

Research Submission

Botulinum Toxin Type A as Migraine Preventive Treatment in Patients Previously Failing Oral Prophylactic Treatment Due to Compliance Issues

Roger Cady, MD; Curtis Schreiber, MD

Objective.—To examine the efficacy and safety of and satisfaction with botulinum toxin type A (BoNTA; BOTOX®; Allergan, Inc., Irvine, CA) for prophylactic treatment of migraine headache in patients previously failing prophylaxis because of issues pertaining to compliance.

Background.—Numerous factors (eg, adverse effects, tolerability, cost, frequency of dosage, hesitancy to take daily medication, failure to complete treatment) negatively influence compliance with the preventive pharmacology for migraine prophylaxis. BoNTA may offer benefit in improving compliance because of its long duration of action, injectable route of administration, and its tolerability (adverse event [AE]) profile.

Methods.—This was a randomized, double-blind, single-center, placebo-controlled study (months 1 to 3) of BoNTA with a cross-over to open-label BoNTA treatment (months 4 to 6). Criteria for enrollment included patients with disabling headache (International Headache Society, International Classification of Headache Disorders [ICHD-I] diagnosis 1.1, 1.2, 1.7, or 2.2, and Headache Impact Test [HIT]-6 scores ≥ 56) previously failing prophylaxis because of compliance, tolerability, or adherence issues. After baseline evaluation, subjects were randomized 2 : 1 to a single set of BoNTA (139 units [U] total; 17 sites/6 muscle groups) or placebo injections. After month 3, only placebo-treated subjects were eligible to receive BoNTA in the open-label continuation study. Treatment outcomes were evaluated by headache episodes and days and maximum headache severity. Headache impact was assessed by the HIT-6, Migraine Disability Assessment (MIDAS) score, and Quality of Life (QoL) questionnaires. Treatment satisfaction was assessed with the Migraine Impact Questionnaire (MIQ), which included MIDAS and QoL.

Results.—Of the 73 subjects screened, 61 (40 BoNTA; 21 placebo) with migraine headache diagnosis 1.1 and 1.2 who met all study criteria were enrolled in the 3-month, blinded study, with 54 completing the study; 19 of 21 placebo-treated subjects participated in the open-label period (months 4 to 6), with 18 completing the study. Between-group comparisons, demonstrated through analysis of the subjects' headache diaries, did not reach statistical significance at months 1 to 3 for the number of headache episodes or days (primary endpoint). At month 2, a decrease from baseline in the number of headache episodes (-0.99 ± 2.38 ; $P = .0147$ vs 0.42 ± 3.23 ; $P =$ not significant [NS]) and headache days (-1.52 ± 3.84 ; $P = .0194$ vs 0.23 ± 4.67 ; $P =$ NS) was noted in the BoNTA-treated subjects but not in the placebo-treated subjects, respectively. During the open-label study, BoNTA-treated subjects had a decrease in the number of headache episodes at months 5 and 6 (-1.58 ± 2.88 and -1.58 ± 2.85 , respectively; $P < .05$ vs baseline for both) and headache days at months 5 and 6 (-2.84 ± 4.47 and -2.73 ± 4.86 , respectively; $P < .05$ vs baseline for both). BoNTA did not affect maximum headache severity compared with baseline or placebo during the first 3 months of the study. A decrease in HIT-6 scores was significantly greater for BoNTA-treated subjects than for placebo-treated subjects at month 3 (-7.77 vs -3.58 , $P = .0466$). Within-group decreases in HIT-6 scores were significant in BoNTA-treated subjects during each month of the blinded trial (-5.10 ± 8.85 , -6.63 ± 7.49 , -7.77 ± 8.78 for months 1 to 3, respectively; $P < .0001$ for all vs baseline) and throughout the open-label portion of the study (-7.89 ± 6.48 , -10.39 ± 10.81 ,

From the Headache Care Center, Springfield, MO, USA.

Address all correspondence to Dr. Roger Cady, Headache Care Center, Springfield, MO, USA.

Accepted for publication September 3, 2007.

Conflict of Interest: None

-9.00 ± 11.12 for months 4 to 6, respectively; $P < .01$ for all vs baseline). The within-group decrease in placebo-treated subjects was significant at months 1 and 3 (-3.35 ± 6.07 and -3.58 ± 5.40 , respectively; $P < .05$ for both). At 3 months, BoNTA was significantly better than placebo ($P = .001$) in the reduction of MIDAS total score. The change from baseline in the MIDAS total scores was significant in BoNTA-treated subjects (-21.62 ± 38.70 ; $P < .0001$) but not in placebo recipients (4.76 ± 18.85 ; $P = \text{NS}$). BoNTA-treated subjects showed improvement in 11 of 13 and 7 of 13 assessments of treatment satisfaction in MIQ at months 3 and 6, respectively, while the placebo group showed no improvement at any measured time interval in the study. At month 3 (blinded period), there were no treatment-related AEs reported in both groups. However, there were 18 possible/probable occurrences of treatment-related AEs in the BoNTA group. At month 6 (open-label period), 4 treatment-related AEs were reported, along with 2 possible occurrences. The majority of treatment-related AEs were transient and mild to moderate in severity, with no subjects discontinuing the study because of AEs.

Conclusions.—BoNTA-treated subjects showed improvements from baseline in measures of headache frequency, and improvements from baseline and in comparison with placebo treatment in headache impact and treatment satisfaction at multiple time points in this study. However, BoNTA-treated subjects did not differ from placebo-treated subjects in measures of headache frequency and severity. BoNTA may be a useful treatment option for headache patients demonstrating poor compliance, adherence, or AE profile with oral prophylactic regimens.

Key words: migraine headache, botulinum toxin type A, prophylaxis, double-blind, placebo-controlled

Abbreviations: AE adverse event, BoNTA botulinum toxin type A, HIT Headache Impact Test, ICHD International Classification of Headache Disorders, IHS International Headache Society, MIDAS Migraine Disability Assessment, MIQ Migraine Impact Questionnaire, NS not significant, QoL quality of life, U units

(*Headache* 2008;48:900-913)

INTRODUCTION

Migraine headache is a primary headache disorder affecting 6-8% of men and approximately 18% of women in Europe and America.¹⁻³ It is often accompanied by nausea, vomiting, sensitivity to light and/or sound, and irritability.⁴ Importantly, migraine sufferers experience impaired quality of life as well as reduced work capacity and social activity.³ Comorbidity or co-sensitization with major depressive disorder occurs in 29.1% of migraineurs.^{5,6} The direct medical costs of migraine (cost of health care) and indirect costs (missed activities and decreased productivity) total billions of dollars each year.^{7,8}

