
Research Submission

Botulinum Toxin Type A in the Treatment of Chronic Migraine Without Medication Overuse

Frederick G. Freitag, DO; Seymour Diamond, MD; Merle Diamond, MD; George Urban, MD

Introduction.—Chronic migraine is a recent diagnostic term that has undergone evolution from its original description. Clinically it has been believed that medication overuse contributed to its development and would block attempts at prevention. Previous studies with Botulinum Toxin Type A have demonstrated that it is effective even in patients with medication overuse. This study undertakes to examine the effects of Botulinum Toxin Type A in the absence of medication overuse in patients with chronic migraine.

Study Design.—Double-blind placebo-controlled randomized trial of Botulinum Toxin Type A 100 units administered in a fixed dose and site paradigm.

Patients.—In total, 86 patients were enrolled. A total of 60 patients were randomized and 41 patients were treated with the study medication or placebo. Five patients failed to complete the study, which lasted 4 months after the study medication was injected.

Results.—Botulinum Toxin Type A was statistically superior to placebo for the primary endpoint of reduction in migraine headache episodes. Six patients on Botulinum Toxin Type A compared with 3 patients on Placebo had at least a 50% reduction in their migraine episodes. Active treatment was superior to placebo for the secondary endpoints of total headache days, headache index, and quality of life measures. It showed numerical superiority to placebo for acute medication use and Migraine Disability Assessment Scores. Adverse events were rare and similar in both treatment groups.

Conclusions.—The use of Botulinum Toxin Type A may be an effective treatment for chronic migraine when the patient does not have concomitant medication overuse. It was well tolerated in this trial.

Key words: Botulinum Toxin Type A, chronic migraine, medication overuse headache, headache index

Abbreviations: BoNTA Botulinum Toxin Type A, CM chronic migraine, MOH medication overuse headache, HAI headache index

(*Headache* 2008;48:201-209)

From the Diamond Headache Clinic, Chicago, IL, USA (Drs. Freitag, Diamond, Diamond, and Urban); Department of Family Medicine, Chicago Medical School at Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA (Dr. Freitag); Family Medicine, Chicago College of Osteopathic Medicine/Midwestern University, Downers Grove, IL, USA (Dr. Freitag); Chicago Medical School at Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA (Dr. Diamond); Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA (Drs. Diamond and Urban).

Address all correspondence to Dr. Fred G. Freitag, Diamond Headache Clinic, 467 W. Deming Pl., Chicago, IL 60614, USA.

BOTOX® is approved by the United States Food and Drug Administration for the treatment of cervical dystonia and other indications but is not yet approved for treatment of post-stroke spasticity or chronic headache.

Accepted for publication August 22, 2007.

Conflict of Interest: This analysis was supported by Allergan, Inc., Irvine, CA, USA. Dr. Freitag has received research grant support and consulting fees from Allergan.

INTRODUCTION

Migraine headaches occur in approximately 18% of women and 6% of men, resulting in significant disability, decreased quality of life (QOL), and a major financial burden on society.¹ Migraine patients may be at risk for progression of their disease to a more chronic form of the disorder marked by an increase in the frequency of headache days.¹⁻⁴ Chronic migraine (CM) is in the subset of the chronic daily headache (CDH) disorders. At the time of the study, it was not recognized by the International Headache Classification Committee as a distinct diagnosis. CM was first characterized by Silberstein and Lipton,^{5,6} and includes: head pain occurring on 15 or more days per month, headache duration of 4 or more hours and increasing headache frequency with decreasing symptom severity over a 3-month period.^{5,6} CDH comprises a group of heterogeneous disorders characterized by the occurrence of headaches at least 15 days per month.⁷ While most CDH patients are categorized as having transformed migraine (TM),^{8,9} others may have chronic tension type headache. TM is often associated with medication overuse headache (MOH).^{10,11} Patients with CM may have MOH or they may evolve for other reasons.

Preventive migraine treatment is recommended for patients experiencing frequent, severe, recurring migraines that interfere with daily activity.¹² From the American Migraine Prevalence and Prevention Study, it was estimated that 38.8% of patients with migraine were candidates for preventive medications yet only 13% were currently receiving potential treatment.¹³ At the time of this study, clinical trials had been conducted in CDH but not in CM.

