Research Submission

A Double-Blind Comparison of OnabotulinumtoxinA (BOTOX®) and Topiramate (TOPAMAX®) for the Prophylactic Treatment of Chronic Migraine: A Pilot Study

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Background.—There is a need for effective prophylactic therapy for chronic migraine (CM) that has minimal side effects.

Objective.—To compare the efficacy and safety of onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) and topiramate (TOPAMAX®, Ortho-McNeil, Titusville, NJ) prophylactic treatment in patients with CM.

Methods.—In this single-center, double-blind trial, patients with CM received either onabotulinumtoxinA, maximum 200 units (U) at baseline and month 3 (100 U fixed-site and 100 U follow-the-pain), plus an oral placebo, or topiramate, 4-week titration to 100 mg/day with option for additional 4-week titration to 200 mg/day, plus placebo saline injections. Onabotulinumtoxin A or placebo saline injection was administered at baseline and month 3 only, while topiramate oral treatment or oral placebo was continued through the end of the study. The primary endpoint was treatment responder rate assessed using Physician Global Assessment 9-point scale (+4 = clearance of signs and symptoms and −4 = very marked worsening [about 100% worse]). Secondary endpoints included the change from baseline in the number of headache (HA)/migraine days per month (HA diary), and HA disability measured using Headache Impact Test (HIT-6), HA diary, Migraine Disability Assessment (MIDAS) questionnaire, and Migraine Impact Questionnaire (MIQ). The overall study duration was approximately 10.5 months, which included a 4-week screening period and a 2-week optional final safety visit. Follow-up visits for assessments occurred at months 1, 3, 6, and 9. Adverse events (AEs) were documented.

Results.—Of 60 patients randomized to treatment (mean age, 36.8 ± 10.3 years; 90% female), 36 completed the study at the end of the 9 months of active treatment (onabotulinumtoxinA, 19/30 [63.3%]; topiramate, 17/30 [56.7%]). In the topiramate group, 7/29 (24.1%) discontinued study because of treatment-related AEs vs 2/26 (7.7%) in the onabotulinumtoxinA group. Between 68% and 83% of patients for both onabotulinumtoxinA and topiramate groups reported at least a slight (25%) improvement in migraine; response to treatment was assessed using Physician Global Assessment at months 1, 3, 6, and 9. Most patients in both groups reported moderate to marked improvements at all time points. No significant between-group differences were observed, except for marked improvement at month 9 (onabotulinumtoxinA, 27.3% vs topiramate, 60.9%, $P = .0234$, chi-square). In both groups, HA/migraine days decreased and MIDAS and HIT-6 scores improved. Patient-reported quality of life measures assessed using MIQ after treatment with onabotulinumtoxinA paralleled those seen after treatment with topiramate in most respects. At month 9, 40.9% and 42.9% of patients in the onabotulinumtoxinA and topiramate groups, respectively, reported ≥50% reduction in HA/migraine days. Forty-one treatment-related AEs were reported in 18 onabotulinumtoxinA-treated patients vs 87 in 25 topiramate-treated patients, and 2.7% of patients in the onabotulinumtoxinA group and 24.1% of patients in the topiramate group reported AEs that required permanent discontinuation of study treatment.

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Conflict of Interest: Dr. Mathew is on the scientific advisory board of Merck, Allergan, and Ortho-McNeil. He is also on the speaker's bureau for Merck, GSK, Endo Pharmaceuticals, and Allergan. Dr. Jaffri has nothing to disclose.

Conclusions.—OnabotulinumtoxinA and topiramate demonstrated similar efficacy in the prophylactic treatment of CM. Patients receiving onabotulinumtoxinA had fewer AEs and discontinuations.