Clinically, migraine can be observed as a progressive or pervasive disorder. It is hypothesized that prophylactic treatment may slow or prevent such progression.^{5,9} Some patients, particularly those having frequent debilitating or prolonged attacks for which acute treatment is impractical or ineffective, require prophylactic treatment, while most others require both acute and preventive therapy.^{4,9} Migraine prophylaxis is usually considered when patients experience more than 2 migraine episodes per month.⁶ A recent study estimated the prevalence of migraine sufferers who might benefit from prophylactic treatment and evaluated current patterns of prophylactic

migraine treatment.^{10,11} It found that 25.7% of migraineurs aged ≥ 12 years should be offered prophylactic treatment and an additional 13.1% should be considered for prophylactic treatment. Only 12.4% of migraineurs were currently receiving preventive treatment.¹¹

Botulinum neurotoxin has been used clinically as a migraine preventive therapy for a number of years and is used to treat a variety of conditions; botulinum toxin type A (BoNTA) is the most widely studied and frequently used for therapeutic purposes.¹² When injected locally, BoNTA inhibits cholinergic transmission at neuromuscular and autonomic postganglionic synapses.¹³ It also inhibits the release of nociceptive mediators such as glutamate, substance P, and calcitonin gene-related peptide from nociceptive neurons (a direct antinociceptive action distinct from its neuromuscular activity).¹⁴⁻¹⁶ Evidence suggests that BoNTA administration is an effective and safe therapy for prophylactic treatment of migraine headaches and chronic daily headache.¹⁷⁻²¹ Besides having a good safety and tolerability profile, compliance can be guaranteed with BoNTA because of its method of administration and long duration of action.²² Thus, BoNTA may be an ideal prophylactic agent for use in patients with frequent disabling headache patterns

who are poorly controlled with other preventive therapies because of poor compliance, adherence, or inability to use standard preventive therapies as a result of adverse events (AEs).

The purpose of this study was to examine the efficacy and tolerability of preventive treatment with BoNTA in migraineurs who were noncompliant, non-adherent, or experienced AEs that precluded use of standard oral preventative treatment; a group of patients in which the need for and utility of an agent such as BoNTA is particularly well suited. The study evaluated changes in headache frequency and intensity, as well as variables of headache disability, impact, and patient satisfaction in this population following a fixed-site injection of BoNTA.

METHODS

Study Design.—This was a randomized, double-blind, placebo-controlled study of BoNTA (BOTOX®, Allergan, Inc., Irvine, CA, USA) compared with placebo as headache prophylaxis in subjects with disabling headache who had failed at least one trial with another preventive agent because of noncompliance, non-adherence, or AEs that precluded continuation of therapy. After randomization, subjects were treated with a single series of injections and followed for 3 months through biweekly phone calls from a research coordinator; they completed paper daily diaries and monthly questionnaires. At the completion of the 3-month blinded trial, placebo recipients were offered the option of receiving a single set of BoNTA injections in a 3-month open-label continuation of the study. The follow-up protocol was identical to that used during the blinded study.

This study was conducted in compliance with institutional review board regulations, informed consent regulations, the Declaration of Helsinki, and the International Headache Society guidelines for studies of the prevention of migraine.

Participant Characteristics.—*Inclusion Criteria.*—Adults over the age of 18 years with a history (≥ 6 months) of headache (IHS International Classification of Headache Disorders, 2nd edition diagnosis 1.1 [migraine without aura], 1.2 [migraine with aura], 1.7 [migrainous disorder not fulfilling above criteria], or 2.2 [chronic tension-type headache])²³ with onset

before the age of 50 years and a Headache Impact Test (HIT)-6 score greater than 56 were eligible to participate. Subjects with both episodic and chronic headache were eligible and were required to have a stable headache severity and pattern and to have failed at least one attempt with preventive medications because of compliance, adherence, or AE issues (adverse effects, tolerability, cost, frequency of dosage, hesitancy to take daily medication, or failure to complete treatment period). Women of childbearing potential were required to be taking approved birth control measures and to have a negative urine pregnancy test prior to administration of study medications. All eligible subjects were required to be able to understand the study instructions, complete all questionnaires, and maintain a daily diary record of headache as well as be willing to give informed consent.

Exclusion Criteria.—Subjects were excluded from the study if they had any medical condition that might put them at risk with BoNTA exposure (eg, myasthenia gravis, Eaton-Lambert Syndrome, amyotrophic lateral sclerosis), had any disease that might interfere with neuromuscular function, had uncontrolled systemic disease, had abnormal pathology contributing to headaches, had concurrent infection at proposed injection sites, or were pregnant or breast-feeding. Subjects were also excluded if they were currently using aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function; had undergone injection of anesthetics or steroids, within 1 month immediately prior to enrollment, into the muscles to be injected in the study; or had previously received BoNT treatment with any serotype. Subjects were also excluded if they were currently participating in another drug or device study or had done so within the 30 days before the baseline period, had suspected hypersensitivity to BoNTA or any of the ingredients in the proprietary formulation, or had known or suspected drug or alcohol abuse.

Treatment Schedule and Protocol.—The treatment schedule and protocol is outlined in Figure 1. Subjects attended a screening visit (visit 1) for initial assessment: confirmation of diagnosis, evaluation of inclusion and exclusion criteria, medical and medica-

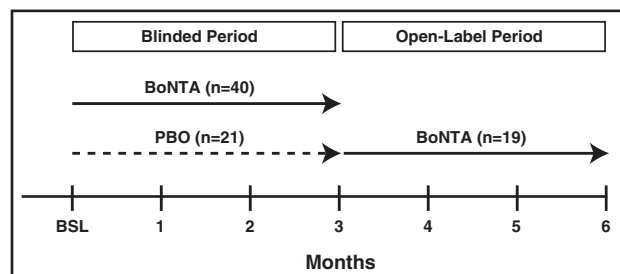


Fig 1.—Diagram of study design and treatment regimen. BoNTA = botulinum toxin type A; BSL = baseline; PBO = placebo.

tion history, physical and neurological examinations, baseline HIT-6, Migraine Impact Questionnaire (MIQ) that included the Migraine Disability Assessment (MIDAS) and Quality of Life (QoL) components, and instructions on the use of daily diaries. After 1 month (visit 2), subjects returned for enrollment, randomization to treatment arm, and injection of BoNTA or placebo. Subjects were followed biweekly by phone over the 3-month trial period to confirm active participation. At the end of each month, subjects completed their HIT-6 questionnaire and MIQ and sent them in with their daily diaries. At the end of 3 months, subjects attended a final study visit (visit 3) for update of medical and migraine history, review of diaries, and final HIT-6 questionnaire and MIQ. This visit completed the blinded portion of the study.