It was traditionally believed that patients are refractory to preventive treatments until acute headache pain medications are withdrawn.¹⁴ Overuse of medication to treat headaches, such as analgesics, ergotamine, and triptans, can contribute to the symptoms of chronic headache disorders and often confounds both diagnosis and prevention of CM.^{9,15-17} It had been traditionally believed that patients with MOH were relatively refractory to preventive medications until they had been withdrawn from these offending agents.¹⁴ The definition used for MOH in itself is one that has only recently come in to use with

the current International Classification of Headache Disorders, 2nd edition (ICHD-II) and has evolved further since its publication. At the time of the trial, headaches could be “induced” by acute headache medications or there could be headaches associated with “abuse” of acute headache medications (ICHD-I),¹⁸ in both cases termination of the offending agent was required to prove the diagnosis, a situation which continued to exist until the most recent revision of the classification of MOH. Even though the ICHD did not recognize the terminology of MOH and CM at the time this study was initiated, many clinicians in the United States had begun to attempt to define what they appreciated clinically among their patients.

Many CM patients have MOH as a coexisting process, which may influence the effectiveness of preventive medications. In 2 large placebo-controlled trials,^{19,20} Botulinum Toxin Type A (BoNTA) has been demonstrated safe and efficacious in patients with CM. Patients with CM with MOH had a robust response to treatment with BoNTA. However, a substantial proportion of patients with CM do not have MOH associated with it. There is a need to assess the efficacy and safety of BoNTA in patients not overusing acute medications. Furthermore, these studies of CM have not specifically separated out the effects of MOH and therefore have failed to address the true effectiveness of BoNTA in CM without MOH.

METHODS

Participants.—Patients were recruited for the study who met the diagnosis of CM as defined by Silverstein and Lipton; that is, the patients had head pain occurring on 15 or more days per month with headache duration of 4 or more hours. The headache frequency had been increasing, however; the associated symptoms had been decreasing in severity over a 3-month period. Patients were recruited from the outpatient clinic population as well as from research department database. A nationwide institutional review board approved the protocol and informed consent. Patients were provided with written informed consent. After obtaining written informed consent male and female patients between the ages of 18 and 65 years underwent a review of their general medical and surgical history and their headache history was

obtained. They had a brief general physical examination and vital signs obtained along with a neurological examination.

Patients were required to have a 6-month history, prior to baseline, of CM. In addition, they were required to have migraine episodes meeting the criteria 1.1 or 1.2 of the ICHD-I and 15 headache days during the prospective baseline phase. If they were on preventive medications, then they must have been on stable doses of preventive medications for 60 days prior to study entry and be willing to remain on them at those same doses for the duration of the study. Females were required to be practicing an acceptable method of contraception and have a pregnancy test or to be incapable of pregnancy.

Patients were excluded from the study if they had taken previous botulinum toxin of any serotype for any therapeutic reason. Additionally, if they had a history of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or other disorder of neuromuscular function or if they were using concomitant aminoglycoside antibiotics, curare-like agents or other agents that might interfere with neuromuscular function, they were excluded. Patients with diagnoses of migraine beginning for the first time after age 50 years, cluster headaches or basilar, ophthalmoplegic, or hemiplegic migraine, exclusively having migraine aura without headache also were excluded. Patients were excluded if they had a more painful condition than their migraine pain, progressive neurological disorders, or a structural disorder of the brain from birth, trauma, or past infection. Patients were excluded if they had received injections or oral corticosteroids within 30 days prior to the baseline diary initiation visit. Patients with a significant major psychiatric disorder (eg, major depression) or receiving antipsychotic medication, or who had a Beck Inventory of Depression Scores greater than 24 were also excluded. Patients who have received an investigational drug or used an investigational device within 30 days of study entry could not participate.

