whether statistical analysis included adjustment for differences in baseline variables. The article did not give details about the randomization method. No between-group comparisons were

offered for age, headache severity or headache frequency. Overall study quality is poor. After 2 months, the primary outcome of pain severity was analyzed using the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) at enrollment and at 2 months and a visual analog scale (VAS) recorded by the patient in a daily headache diary. Differences between baseline and follow-up values were not significant in the treatment group compared to placebo control. Out of 11 measures on WHYMPI and 8 measures on VAS recorded and analyzed, 2 showed significant changes from baseline in the treatment compared to the placebo group (95% confidence level); on average, 1 would be expected by random chance alone. There were also no significant differences in percentage of responders, headache frequency, use of analgesic drugs, or activity level.

Rollnik et al. (2001) randomized 4 patients to 550 U Dysport™ and 4 to saline injection placebo. The randomization method was not described, but the following baseline characteristics appeared to be comparable: headache frequency, AUC, age, gender Beck Depression Inventory scores, height and weight. There was a 30% difference between groups in the duration of headache and the article did not specify if the analysis used statistical adjustment for baseline differences. It is unclear how many of the randomized patients were included in the analysis. The overall quality rating for this study is poor. The primary outcome was AUC at 1.5 and 3 months. There were no significant differences between treatment groups in this measure or in headache prevalence at either follow-up time point. This was true despite EMG evidence of a reduction in resting muscle activity in BTX-A treated patients.

Earlier, Rollnik et al. (2000, 2002) had conducted a similar trial of 200 U Dysport™ in patients with episodic or chronic tension headache, randomizing 11 patients to treatment and 10 patients to placebo. Groups were comparable in age, gender, and headache severity. Groups differed by 26% in the proportion with chronic headache and by 30% in mean headache frequency. No details were provided for the randomization method, use of statistical adjustment for confounders or whether all randomized patients were analyzed, thus this study was given a poor quality rating. Pain intensity measured by VAS decreased similarly for both treatment arms; no significant differences were found in pain intensity, headache frequency, duration or use of analgesics.

Smuts et al. (1999) randomized 41 patients to 100 U Botox® or saline injection placebo. Patients were recruited from a neurology private practice or service and had IHS-defined chronic tension headache and a history of failed prophylactic drug treatment. Thirty-eight percent of patients also had migraines, but no more than 1 per month prior to enrollment. The article gave no details on the randomization method, baseline patient characteristics or whether the analysis used adjustment for confounders,. Four patients (9.8%) were excluded from the analysis. The overall quality of this study is poor. Treated patients showed a statistically significant effect on change in headache severity score and increase in number of headache-free days. Statistical tests were not reported for percent with 25% or more improvement in headache score or change in chronic pain index.

Tension Headache Summary. Five of 8 studies on tension headache identified a primary outcome, but no statistically significant differences favoring BTX-A over placebo for the primary outcome were observed. The primary outcome was area under the headache curve (AUC) in 2 studies (Schulte-Mattler et al. 2004; Rollnik et al. 2001), headache severity in 2 studies (Padberg et al. 2004) and headache frequency in 1 study (Ondo et al. 2004). The largest study (Schulte-Mattler et al. 2004, n=107) was 1 of 2 with higher quality ratings (fair) and found no differences between groups on 6 outcomes. The second study rated as fair in quality (Padberg et al. 2004) found no significant differences on 5 outcomes. Three of the 6 studies rated as poor in quality found inconsistent significant results. In the study by Ondo et al. (2004) there did not appear to be a statistically significant result on the primary outcome or 4 other outcomes, while 3 global rating scales significantly favored the BTX-A group. Groups differed greatly on the baseline mean frequency of headaches and the authors did not mention adjustment for confounding in the data analysis. Two other poor-quality studies finding selected significant differences between groups (Relja and Telarovic, 2004; Smuts et al. 1999) did not evaluate comparability of groups on any baseline characteristics or specify that analyses used adjustment techniques, so it is unclear whether findings were influenced by confounding.

In summary, the failure of 2 better-quality studies to find between-group differences calls into question the weakly positive findings of 3 poor quality studies. The addition of 4 recent studies to the 4 studies available in the 2002 TEC Assessment does not provide evidence to support conclusions about the effects of BTX-A on tension headaches.

Cluster Headaches

Other than case reports, no studies of BTX-A treatment for the prevention of cluster headaches have been reported. Thus, no evidence exists to evaluate the effect of BTX-A injections on cluster headache.

Adverse Events

In general, all trials of BTX-A preventive treatment for primary headache syndromes that reported on adverse events indicated few, short-term, and relatively minor adverse events associated with BTX-A vs. saline control, including eyelid ptosis, acute headache, mild neck weakness, nausea, pain at the injection site, and diplopia.

2. Do BTX injections abort acute headache attacks in patients with primary chronic headache syndromes who are refractory to conventional pharmaceutical treatment?