Subjects receiving placebo during the blinded study period were given the option of BoNTA treatment in an open-label continuation of the study. Subjects opting to continue received BoNTA injections at Visit 3 and were given new diaries to complete. As in the blinded trial, subjects were followed biweekly by phone over the course of the study to confirm active participation. As before, they completed the monthly HIT-6 questionnaire and MIQ and sent them in with their daily dairies. After 3 months, subjects attended a final study visit (Visit 4) for update of medical and migraine history, review of diaries, and completion of final HIT-6 questionnaire and MIQ.

BoNTA Treatment Schedule, Dosing, and Preparation.—Subjects were randomized 2:1 to receive BoNTA or placebo injections. In order to maintain the double-blind protocol, a research coordinator who was not directly involved with the sub-

jects managed the randomization and preparation of injections. Injections were administered with a 30-G needle for a total of 139 units (U) of BoNTA or a similar volume of placebo injected into specific muscle groups as outlined in Table 1. Subjects were permitted to treat headaches that occurred during the study according to their customary migraine therapy as approved at screening by the investigator.

BoNTA Formulation and Preparation of Solution.—BOTOX[®] was used in this study. Each vial of BOTOX[®] contained 100 U of *Clostridium botulinum* toxin type A, 0.5 mg of human albumin serum, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative. Each vial of placebo contained 0.9% sterile saline. The amount of placebo and the injection sites used were identical to those used for active BOTOX[®].

Dilution Technique.—Two vials were prepared for each subject with identifying number and initials written on the labels and subject visit form. Four mL of sterile saline was drawn up and injected slowly into each BoNTA or placebo vial and rotated gently to mix for a dilution of 2.5 U/0.1 mL. The reconstituted BoNTA or placebo was used within 4 hours of injection; it was stored in a refrigerator (2-8°C) if not used immediately.

Outcome Measures.—Headache Diaries.—Subjects were given headache diaries to complete daily to catalogue the incidence (number of headache episodes, days with headache, and headache-free days per 30 days; percentage of headache episodes with aura) and severity of headaches throughout the study period. Diaries were collected monthly by mail.

Table 1.—Injection Protocol for Botulinum Toxin Type A

Muscle group	Number of injection sites	Units/site	Units/muscle group
Corrugator	2 bilateral	6	12
Splenius capitis	2 bilateral	10	20
Trapezius	4 upper	10	40
Temporalis	4	10	40
Procerus	1	3	3
Frontalis	4	6	24
Total	17	45	139

Questionnaires.—HIT-6.—Subjects were asked to complete the HIT-6 questionnaire at the screening visit and monthly by mail for 3 months and, for those participating in the open-label portion of the study, for another 3 months. The HIT-6 is a series of 6 questions covering areas of pain, ability to carry out usual activities, social functioning, energy/fatigue, cognition, and emotional stress.²⁴ It is considered a valid, reliable, and precise measurement of headache impact.²⁵

MIQ.—The impact of treatment was evaluated using the MIQ, a 21-question form (developed by Allergan, Inc.)²⁶ concerning subject satisfaction with acute and prophylactic treatment and ability to manage migraine symptoms, at screening and monthly as mentioned above in the HIT-6 section. The MIQ included the MIDAS and QoL component questionnaires.

MIDAS.—The MIDAS questionnaire is a validated tool for assessment of disability associated with migraine and consists of 5 scored questions and 2 unscored questions.²⁷ The scored questions concern days of missed activity and reduced productivity in work/schoolwork and household chores and days of missed social/family/leisure activities; the unscored questions assess headache frequency and pain intensity.

Safety Measures.—Safety and tolerability were assessed by reports of AEs. Subjects were instructed to record all unpleasant symptoms, reactions, changes in medical condition, and exacerbations of pre-existing conditions that occurred after the study medication was taken as AEs, regardless of their relationship to study medication.

Statistical Analysis.—Statistical analyses were performed using SAS version 9 (SAS, Cary, NC, USA). Demographic data were analyzed using *t*-test (eg, age) or Fisher's exact test (eg, gender and baseline headache characteristics). Frequency of headache days and episodes and maximum severity of headache episodes were analyzed using appropriate *t*-tests for within-group and between-group comparisons. Mean change from baseline data was analyzed using *t*-test or Wilcoxon signed rank test, depending on the normality of data distribution; the Wilcoxon rank-sum test was used for between-group comparisons

where noted. The specific tests used in particular situations are noted in table and figure legends as well as the text.

RESULTS

Subject Characteristics and Demographics.—In this study, 73 subjects were screened and 61 enrolled (85.2% female). No power calculation was performed to determine the sample size. The mean age of enrolled subjects was 42.1 ± 11.5 years. The distribution of subjects in the BoNTA and placebo groups did not differ in mean age or gender. Of the 61 enrolled subjects, 59 received study medication (40 BoNTA, 19 placebo) and 54 completed the study (36 BoNTA, 18 placebo). Of the enrolled subjects who did not complete the study, 4 were lost to follow-up (2 BoNTA subjects and 2 placebo recipients), 2 withdrew consent (one from each group), and one from the BoNTA group dropped out because of unknown circumstances. Baseline headache characteristics and history are presented in Table 2. The study received enrollment of subjects with diagnostic criteria 1.1 and 1.2 only. All subjects had previously received oral prophylactic medications. Most subjects in both groups presented with migraine without aura (52.5% in the BoNTA group and 57.1% in the placebo group, respectively) or mixed migraine with and without aura (42.5% in the BoNTA group and 38.1% in

Table 2.—Baseline Migraine Characteristics and History

	Total (N = 61)	Botulinum toxin type A (n = 40)	Placebo (n = 21)
Migraine history			
Diagnosis, n (%)			
Migraine with aura	3 (4.9)	2 (5.0)	1 (4.8)
Migraine without aura	33 (54.1)	21 (52.5)	12 (57.1)
Migraine with/without aura	25 (41.0)	17 (42.5)	8 (38.1)
Previous prophylactic medications, n (%)	61/61 (100)	40/40 (100)	21/21 (100)

Groups were not significantly different ($P = .9026$, Fisher's exact test).