At the time of the study, medication overuse guidelines were not specific. We utilized the following criteria (Table 1). Patients were excluded from study enrollment or from randomization to treatment if they were taking triptans more than 3 days per week,

Table 1.—Criteria for Medication Overuse Headache

Type of medication	Medication overuse criteria
Simple analgesics	>1000 mg aspirin/ acetaminophen, >5 days/week
Combination analgesics (caffeine, barbiturate- containing medication)	>3 tablets/day, >3 days/week
Narcotics	>1 tablet/day, >2 days/week
Any combination of above	>4 days/week
Ergotamine/dihydroergotamine	1 dose/day >2 days/week
Triptans	1 dose/days >3 days/week
Any combination of ergots/triptans	1 dose>2 days/week
Caffeine	>500 mg/day

ergotamine more than 2 days per week, or dihydroergotamine more than 2 days per week. Patients were also excluded from enrollment if they were taking any combination of the above medications more than 3 days per week.

Patients were excluded from enrollment in the study if they were consuming caffeine from dietary and medicinal sources in excess of 500 mg per day on a daily basis in excess of 28 days prior to study enrollment.

Analgesic exclusions were for patients taking opioids more than 2 days per week, simple analgesics on average more than 2 tablets per day 5 or more days per week for at least 28 days. Additionally, those taking combination analgesics on average more than 3 tablets per day and 3 or more days per week for at least 28 days were also excluded from enrollment or randomization. Patients were excluded from enrollment or randomization to treatment if they were using a combination of any of the previous on 4 or more days per week for at least 28 days.

All patients after providing written informed consent were enrolled in the study. They entered a 28-day screening phase to assess for the inclusion and exclusion criteria. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized to their respective treatment groups to receive either BoNTA or placebo and entered the baseline diary phase. Patients were provided with instruction in keeping their headache diary at the end

Table 2.—Study Drug Injection Sites and Dosage of BoNTA

	Total units	Number of injections
Glabella	20	4
Temporal	20	4
Frontal	10	4
Suboccipital	30	6
Trapezius	20	4
Total	100	22

BoNTA = Botulinum Toxin Type A.

of baseline diary phase, patients continuing to fulfill study criteria had a brief physical examination and vitals signs and received treatment with either BoNTA 100 units or an identical appearing placebo injection.

Patients were seen subsequently at 4-week intervals for the remaining 16 weeks of the study. At each study, visit diaries were collected and reviewed, Migraine Disability Assessment Scores (MIDAS) and quality of life assessments made. The patient was queried regarding adverse events. At the final visit, the patient also underwent a brief physical examination.

Headache diary data collected consisted of date and duration (clock times) of each headache the patient experienced. For each headache, the patient noted the maximal pain experienced associated symptoms with the headache of nausea, vomiting, photophobia, phonophobia, exacerbation by physical activity, location, pain characteristics, medication taken, and dosing. Additionally, the patient kept record in the diary of any adverse events experienced including start and stop date and severity, concomitant medications, and reason(s) for use.

Interventions.—Botulinum Toxin Type A (BOTOX[®], Allergan, Inc., Irvine, CA, USA) 100 units or placebo (sterile saline) in identical volumes was administered subcutaneously using a fixed dose and site paradigm as outlined below (Table 2).

OBJECTIVES

The objective of this study was to assess the efficacy and safety of BoNTA compared with placebo in the treatment of CM not associated with MOH.

Outcomes.—The primary efficacy parameter was the change in monthly migraine episode frequency per 4-week assessment period compared with baseline. Secondary efficacy parameters also assessed change from the baseline by 4-week assessment periods for the BoNTA and placebo groups.

These assessments included the change number of total headache days, and the headache index (HAI). The HAI (Table 3) being calculated by multiplying the maximal severity of a headache in a headache days times the duration of the headache in fraction of the 24-hour day the headache was experienced by the patient, summing the total of all the headaches for the evaluation period then dividing by the number of the days in the evaluation period.

Additional secondary outcome parameters assessed included the 50% responder rate (the percentage of patients who experience a 50% or greater reduction in their monthly migraine episode frequency), change in the amount of acute medication used, change in MIDAS, and change in the Headache Pain Specific Quality of Life measure. Safety and tolerability were determined by the presence and severity of adverse effects (AEs) in each treatment group.