Key words: onabotulinumtoxinA, chronic migraine, prophylaxis, adverse events, headache, BOTOX, TOPAMAX, topiramate

Abbreviations: AE adverse event, CDH chronic daily headache, CM chronic migraine, CTTH chronic tension-type headache, HA headache, HRQoL health-related quality of life, HIT-6 Headache Impact Test, MIDAS Migraine Disability Assessment, MIQ Migraine Impact Questionnaire, QoL quality of life, SD standard deviation, U units

INTRODUCTION

In the United States, headaches (HAs) are the 7th leading presenting complaint in ambulatory medical care.[1] Migraine HA affects ~12% of the adult population in Western countries.[2] Chronic migraine (CM) is a severely disabling condition that results in a substantial financial burden for those affected and for societal healthcare systems.[3] Previously described as transformed migraine,[4,5] CM is now the accepted terminology to describe the condition of very frequent (≥15 HA days per 30 days for >3 months) migraine attacks.[6]

For many, especially those with chronic HA, acute pharmacologic and nonpharmacologic treatments are not sufficient. Prophylactic treatment of chronic daily headache (CDH) and CM to reduce the frequency and severity of HA has become an important option for these patients.[7] Furthermore, almost all CM patients require prophylactic treatment to reduce the overuse of acute HA pain medications, which is more common in the CM population compared with the other CDH subtypes, ie, chronic tension-type headache (CTTH) and new daily persistent HA.[4,8] Recent studies suggest that a substantial portion of patients who could benefit from preventive therapy are not receiving it.[3,9] In fact, one CM population-based study reported that only 33.3% of those with CM were currently using preventive medications.[3]

A number of drug classes in clinical use for the prevention of migraine HA, including β-blockers, antidepressants, antiepileptic agents, and calcium channel blockers[2] have demonstrated efficacy and safety.[10] However, tolerability issues often arise that may result in poor adherence to prescribed regimens.[11] To date, only topiramate, gabapentin, tizanidine, fluoxetine, amitriptyline, and onabotulinumtoxinA have been investigated as prophylactic treatment in the CDH or CM population in randomized, double-blind, placebo-controlled, or active comparator-controlled clinical trials.[7,12,13]

OnabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) is a neurotoxin that reversibly blocks presynaptic acetylcholine release. It has been shown to be effective in reducing myogenic pain associated with cervical dystonia,[14-16] chronic limb spasticity,[17] and hand dystonia.[18] In large multicenter, randomized, placebo-controlled phase II trials in patients with CDH, onabotulinumtoxinA has been shown to be safe, tolerable, and effective in several key measures, such as the reduction of 50% or more in the frequency of HA days at 6 months.[19,20] OnabotulinumtoxinA has been postulated to prevent migraine attacks by inhibiting peripheral sensitization and thereby indirectly reducing progression of central sensitization.[21-23]

Topiramate (TOPAMAX®, Ortho-McNeil, Titusville, NJ) is approved by the US Food and Drug Administration for migraine prophylaxis. Several studies indicate efficacy with daily doses of 100 mg and 200 mg of topiramate.[24,25]

The current pilot study was conducted to compare the efficacy and safety of onabotulinumtoxinA and topiramate prophylactic treatment in patients with CM. The primary endpoint was treatment responder rate.

METHODS

Study Design and Treatment Protocol.—This was a single-center, prospective, double-blind study performed in patients diagnosed with CM who were naïve to onabotulinumtoxinA and topiramate.
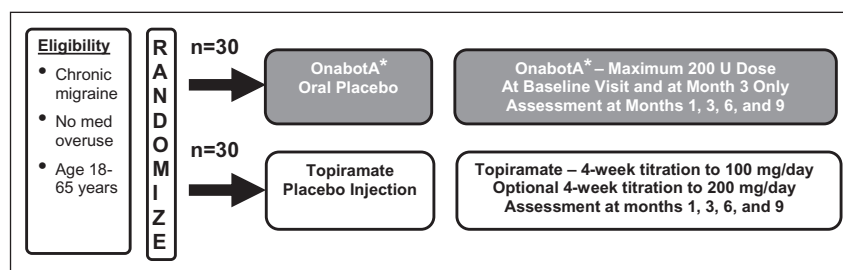
Fig 1.—Flow diagram of study protocol. *OnabotulinumtoxinA.