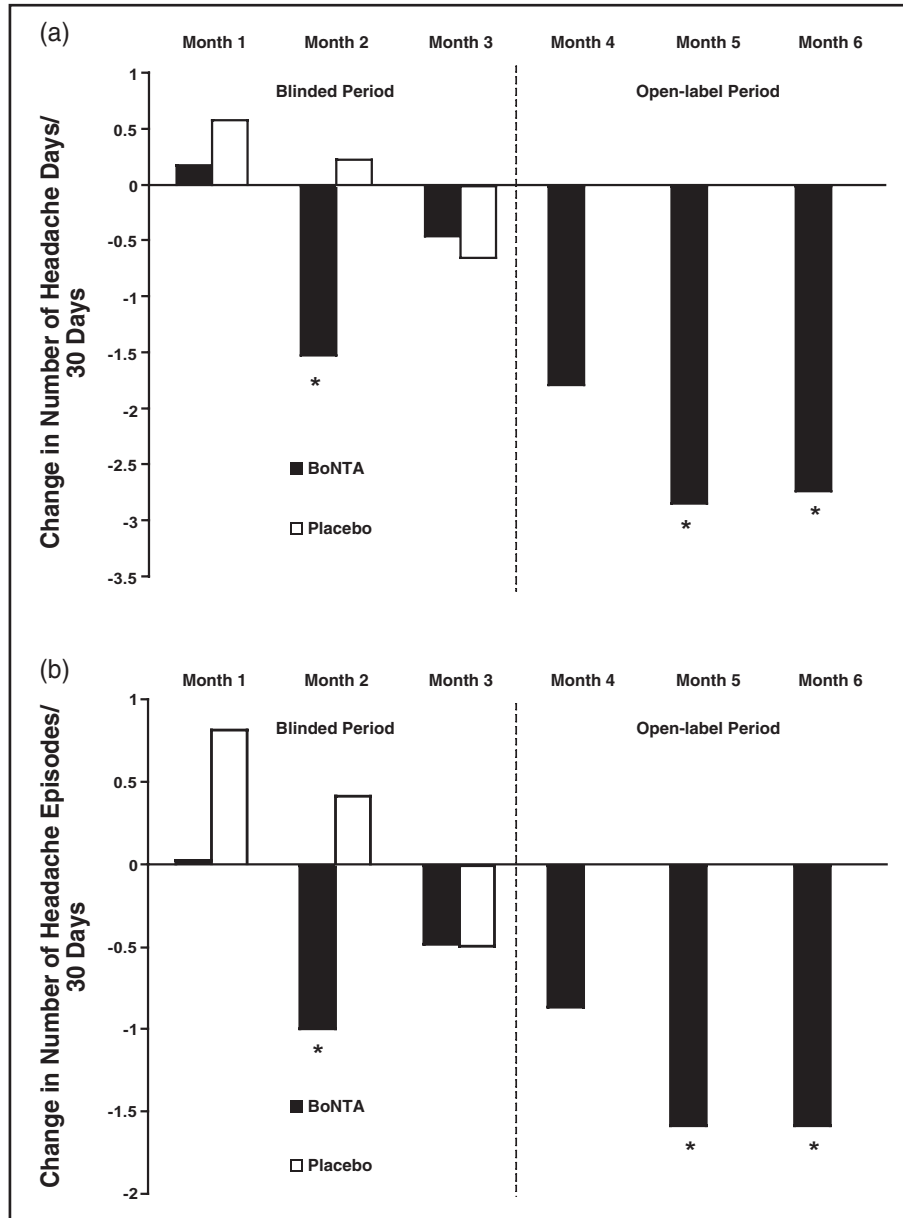


Fig 2.—Mean change from baseline in number of headache days (a) and headache episodes per 30-day period (b). Data from headache diaries are presented as mean change from baseline \pm SD for 3 months of the blinded period (months 1 to 3) and 3 months of the open-label period (months 4 to 6). * $P < .05$ for within-group comparisons vs baseline (t -test). There were no significant differences between groups during the blinded period (t -test).

the placebo group, respectively). The remaining subjects in each group presented with migraine with aura.

Headache Diaries.—The mean number of headache days and headache episodes per 30 days at baseline did not differ between the BoNTA and placebo groups (7.93 ± 4.71 vs 8.90 ± 4.72 ; $P = .4461$ and 4.85 ± 2.24 vs 5.30 ± 2.47 ; $P = .4688$, respectively, by

t -test). The mean decrease from baseline in both number of headache days and headache episodes per month was significant at month 2 in subjects receiving BoNTA but not at months 1 and 3 and not in those receiving placebo at any time point (Fig. 2). At month 2, the difference between the mean decrease in headache episodes per month in subjects receiving BoNTA compared with placebo approached signifi-

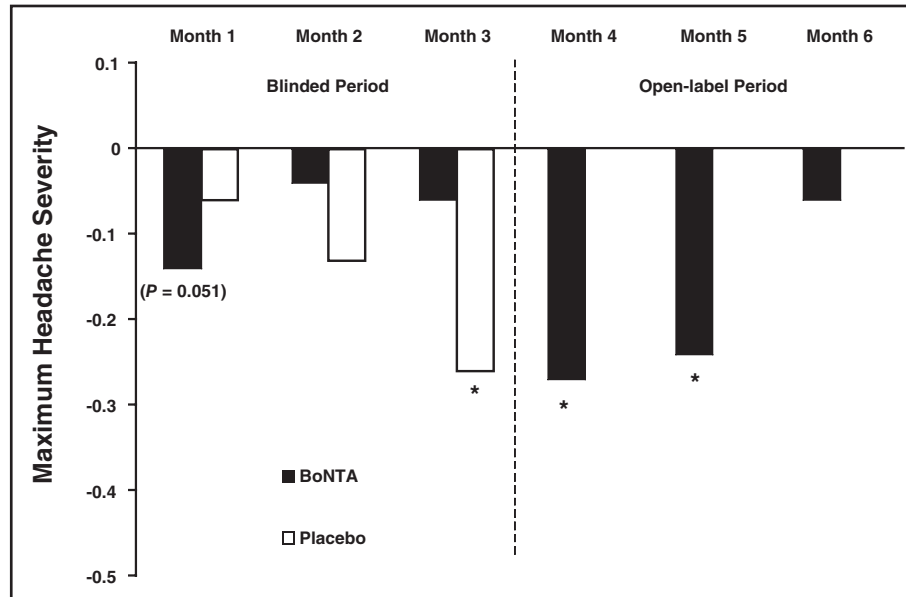


Fig 3.—Mean change from baseline in maximum headache severity. Data from headache diaries are presented as mean change from baseline \pm SD for 3 months of the blinded period (months 1 to 3) and 3 months of the open-label period (months 4 to 6). * $P < .05$ for within-group comparisons vs baseline (t -test). There were no significant differences between groups during the blinded period (t -test).

cance ($P = .0642$). No other between-group comparisons were significant. During the open-label period with BoNTA, the mean decrease from baseline in both number of headache days and headache episodes was significant at months 5 and 6 (Fig. 2).

The maximum headache severity at baseline was similar between subjects receiving BoNTA and placebo (2.18 ± 0.35 vs 2.14 ± 0.52 ; $P = .7556$ by t -test). BoNTA treatment did not affect maximum headache severity compared with baseline in the first 3 months of the study (blinded period), although the decrease in severity at month 1 approached significance (-0.14 ± 0.42 ; $P = .0510$ by t -test) (Fig. 3). At 3 months, the mean decrease from baseline in maximum headache severity was significant in the placebo-treated group. During the open-label period with BoNTA, the mean decrease from baseline in maximum headache severity was significant at 4 and 5 months (Fig. 3).