Sample Size.—There had been no previous studies in CM and the trials that had been conducted with BoNTA to date at the time of the study initiation ranged from small to large without apparent correlation of study outcome to number of participants. For this pilot trial, an estimated 60 patients were to be enrolled and treated.

Randomization.—This was a double-blind placebo-controlled randomized study. Patients were blind to their treatment allocation and randomized to active or placebo treatment using a list generated in

Table 3.—Headache Index (HAI)

$$\frac{\sum [\text{maximal headache severity} \times (\text{duration of the headache in hours} / 24 \text{ hours})]}{\text{days in evaluation period}}$$

Microsoft Excel (Redmond, WA, USA). The study medication BoNTA or placebo was prepared by a registered nurse in the research department familiar with the preparation of BoNTA following the pre-assigned randomization schedule. The research nurse responsible for the monitoring of the patient, review of diary logs, and completion of case report forms was different from the nurse preparing the study medication. The study medication was delivered to the injecting physician in identical appearing syringes for subcutaneous injection. Each syringe contained an identical amount of solution. The injecting physician did not have access to the randomization code and was not involved in the preparation of the study medication.

Statistical Methods.—Statistical comparisons were made using analysis of covariance (ANCOVA) using SPSS software version 11.5 (Chicago, IL, USA) for the primary outcome parameter and the secondary outcome parameters other than the adverse events, which were assessed by tabulation, and the 50% responder rate for which no statistical comparison was made. Missing data were handled by last observation carried forward.

RESULTS

Flow of Patients (Fig 1).—In total, 86 patients provided informed consent and were enrolled in the study. A total of 26 patients, however, were discontinued prior to randomization to BoNTA or placebo