There were no studies meeting inclusion criteria that tested BTX for the treatment of acute headache attacks. Only one excluded, open-label study tested Botox® injections for the treatment of acute migraine (Binder et al. 2000). Of 10 patients treated, 7 reported elimination of symptoms within 1 to 2 hours after treatment. The evidence is insufficient to determine whether or not BTX-A is an effective treatment for acute migraine episodes.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether the treatment of primary chronic headache disorders with botulinum toxin meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In December 1989, the U.S. Food and Drug Administration (FDA) approved a commercial preparation of botulinum toxin A (Botox®) for therapeutic use in patients with strabismus, certain movement disorders (blepharospasm) and VII nerve disorders (e.g., hemifacial spasm). On December 21, 2000, supplemental approval was granted for the indication of cervical dystonia. Finally, on April 12, 2002, supplemental approval was granted to include the indication of treatment of glabellar lines. Myobloc™ (BTX-B), was approved on December 8, 2000, for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain. Treatment of primary chronic headache represents an off-label indication.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Included studies for this Assessment were required to be randomized, injection placebo-controlled, double-blinded trials published as a primary study in a peer-reviewed journal. Due to a well-documented and substantial placebo effect in trials of both abortive and preventive pharmacologic therapy for the treatment of primary headache disorders, uncontrolled and unblinded trials were excluded.

All reported trials of BTX injections for the treatment of primary headache syndromes have used commercial preparations of botulinum toxin type A. No evidence exists for the use of toxin types B through G.

The evidence was judged insufficient to meet the second TEC criterion for any of the indications evaluated.

BTX for Headache Prophylaxis

Migraine. Since the 2002 TEC Assessment, 1 new study meeting selection criteria has appeared. Published in 2004 (n=60), this trial randomized patients to saline placebo, low-dose BTX-A or high-dose BTX-A. No significant differences were reported at 3 months for any of 7

pain-related outcomes. The low dose of BTX-A had a lower rate of accompanying symptoms (photophobia, phonophobia, nausea and vomiting), compared with the placebo and high-dose groups. A study from 2000 (n=123) provided mixed results for the use of BTX for migraine prophylaxis. This moderately sized trial reported only short-term outcomes, and questions remain regarding the variability of effect at different time points, as well as variability of dose and injection site. Isolated findings of statistical significance favoring BTX-A in these 2 studies could be explained by chance alone and evidence is judged insufficient for conclusions.

Tension Headaches. The 2002 TEC Assessment reviewed 4 trials providing data for 125 patients. Only 1 of these studies gave data suggesting better outcome for BTX-A over placebo. Four additional studies with data for 223 patients have appeared subsequently. Taking previously available and recent studies together, among 5 of 8 studies which identified a primary outcome, none found statistically significant differences favoring BTX-A over placebo for that outcome. In 2 studies, the primary outcome was area under the headache curve (AUC), computed as the sum of the product of headache duration and severity across days. The primary outcome was headache severity in 2 studies and headache frequency in 1 study.

Two of the 8 studies had fair quality ratings, while the other 6 were rated as poor. Neither of the two better-rated studies found significant differences between placebo and BTX-A groups. The largest study (n=107) found no differences between groups on 6 outcomes. The second study rated as fair in quality found no significant differences on 5 outcomes. Three of the 6 studies rated as poor in quality found inconsistent significant results. In 1 of these studies, there did not appear to be a statistically significant result on the primary outcome or 4 other outcomes, while 3 global rating scales significantly favored the BTX-A group. Groups differed greatly on the baseline mean frequency of headaches and the authors did not mention adjustment for confounding in the data analysis. Two other poor-quality studies finding selected significant differences between groups did not evaluate comparability of groups on any baseline characteristics or specify that analyses used adjustment techniques, so it is unclear whether findings were influenced by confounding.

The failure of 2 better-quality studies to find between-group differences calls into question the weakly positive findings of 3 poor quality studies. Overall, the evidence is not sufficient to support conclusions about the effects of BTX-A on tension headaches.

Cluster Headaches. Other than case reports, no studies of BTX-A treatment for the prevention of cluster headaches have been reported. Thus, no evidence of adequate quality exists to evaluate the effect of BTX-A injections on cluster headache.

BTX for Treatment of Acute Headaches

There were no studies meeting inclusion criteria that tested BTX for the treatment of acute headache attacks. Thus, the evidence is insufficient to determine whether or not BTX-A is an effective treatment for acute migraine episodes.

3. **The technology must improve the net health outcome; and**
4. **The technology must be as beneficial as any established alternatives.**

The available evidence does not permit conclusions regarding the prophylactic or abortive effect of BTX-A or any other botulinum toxin type on chronic primary headache syndromes.

5. **The improvement must be attainable outside the investigational settings.**

It has not yet been demonstrated whether botulinum toxin improves health outcomes in the investigational setting. Therefore, it cannot be demonstrated whether improvement is attainable outside the investigational setting.

Based on the above, botulinum toxin therapy for primary chronic headache disorders does not meet the TEC criteria.

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Appendix

Table A. Components of Study Quality

Dimension	Components	Dimension Ratings	Quality Ratings
Initial Assembly of Comparable Groups	Adequate randomization (concealed or centralized)	Yes = all components adequate, satisfied	Good = All dimensions satisfied
	Equal distribution of confounders (at least age, wound size, wound duration)	No = one or more component inadequate, not satisfied	Fair = all dimensions satisfied or partially satisfied
No Differential Loss to F/U or Low Loss to Follow-up	No differential loss to F/U or low overall loss to F/U (>20%)	Partial = one or more components adequate, none inadequate, partially satisfied	Poor = one or more dimension not satisfied
Measurements Reliable, Valid, Equal	Clearly described, reproducible measurement	? = unclear if any components satisfied	
	Blinded outcome assessment		
Interventions Comparable/Clearly Defined			
Appropriate Analysis of Results	Adjustment for confounders		
	Intention-to-treat analysis (all randomized analyzed to 5% or less loss)		

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