Questionnaires.—Headache Impact Assessment.—Results from subjects' responses to the HIT-6 questionnaire are illustrated in Figure 4. HIT-6 scores at baseline were similar between the BoNTA and placebo groups (66.6 ± 4.88 vs 65.48 ± 4.45 ; $P = .3824$ by t -test). The mean decrease from baseline in HIT-6

scores was significant at months 1, 2, and 3 for subjects receiving BoNTA and at months 1 and 3 for subjects receiving placebo. At month 3, the mean decrease in HIT-6 scores for subjects receiving BoNTA was significantly greater than for those receiving placebo ($P = .0466$, Wilcoxon rank-sum). In the open-label period with BoNTA, mean decreases from baseline in HIT-6 scores were significant at months 4, 5, and 6.

MIDAS.—Baseline total MIDAS scores were not significantly different for the groups receiving BoNTA and placebo (40.05 ± 41.55 vs 25.90 ± 17.47 ; $P = .1563$ by Wilcoxon rank-sum). The mean change from baseline in total MIDAS scores at 3 months was significant for the BoNTA group (-21.62 ± 38.70 ; $P < .0001$ by Wilcoxon signed rank test) but not for the placebo group (4.76 ± 18.85 ; $P = .4405$ by Wilcoxon signed rank test). At 3 months, the difference between the BoNTA and placebo groups was also significant ($P = .0010$ by Wilcoxon rank-sum).

The distribution of MIDAS disability grades was similar in the BoNTA and placebo groups at baseline ($P = .1399$ by Wilcoxon rank-sum). At 3 months, these distributions were significantly different ($P = .0364$ by Wilcoxon rank-sum). At baseline, 0% of the BoNTA group was in the least disabled category (little or no

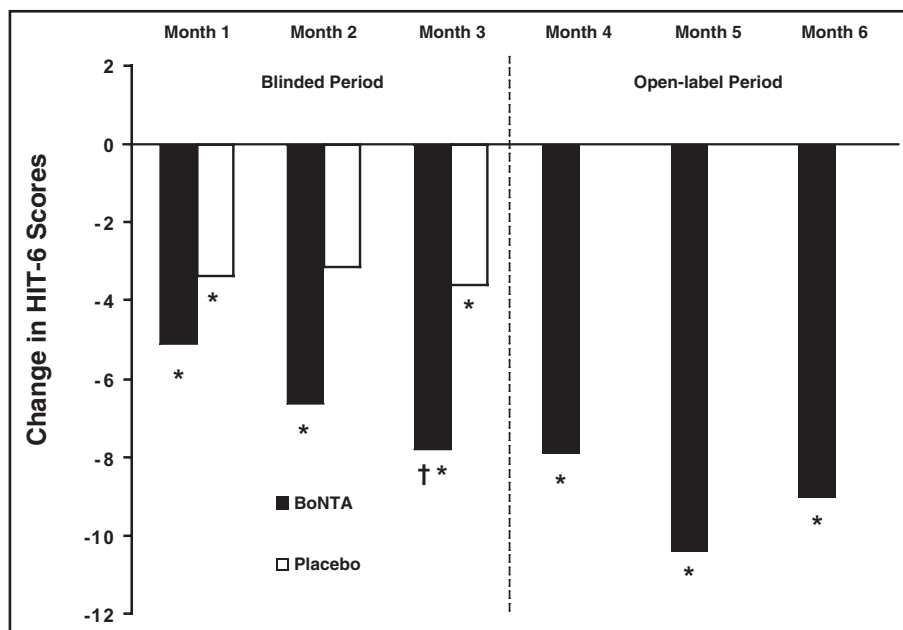


Fig 4.—Mean change from baseline in Headache Impact Test-6 scores. Data from questionnaires are presented as mean change from baseline \pm SD for 3 months of the blinded period (months 1 to 3) and 3 months of the open-label period (months 4 to 6). * $P < .05$ for within-group comparisons vs baseline (Wilcoxon signed rank test or t -test). † $P < .05$ vs placebo at the same time point (Wilcoxon rank-sum test).

disability, 0-5); at 3 months 31.4% achieved this rating. In contrast, the placebo group had no change in the percentage of subjects with the lowest disability grade (10.0% at baseline vs 11.1% at 3 months). Similarly, the percentages of subjects with the highest disability grade (score >21) at baseline were 74.4% and 55.0% for the BoNTA and placebo groups, respectively. At 3 months, 37.1% of BoNTA subjects compared with 66.7% of the placebo group were in this category. In the open-label period, the mean decrease from baseline in total MIDAS scores was not significant (-5.47 ± 23.19 ; $P = .3595$ by t -test). At 3 months, the percentage of subjects with $\geq 50\%$ improvement in MIDAS scores was significantly greater for those receiving BoNTA than for placebo (61.8% vs 5.9%, respectively; $P = .0001$ by chi-square).

MIQ.—For the MIQ during the blinded study, at month 3, subject global assessment scores improved by 1.97 ± 1.36 ($P < .0001$) for subjects receiving BoNTA and by 0.89 ± 1.45 ($P = .0195$) for placebo recipients. The improvement seen in the BoNTA group was significantly greater than that in the placebo group ($P = .0104$). Global assessment scores

for BoNTA also improved significantly during the open-label period (2.11 ± 1.49 at month 6 vs baseline; $P = .0001$).

At the end of the blinded trial, subjects in the BoNTA group showed significant improvement from baseline in all MIQ parameters regarding “satisfaction with treatment,” except “effectiveness of prescription treatments” and “amount of money spent on migraine preventive treatment”; in contrast, subjects in the placebo group showed no improvement relative to baseline in any of them (Table 3). Improvement in scores for the BoNTA group separated statistically from the scores for the placebo group for several of these parameters, including efficacy of treatment for frequency and severity of migraine symptoms. BoNTA yielded significant improvements in a number of parameters in the open-label period as well, including efficacy of treatment for frequency and severity of migraine, side effects, and amount of money spent on migraine preventive treatment.