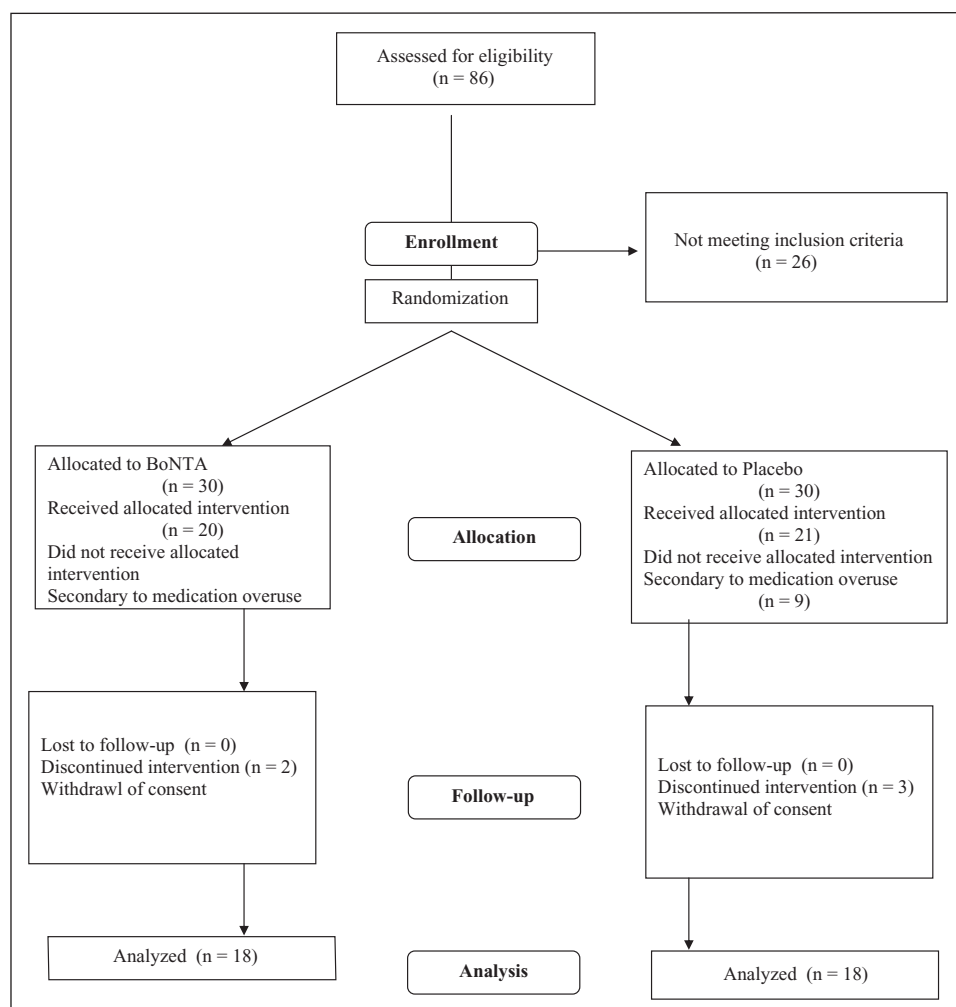


Fig 1.—Patient flow.

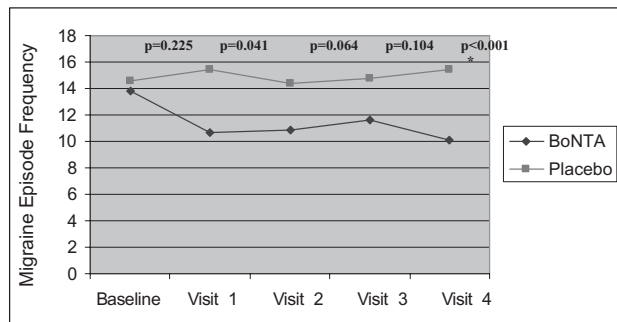


Fig 2.—Reduction in monthly migraine episode frequency following BoNTA treatment. BoNTA = Botulinum Toxin Type A.

for failure to meet criteria for CM during the screening baseline phase having less than 15 migraine headache episodes and less than 15 headache days during the baseline period. Additionally, 19 patients failed to randomize secondary to medication overuse during the baseline phase. In total, 41 patients were randomized and received treatment with either BoNTA 100 units per the previous described treatment protocol or identically appearing placebo. In total, 41 patients were included in the intent-to-treat (ITT) analysis. In total, 20 of these patients were randomized to and received BoNTA. A total of 21 patients were in the ITT group that received placebo. Five patients discontinued the trial prior to completion of the entire 4-month active treatment phase. Two of these patients were in the BoNTA group and 3 were in the placebo group. None of these patients withdrew from the study related to efficacy or tolerability issues related to the study drug. All 41 patients were considered in the intent to treat analysis and safety analysis.

Baseline Data.—A total of 41 patients were randomized and received treatment with the study medication and included in the ITT analysis. BoNTA patients were a mean age of 42.2 years (range: 19-64), with 15 females and 5 males and all but 2 were Caucasian. The placebo group similarly was almost exclusively Caucasian (one Pacific Islander) with 15 females and 6 males and a mean age of 42.4 ranging from 25 to 55 years of age.

Outcomes and Estimation.—The primary outcome parameter was the change in the number of monthly migraine episodes. This declined in the BoNTA arm from 13.8 during baseline to 9.6 (–31%) in the final

month and from 14.6 attacks during baseline for placebo to 13.3 (–8.9%) at the final visit ($P < .001$, Correlation Coefficient = 0.963) (Fig. 2).

Statistical significant change was seen by the first month following treatment when the attack frequency for BoNTA dropped to 10.7 but rose to 15.4 for placebo ($P = .041$, Correlation Coefficient = 0.515). Comparing baseline to end of study for BoNTA, the decline in attack frequency from 13.8 to 10.1 attacks per month was statistically significant ($P = .001$, Correlation Coefficient = 0.695), compared with the change for the placebo arm frequency at baseline of 14.6 rising to 15.4 at end of study ($P = .046$, Correlation Coefficient = 0.475).

Six of 18 (33%) completers on BoNTA had at least a 50% reduction in migraine episodes compared with 3 of 18 (16.7%) placebo patients.