Patients were randomized to 1 of 2 treatment groups (Fig. 1): onabotulinumtoxinA or topiramate. The maximum dose of onabotulinumtoxinA was 200 U at the baseline visit and month 3 (100 U fixed-site and 100 U follow-the-pain) plus an oral placebo (manufactured to be identical in appearance to 25 mg tablets of topiramate). Patients randomized to receive topiramate were given a 4-week titration to 100 mg/day, with an optional (at investigator's discretion) additional 4-week titration to 200 mg/day plus placebo (saline) injections. Patients receiving oral placebo also underwent the same method of titration employed in the topiramate group. Therapy with topiramate or oral placebo commenced with 25 mg/day for week 1; then the dose was increased 25 mg/week until a total daily dose of 100 mg or 200 mg was achieved, as necessary. OnabotulinumtoxinA treatment or placebo injection was completed with the month 3 injection, while topiramate oral treatment or oral placebo continued through the end of the study.

Prior to study initiation, investigators received Research Ethics Board approval. This study was conducted in compliance with the Declaration of Helsinki ethical principles on biomedical research on human patients and with consent regulations. Patients were required to be able to understand the requirements of the study, including completing questionnaires, maintaining an HA diary, and signing informed consent and American Health Insurance Portability and Accountability Act forms (Supplements I and II).

The overall duration of the study was approximately 10.5 months. A screening visit occurred at month −1, followed by randomization and a baseline visit at day 0. Follow-up visits for assessments occurred at months 1, 3, 6, and 9. A final optional safety visit approximately 2 weeks after month 9 was included to ensure that the patient had safely discontinued study medication. For patients who left the study prematurely, every effort was made to complete the month 9 assessments at the time of exit. Patients were encouraged to report any adverse events (AEs) to the investigator between scheduled study visits.

Inclusion Criteria.—The study included outpatient male and female patients of any race between the ages of 18 and 65 years who were diagnosed with CM not attributable to another cause. CM HA[5,26] was defined as migraine HA with or without aura occurring on ≥15 days/month for >3 months in the absence of medication overuse. HA had at least 2 of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and/or aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs). Also, at least 1 of the following occurred during HA: nausea and/or vomiting or photophobia and/or phonophobia. Patients were required to have stable HA severity and pattern as determined by the investigator; and HA data for at least 6 months prior to study drug administration (day 0).

Exclusion Criteria.—The following criteria were grounds for exclusion: female patients who were pregnant (positive urine pregnancy test) or planning to become pregnant during the study period, were breast feeding, or were of childbearing potential and not practicing a reliable method of birth control; patients with CTTH based on recognized criteria[26] and as assessed by the investigator; patients with evidence of underlying conditions judged to preclude treatment with either test medication; patients who previously used study medications for any reason; patients unable to discontinue any prohibited

medication(s), including carbonic anhydrase inhibitors (eg, acetazolamide, dichlorphenamide), digoxin, metformin, central nervous system depressants (including alcohol), nonstudy migraine prophylaxis medications (eg, propranolol, amitriptyline, divalproex sodium), nonstudy anticonvulsant or anti-epileptic medications, agents that might interfere with neuromuscular function (eg, aminoglycoside antibiotics, curare-like agents), or hormonal contraceptives; or patients with evidence of recent alcohol/drug abuse or acute medication overuse. Acute HA medication overuse was verified based on the patient's history.

Primary and Secondary Endpoints.—The primary endpoint was the treatment responder rate based on the 9-point Physician Global Assessment, Response to Treatment metric (where +4 = clearance of signs and symptoms and −4 = very marked worsening [about 100% worse]). Patients achieving ≥+2 (ie, improvement of 50% or greater) were treated as treatment responders. Secondary endpoints assessed included mean change from baseline in number of HA/migraine days per month, HA/migraine-free days per month, days on HA medication, and average severity of HA/migraine episodes per month taken from data included in the patient HA diaries. Impact of HA disorder and associated disability, including quality of life (QoL), was assessed through the Headache Impact Test (HIT)-6, Migraine Disability Assessment (MIDAS) questionnaire, and Migraine Impact Questionnaire (MIQ). From the MIQ, the amount of money spent by the patient on prescription and nonprescription drugs was also assessed. Safety and tolerability of the treatment regimens were assessed by monitoring frequency and severity of AEs and frequency and reasons for premature withdrawal from the study.