At 3 months, BoNTA was significantly better than placebo in each QoL parameter assessed. Table 4 shows subject responses to the series of

Table 3.—MIQ Results: Patient Satisfaction with Treatment of Migraine Symptoms (Blinded and Open-Label Periods)

	Study period	Botulinum toxin type A (<i>P</i> value)	Placebo (<i>P</i> value)	<i>P</i> value (between-group)
Effectiveness of non-Rx treatment	BP	1.12 ± 1.20 (.0001*)	-0.33 ± 1.50 (.5156)	.0028†
	OLP	0.33 ± 1.73 (.5796)		
Effectiveness of Rx treatment	BP	0.48 ± 1.62 (.1448)	0.42 ± 1.39 (.2500)	.7833
	OLP	0.47 ± 1.33 (.1635)		
Effectiveness of current Tx on frequency of migraine symptoms	BP	1.38 ± 1.72 (<.0001*)	0.00 ± 1.32 (1.0000)	.0109†
	OLP	1.29 ± 1.68 (.0135*)		
Effectiveness of current Tx on severity of migraine symptoms	BP	1.52 ± 1.77 (<.0001*)	0.11 ± 1.37 (.8633)	.0021†
	OLP	0.81 ± 1.22 (.0179*)		
Feelings with current preventive migraine treatment	BP	1.67 ± 1.85 (.0012*)	0.36 ± 1.91 (.5703)	.0868
	OLP	0.82 ± 2.32 (.2685)		
Side effects of current preventive migraine treatment	BP	1.71 ± 1.79 (.0009*)	0.50 ± 1.57 (.3750)	.0506
	OLP	1.36 ± 1.12 (.0024*)		
Number of doses required for migraine preventive treatment	BP	1.29 ± 1.95 (.0137*)	-0.15 ± 1.72 (.6992)	.0348†
	OLP	0.77 ± 2.20 (.2322)		
Overall effectiveness of current migraine preventive treatment	BP	1.44 ± 2.13 (.0169*)	0.11 ± 0.93 (1.0000)	.0900
	OLP	0.70 ± 2.26 (.3536)		
Ability to self-manage migraine symptoms	BP	1.00 ± 1.33 (<.0001*)	-0.11 ± 1.29 (.8518)	.0084†
	OLP	0.89 ± 1.75 (.0453*)		
Amount of money spent on migraine preventive treatment	BP	1.00 ± 2.12 (.1016)	0.00 ± 0.00	.3294
	OLP	1.17 ± 0.98 (.0335*)		

**P* < .05 vs baseline. Within-group analysis during blinded period by signed rank test. Within-group analysis during open-label period by *t*-test.

†*P* < .05 botulinum toxin type A vs placebo. Between-group analysis during blinded period by Wilcoxon test.

BP = blinded period; data shown is for month 3. OLP = open-label period; data shown is for month 6; Rx = over the counter medication; Tx = treatment. Values expressed as mean ± SD.

questions focusing on QoL (presented as mean change from baseline). Baseline scores for subjects receiving BoNTA and placebo were similar for each question. For all 6 questions, improvements were noted (decreasing values denote improvement) at each point in the 3-month, blinded study for subjects receiving BoNTA but not placebo. During the open-label period with BoNTA, statistically significant improvements were shown at each month (months 4 to 6) for “mood,” “normal work,” and “enjoyment of life,” and in months 4 and 5 for “sleep,” “ability to walk or move about,” and “recreational activities.”

In the MIQ, subjects rated their current migraine symptoms compared with 3 months previously (5-point scale from -2 to +2). The BoNTA group showed improvement over the course of the blinded period while those receiving placebo did not (Fig. 5). At months 2 and 3, the improvements in subjects receiving BoNTA were significant compared with placebo.

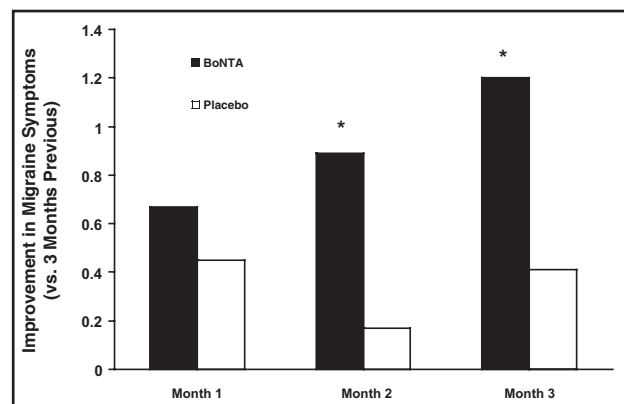


Fig 5.—Mean change from baseline in improvement of migraine symptoms (current symptoms compared with 3 months ago) on a 5-point scale from -2 to +2. Data from the quality of life portion of the Migraine Impact Questionnaire are presented as mean change from baseline ± SD for 3 months of the blinded period (months 1 to 3). **P* < .05 for between-group comparisons: botulinum toxin type A (BoNTA) vs placebo (Wilcoxon rank-sum test).

Table 4.—Migraine Impact Questionnaire Results: Quality of Life (Blinded Period)

Question	Month	Botulinum toxin type A (<i>P</i> value)	Placebo (<i>P</i> value)	<i>P</i> value (between group)
1 Mood	1	-0.54 ± 1.23 (.0136*)	-0.20 ± 1.06 (.5176)	.3784
	2	-0.84 ± 1.22 (.0001*)	-0.33 ± 1.08 (.1975)	.1302
	3	-1.11 ± 1.18 (<.0001*)	-0.39 ± 0.92 (.1465)	.0375†
2 Ability to walk or move about	1	-0.46 ± 1.07 (.0125*)	-0.10 ± 1.07 (.7449)	.2010
	2	-0.66 ± 1.07 (.0004*)	0.11 ± 0.90 (.7949)	.0153†
	3	-0.60 ± 1.09 (.0015*)	0.17 ± 0.79 (.5625)	.0169†
3 Sleep	1	-0.74 ± 1.31 (.0007*)	-0.35 ± 0.81 (.1191)	.3436
	2	-0.76 ± 1.10 (<.0001*)	-0.06 ± 1.21 (1.0000)	.0389†
	3	-0.83 ± 1.04 (<.0001*)	-0.22 ± 0.81 (.3984)	.0458†
4 Normal work	1	-0.72 ± 1.05 (<.0001*)	-0.35 ± 0.93 (.1699)	.3211
	2	-0.87 ± 1.14 (<.0001*)	-0.11 ± 0.90 (.7949)	.0308†
	3	-1.09 ± 1.01 (<.0001*)	-0.33 ± 0.84 (.1826)	.0143†
5 Recreational activities	1	-0.51 ± 1.12 (.0066*)	0.11 ± 0.88 (.5547)	.0471†
	2	-0.58 ± 1.00 (.0005*)	0.33 ± 1.03 (.2734)	.0034†
	3	-0.86 ± 1.03 (<.0001*)	0.22 ± 1.17 (.5596)	.0041†
6 Enjoyment of life	1	-0.56 ± 1.17 (.0039*)	-0.20 ± 0.95 (.4839)	.3266
	2	-0.68 ± 1.30 (.0019*)	0.00 ± 1.08 (1.0000)	.0858
	3	-0.97 ± 1.10 (<.0001*)	-0.22 ± 1.06 (.4893)	.0348†

**P* < .05 vs baseline. Within-group analysis by Wilcoxon signed rank test.

†*P* < .05 for botulinum toxin type A vs placebo. Between-group analysis by Wilcoxon rank-sum.