The HAI (Fig. 3) declined from a mean of 18 at the baseline visit to a mean of 14.2 (–21%) ($P > .001$, Correlation Coefficient = 0.754) at the last 4-week assessment in the placebo arm compared with a decline from means of 20.3 to 14.2 (–30.5%) ($P > .001$, Correlation Coefficient = 0.820) in the BoNTA treatment arm at the same time points. At the 16 weeks following treatment, there was a statistical difference between BoNTA and P ($P = .003$, Correlation Coefficient = 0.754). There were no statistical differences for this endpoint at other study time points.

Total days with headache in a 28-day evaluation period declined for both the BoNTA and P. At baseline, both groups had a mean of 23 days with headache per 28-day period (range 16-28 days for both groups). There was a statistically significant difference between the treatment groups from beginning to end

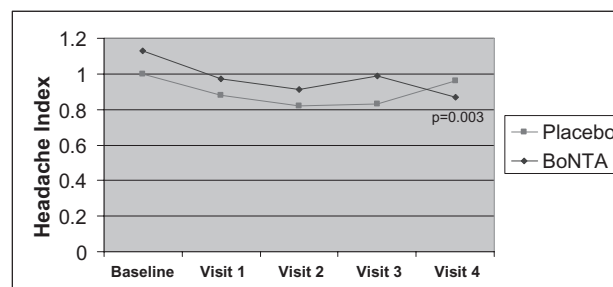


Fig 3.—Headache index (HAI). BoNTA = Botulinum Toxin Type A.

of study for BoNTA ($P > .001$, Correlation Coefficient 0.797) and for P ($P > .001$, Correlation Coefficient 0.881). At the last visit, there was a statistically significant decline from the baseline visit in favor of BoNTA with 19 total headaches days/28 days compared with 21 days for P ($P = .018$, Correlation Coefficient = 0.549).

Acute medications were totaled across all types and formulations. There was substantial variation in acute medication use within both groups. At baseline, the BoNTA group used an average of 19 doses per month (range 5-46 doses) as compared with P with a mean of 21 doses per month per patient (range 5-36 doses) ($P = .174$, Correlation Coefficient = 0.335). At the final visit, acute medication use had declined to 18 doses per month per patient for the BoNTA group (range 0-48) but did not change for P (21 doses per month, range 0-60) ($P = .72$, Correlation Coefficient = 0.089).

Several other measures were also employed to assess outcome. These were the MIDAS, and change in the Headache Pain Specific Quality of Life measure. MIDAS scores at baseline were 62 in the BoNTA group and 61 in P ($P = .259$, Correlation Coefficient = -0.289). While the BoNTA group improved by 11 points to a final MIDAS score of 51 and the P group worsened to a score of 63, these changes were not significant ($P = .445$, Correlation Coefficient = 0.199). For both BoNTA and P, the changes from baseline to end of trial were significantly different ($P = .004$, Correlation Coefficient 0.646 for BoNTA and $P = .019$, Correlation Coefficient = -0.563 for P).

The QOL instrument revealed no substantial difference between BoNTA and P at baseline. Cumulative score mean 164 for BoNTA (range 80-244) and 169 for P (range 19-262) ($P = .769$, Correlation Coefficient = 0.074). There was a positive trend which did not reach significance for the difference in QOL scores between BoNTA and P. Final QOL cumulative score mean for BoNTA was 178 (range 50-260) compared with P with a final score of 191 (range 44-282) ($P = .078$, Correlation Coefficient 0.426). While the change from baseline to end study was not significantly different for P ($P = .192$, Correlation Coefficient = 0.322), there was a significant change for BoNTA ($P = .013$, Correlation Coefficient = 0.570).

Table 4.—Adverse Events

Adverse event	Botulinum Toxin Type A	Placebo
Fever	0	2
Backache	0	1
Panic attack	0	1
Heaviness of arm	0	1
Confusion	0	1
Chest heaviness	0	1
Stiff neck	1	1
Dizziness	0	1
Sinus infection	2	0
Hair loss	1	0
Amenorrhea	1	0

Adverse Events.—There were relatively few adverse events reported in this study and there was little difference in the frequency or nature of adverse events reported between BoNTA and P groups. Adverse events are summarized in Table 4.