STATISTICAL ANALYSES

Because this was a pilot study, no formal statistical sample size justification was provided. To detect a clinically significant difference of 35% between treatment groups for treatment responder rates, it was necessary to enroll 30 patients per treatment group for a total of 60 patients. Descriptive statistics were included as mean ± standard deviation (SD) for continuous variables; categorical data were summarized by way of frequency and number of occurrences for each modality of the analyzed variable.

The value of continuous variables at each visit was compared between groups with Student *t*-test or Wilcoxon rank sum test, depending on data normality, which was ruled out if the *P* value for the Shapiro-Wilk test was below .01 in either group.

Comparisons in change from baseline in continuous variables were performed using analysis of covariance (ANCOVA), adjusting for baseline value. If the latter did not have an influence in the model, the same method as described above (*t*-test/Wilcoxon rank sum test) was used. If the baseline value had a significant effect in the model but the other assumptions for ANCOVA were not satisfied, comparisons were performed using the nonparametric equivalent of the ANCOVA, rank ANCOVA.

The value ordinal data at each visit were compared across groups using Wilcoxon rank sum test. Comparisons in change from baseline in ordinal data were performed with a rank ANCOVA, or Wilcoxon rank sum test if the baseline value did not have an influence on the dependent variable in the rank ANCOVA model.

Chi-square tests (or Fisher's exact tests if the chi-square test turned out to be invalid) were utilized for analysis of demographic data, frequency of responders, and frequency of AEs. Paired *t*-test or Wilcoxon signed rank test were used for within-group comparisons, depending on data normality. No attempt was made to adjust for multiple comparisons.

All statistical analyses were conducted using the SAS 9.1 software (SAS, Cary, NC). All tests were 2-sided at the .05 significance level. Last observation carried forward (LOCF) was used to account for missing observations in patients who discontinued the study before the final visit due to treatment-related AEs. All data are presented as mean ± SD, unless otherwise noted.

RESULTS

Demographics and Baseline Data.—A total of 60 patients were enrolled in this study: 30 in the onabotulinumtoxinA group and 30 in the topiramate group. The majority of patients were female (54/60; 90%) and white (46/60; 76.7%). The mean age was

36.8 ± 10.3 years. Patients in the onabotulinumtoxinA and topiramate groups differed in age at onset of migraine (14.9 ± 7.2 and 20.0 ± 9.2 years for the onabotulinumtoxinA and topiramate groups, respectively; $P = .0151$), but not on any other meaningful baseline parameters, including cardiovascular function, or use of caffeine, alcohol, or tobacco. On day 0, patients received a mean dose of 143.7 ± 27.2 U of onabotulinumtoxinA, and at the month 3 visit patients received a mean dose of 142.2 ± 25.7 U of onabotulinumtoxinA. The average oral dose of topiramate administered in month 1 was 92.6 ± 24.1 mg, and in month 9 was 106.9 mg ± 27.1. Topiramate oral dose was increased by 25 mg/week to month 1 in 89.4% (42/47) patients, and was titrated to higher doses over the following 4 weeks in 25.5% (12/47) of

patients. Patients were permitted to take their usual acute HA medications for acute attacks during the study. A majority of patients were taking triptans, nonsteroidal anti-inflammatory drugs, or nasal dihydroergotamine.

Patient Disposition.—At month 9, the study was completed by 63.3% (19/30) of patients in the onabotulinumtoxinA group and 56.7% (17/30) of patients in the topiramate group (Fig. 2). The primary reasons for not completing the study included those lost to follow-up (8 and 5 in the onabotulinumtoxinA and topiramate groups, respectively) and those who discontinued because of AEs (3 and 8 in the onabotulinumtoxinA and topiramate groups, respectively).