Values expressed as mean ± SD.

Adverse Events.—At month 3 (blinded period), there were no treatment-related AEs reported in both groups. However, there were 18 possible/probable occurrences of treatment-related AEs in the BoNTA group. At month 6 (open-label period), 4 treatment-related AEs were reported, along with 2 possible occurrences. The majority of treatment-related AEs were transient and mild to moderate in severity, with no subjects discontinuing the study because of AEs.

DISCUSSION

Migraine incorporates features common to both chronic and episodic pain disorders; from the patients' and physicians' perspectives, it is best described as a chronic disorder with episodic manifestations.²⁸ As is true for other chronic pain disorders, the influence of migraine on disability and QoL issues is an important consideration. Thus, understanding its impact requires an ability to measure its effects in these areas. Increasingly, clinical assessment of such parameters has become an important addition to conventional measures of

headache frequency and severity for evaluation of migraine disorders and the impact of treatment.²⁹

In this study, we examined whether BoNTA prophylaxis of patients who had failed prior trials with other preventive medications resulted in beneficial effects on headache frequency and severity and on measures of disability and QoL. BoNTA had beneficial, albeit limited, effects on measures of migraine frequency and was not effective in lowering headache pain severity during the blinded study. However, this effect was measurable on QoL parameters by subject self-report.

A number of factors may have contributed to this limited response. First, based on baseline headache frequency data, the majority of subjects in this study would fall into the episodic migraine classification (eg, <15 migraine headache days per 30 days; International Classification of Headache Disorders [ICHD-II]).³⁰ Several large, well-controlled trials suggest that BoNTA has not been uniformly effective in reducing headache frequency and severity in patients with episodic migraine.^{17,20,26,31,32} Current data, however, do support the effectiveness of BoNTA in patients

suffering from chronic migraine disorder.^{19,21,33,34} Second, in many headache trials, it has been difficult for treatment modalities to separate from placebo because of generally high placebo effects.³⁵ In light of this, the relatively small group size in this study may not have provided sufficient statistical power to discern differences between the groups.

Contrary to the limited benefit shown in headache diary measures of frequency and severity, BoNTA clearly and consistently demonstrated effectiveness by measures of reduced migraine associated disability (MIDAS), reduced impact (HIT-6), and satisfaction with treatment and QoL (MIQ) in both the blinded and open-label portions of the study. Studies examining the effect of BoNTA treatment on measures of disability and impact of and satisfaction with treatment are limited. Analyses of BoNTA in episodic migraine^{17,20,26,31,32} make limited use of such subjective, questionnaire-based measures, utilize only global measures, and generally exhibit mixed results, with no benefit shown in some studies^{26,32} and some benefit seen in others.^{17,20,31} In contrast, a recent, prospective, open-label study of subjects (N = 61) with chronic (77%) or episodic (23%) migraine that used MIDAS as a primary tool to evaluate the effect of BoNTA found that 62% of subjects were 'responders' (had a $\geq 50\%$ improvement in migraine-related disability).³⁶ For the subgroup of subjects with episodic migraine, the responders' rate was 79%.³⁶ Further studies that focus more attention on "real-world" clinical outcomes as are captured by MIDAS, HIT-6, and other such tools are warranted.

In many of these previous studies, responses to treatment based on diary measures correlated well with responses on metrics such as MIDAS and QoL assessments.^{17,20,31} In this study, that correlation did not appear strong. This difference could be related to a number of subjects and treatment factors, including the small and more challenging nature of this patient population or the tendency for BoNTA to exhibit mixed efficacy results with episodic migraine. Alternatively, the limited correlation may be related to the recalcitrant nature of the study population, or it may reflect the considerable differences in methods of data collection and type between diary-based and questionnaire-based metrics. A recent analysis found

a correlation of 0.63 between headache diary measures and the MIDAS scores, which was considered to be in the "low moderate" range.³⁷ In another recent study that examined the correspondence among headache frequency, pain intensity, and disability (MIDAS) indices, the authors found that MIDAS scores were largely independent of data for self-reported frequency and pain intensity. They concluded that MIDAS captures unique information about the disabling consequences of headache.³⁸ This unique perspective may have important clinical correlation with the outcomes of patients in clinical care.

Various types of oral medication are used to prevent migraine, including β -blockers, antidepressants, antiepileptic agents, and calcium channel blockers.³⁹ The efficacy of these agents has been established in large, well-controlled clinical trials (see Silberstein et al, for review)⁴⁰; recent studies suggest beneficial effects on health-related QoL^{41,42} and resource utilization⁴³ as well.

However, numerous factors negatively influence migraineurs' compliance and adherence with preventive medication management paradigms and consequently severely undermine efficacy observed in clinical trials.³⁹ One obstacle to compliance and patient adherence is that patients may have unrealistically high expectations for immediate or complete relief of migraine or discontinuation of acute treatment medications.⁴² Another challenge is compliance with daily dosing regimens, dosage titration schedules, and the frequency of required medical follow-up; one study found that although the pill counts indicated that the mean compliance rate was 91%, electronic time recordings showed that only 66% of patients were in fact taking their oral prophylaxis as prescribed.^{39,44} This is problematic for management of migraine patients in that at least 2-3 months of medication with titration to an appropriate daily dosage is needed to obtain accurate results in a clinical trial. A third difficulty is that because prophylactics are preventive rather than curative, there is less incentive for adhering to a dosage schedule (as compared with a direct relationship between symptoms and relief from intake of a drug).^{42,44}

In addition, most preventive medications have side effects deemed undesirable by patients, such as

weight gain, drowsiness, fatigue, dizziness, and decreased libido, which contribute to failed adherence to the program. Anxiety regarding the possibility of such effects as well as intolerance related to interactions with drugs prescribed to treat other medical conditions may hinder compliance. Cost of daily medications is also a factor that affects patients' willingness to adhere to prophylactic regimens.⁴²

The exploratory study design, lacking defined primary and secondary outcomes, is a limitation that should be considered in evaluating the results of this study. In addition, the lack of clear primary and secondary analyses in the analytical plan inflated the actual type 1 error rate of the study. Furthermore, the per protocol statistical analysis is limited by the failure to include a combination of analyses of variance, including analyses of covariance. The results should be interpreted with these factors in mind.

BoNTA, as demonstrated in this study and others,^{17-21,31-34} is a generally well-tolerated and safe therapy that has been used extensively to treat a variety of neuromuscular disorders.¹² BoNTA's favorable tolerability profile and relatively infrequent dosing regimen, coupled with its beneficial effects on patient disability, migraine impact, and QoL, suggest that it is useful for preventive management of migraine disorder and may be especially helpful for patients that experience or would be predicted to have an issue with compliance, adherence, or AEs. Based on the promising results of this exploratory study, further analysis of this patient population in larger, well-controlled studies is warranted.