DISCUSSION

This controlled study demonstrated clinical benefit among BoNTA-treated CM patients whose condition was not aggravated by the effect of medication overuse. There were significant reductions in migraine episodes beginning with the first month of treatment. BoNTA was significant superior both compared with P and from the baseline to the end of trial. Twice the number of patients had a 50% or greater reduction in their migraine episodes for the BoNTA group compared with placebo. On other parameters such as total days with headache, the HAI, MIDAS score, and QOL measure BoNTA demonstrated improvement at last visit compared with baseline and in the case for total headache days and QOL was significant superior to P. Acute medication use trended in favor of BoNTA as well.

Given the refractory nature of CM and the idea that the frequency of headache episodes may be a strong predictor of migraine progression,²¹ BoNTA may also help to prevent headache progression by reducing headache frequency. This study supports recent evidence, which shows BoNTA to be an effective prophylactic treatment for CDH in migraineurs.^{19,20,22} The magnitude of response in

monthly migraine frequency obtained in this trial was not as substantial as previous trials in migraineurs with CDH. This may be due to the lower dosage in this trial (100 U vs 105-260 U¹⁹ and 75-225 U²⁰ in previous trials), the lack of repetitive treatment cycles, and/or the inclusion of patients overusing acute medications in previous trials, who seemed particularly responsive to BoNTA.^{19,20}

The small number of AEs in this study demonstrates the high level of safety and tolerability of BoNTA as preventive CM therapy.

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

Acknowledgment: Financial support for this study was provided by an unrestricted grant from Allergan Pharmaceuticals.

REFERENCES

1. Lipton RB, Bigal ME. Migraine: Epidemiology, impact and risk factors for progression. *Headache*. 2005;45(Suppl. 1):S3-S13.
2. Lipton RB, Pan J. Is migraine a progressive brain disease? *JAMA*. 2004;291:493-494.
3. Bigal ME, Lipton RB. When migraine progresses: Transformed or chronic migraine. *Expert Rev Neurother*. 2006;6:297-306.
4. Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology*. 2004;62:788-790.
5. Silberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near-daily headaches: Proposed revisions to the IHS criteria. *Headache*. 1994;34:1-7.
6. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: Field trial of IHS criteria. *Neurology*. 1996;47:871-875.
7. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders (second edition). *Cephalalgia*. 2004;24(Suppl. 1):1-160.
8. Mathew NT. Transformed migraine. *Cephalalgia*. 1993;13:78-83.
9. Silberstein SD, Lipton RB. Chronic daily headache. *Curr Opin Neurol*. 2000;13:277-283.
10. Zwart JA, Dyb G, Hagen K, Svebak S, Stovner LJ, Holmen J. Analgesic overuse among subjects with headache, neck, and low-back pain. *Neurology*. 2004;62:1540-1544.
11. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology*. 2002;59:1011-1014.
12. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-762.
13. 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;65:792.
14. Olesen J, Tfelt-Hansen P, Ramadan N, Goadsby PJ, Welch KMA. *The Headaches*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
15. Kavuk I, Yavuz A, Cetindere U, Agelink MW, Diener HC. Chronic headache: A focus on medication overuse. *Eur J Med Res*. 2004;9:285.
16. Silberstein SD, Lipton RB, Goadsby PJ. Chronic daily headache: Diagnosis and treatment. *Headache in Clinical Practice*, 2nd edn. London: Martin Dunitz Ltd; 1998:101-114.
17. Saper JR, Dodick D, Gladstone JP. Management of chronic daily headache: Challenges in clinical practice. *Headache*. 2005;45(Suppl. 1):S74-S85.
18. International Headache Society. International Classification of Headache Disorders II, section 8.2. *Cephalalgia*. 2004;25:460-465.
19. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C, BOTOX CDH Study Group. 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. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC, BoNTA-039 Study Group. 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.

21. Fanciullacci M, De Cesaris F. Preventing chronicity of migraine. *J Headache Pain*. 2005;6:331-333.
22. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD, BOTOX CDH Study Group. 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;45:293-307.