Dosing and results in this study are specific to the formulation of the BoNTA manufactured by Allergan, Inc. (Irvine, CA). The Allergan, Inc. formulation is not interchangeable with other botulinum toxin products and cannot be converted using a dose ratio.

Acknowledgments: The authors wish to acknowledge the contributions of Ogilvy Healthworld Medical Education (New York, NY) to the writing of this article and Ethica Clinical (Montreal, Quebec, Canada) for statistical analysis.

This study was sponsored by Allergan, Inc., Irvine, CA.

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache*. 2001;41:646-657.
2. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: Epidemiology and patterns of health care use. *Neurology*. 2002;58:885-894.
3. World Health Organization. Headache disorders. Fact sheet No. 277. 2004. Geneva, Switzerland. <http://www.who.int/mediacentre/factsheets/fs277/en/>. Accessed February 12, 2007.
4. Gallagher RM, Mueller LL, Freitag FG. Divalproex sodium in the treatment of migraine and cluster headaches. *J Am Osteopath Assoc*. 2002;102:92-94.
5. Cady R, Farmer K, Dexter JK, Schreiber C. Cosensitization of pain and psychiatric comorbidity in chronic daily headache. *Curr Pain Headache Rep*. 2005;9:47-52.
6. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. *Headache*. 2006;46:1334-1343.
7. Badia X, Magaz S, Gutierrez L, Galvan J. The burden of migraine in Spain: Beyond direct costs. *Pharmacoeconomics*. 2004;22:591-603.
8. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: Disability and economic costs. *Arch Intern Med*. 1999;159:813-818.
9. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist*. 2006;12:204-213.
10. Lipton RB, Diamond M, Freitag FG, Bigal M, Stewart WF, Reed ML. Migraine prevention patterns in a community sample: Results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2005;45:792. Abstract F38.
11. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.
12. Aoki KR. Botulinum toxin: A successful therapeutic protein. *Curr Med Chem*. 2004;11:3085-3092.
13. Dolly O. Synaptic transmission: Inhibition of neurotransmitter release by botulinum toxins. *Headache*. 2003;43(Suppl. 1):S16-S24.
14. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain*. 2004;107:125-133.

15. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache*. 2003;43(Suppl. 1):9-15.
16. Durham PL, Cady R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: Implications for migraine therapy. *Headache*. 2004;44:35-43.
17. Silberstein S, Mathew N, Saper J, Jenkins S, for the BOTOX® Migraine Clinical Research Group. Botulinum toxin type A as a migraine preventive treatment. *Headache*. 2000;40:445-450.
18. Silberstein S. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2005;80:1126-1137.
19. Mathew N, Frishberg BM, Gawel M, et al. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45:293-307.
20. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: A preliminary study. *J Headache Pain*. 2003;4:146-151.
21. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD. Botulinum toxin type A for the prophylaxis of chronic daily headache: Subgroup analysis of patients not receiving other prophylactic medications: A randomized double-blind, placebo-controlled study. *Headache*. 2005;45:315-324.
22. BOTOX® [Package Insert]. Irvine CA: Allergan, Inc.; 2004.
23. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(Suppl. 7):1-96.
24. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: The HIT-6. *Qual Life Res*. 2003;12:963-974.
25. Nachit-Ouinekh F, Dartigues JF, Henry P, et al. Use of the headache impact test (HIT-6) in general practice: Relationship with quality of life and severity. *Eur J Neurol*. 2005;12:189-193.
26. Elkind A, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. *J Pain*. 2006;10:688-696.
27. Stewart WF, Lipton RB, Whyte J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology*. 1999;53:988-994.
28. Lipton RB, Bigal ME, Stewart WF. Clinical trials of acute treatment for migraine including multiple attack studies of pain, disability, and health-related quality of life. *Neurology*. 2005;65(Suppl. 4):S50-S58.
29. Osterhaus JT, Townsend RJ, Gandek B, Ware JE Jr. Measuring the functional status and well-being of patients with migraine headache. *Headache*. 1994;34:337-343.
30. International Headache Society. The International Classification of Headache Disorders, 2nd edition. Headache Classification Subcommittee of the International Headache Society. *Cephalalgia*. 2004;24(Suppl. 1):1-160.
31. Aurora SK, Gawel M, Brandes JL, Pokta S, VanDenburgh AM, for the BOTOX North American Episodic Migraine Study Group. Botulinum toxin type A prophylactic treatment of episodic migraine: A randomized, double-blind, placebo-controlled exploratory study. *Headache*. 2007;47:486-499.
32. Relja M, Poole A, Schoenen J, Pascual J, Lei X, Thompson C, for the European BoNTA Headache Study Group. A multicenter, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A for the prophylaxis of episodic migraine headaches. *Cephalalgia*. 2007;27:492-503.
33. Saper J, Brandes J, Wrubel B, Dodick D, DeGryse R, VanDenburgh AM. Efficacy of prophylactic treatment with botulinum toxin type A in migraineurs with chronic daily headache overusing acute headache pain medications [abstract]. *Headache*. 2005;45:825. Abstract S115.
34. Freitag F, McAllister D, Freund B, Schwartz M, DeGryse R, Barron R. Botulinum toxin type A for the prophylaxis of chronic daily headache in migraineurs: Effect on acute headache pain medication use [abstract]. *Headache*. 2005;45:827. Abstract S119.
35. Tfelt-Hansen P, Block G, Dahlof C, et al. Guidelines for controlled trials of drugs in migraine: Second edition. *Cephalalgia* 2000;20:765-786.
36. Eross EJ, Gladstone JP, Lewis S, Rogers R, Dodick D. Duration of migraine is a predictor for response to botulinum toxin type A. *Headache*. 2005;45:308-314.

37. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain*. 2000;88:41-52.
38. Stewart WF, Lipton RB, Kolodner K. Migraine Disability Assessment (MIDAS) Score: Relation to headache frequency, pain intensity, and headache symptoms. *Headache*. 2003;43:258-265.
39. D'Amico D, Lanteri-Minet M. Migraine preventive therapy: Selection of appropriate patients and general principles of management. *Expert Rev Neurother*. 2006;6:1147-1157.
40. Silberstein SD, Lipton RB. Chronic daily headache. *Curr Opin Neurol*. 2000;13:277-283.
41. Diamond M, Dahlof C, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache*. 2005;45:1023-1030.
42. D'Amico D, Solari A, Usai S, et al. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. *Cephalalgia*. 2006;26:691-696.
43. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache*. 2003;43:171-178.
44. Mulleners WM, Whitmarsh TE, Steiner TJ. Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better. *Cephalalgia*. 1998;18:52-56.