Although only 33 patients completed the study at month 9 or 9.5 (month 9.5 was an optional safety
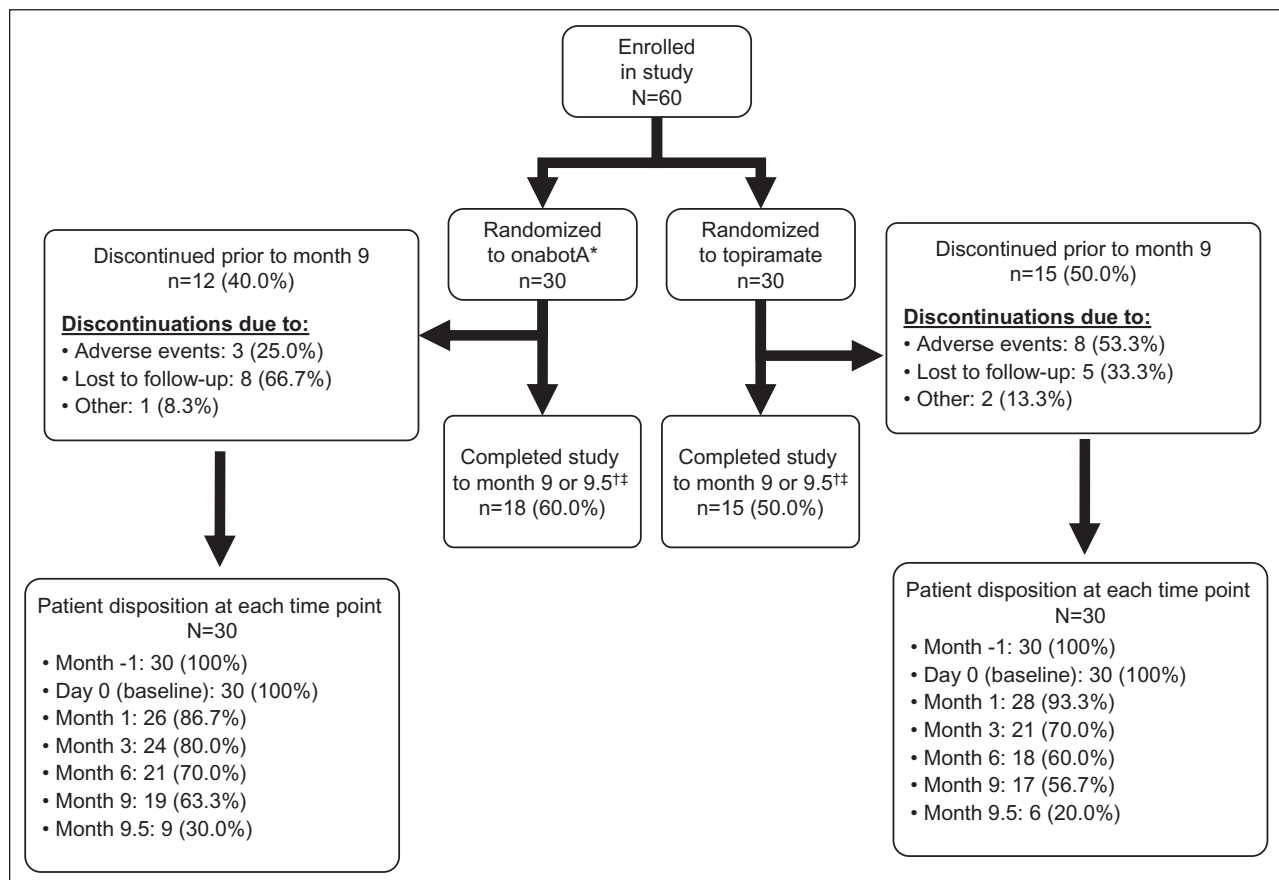

Fig 2.—Patient disposition. *OnabotulinumtoxinA. [†]Although only 33 patients (onabotulinumtoxinA + topiramate) completed the study at month 9 or 9.5, 3 patients performed the final month 9 visit, albeit earlier than scheduled. Provision was made to account for the 9 patients who discontinued the study early due to an AE at least possibly related to the study treatment. Therefore, 45 patients were assessed using the last observation carried forward technique at month 9 (2 patients did not have any postbaseline diary data so the number was limited to 43 for all diary variables). [‡]Month 9.5 was an optional safety visit.

visit), 3 patients performed the final month 9 visit, albeit earlier than scheduled. Moreover, provision was made for the 9 patients who discontinued the study early due to an AE at least possibly related to the study treatment: the LOCF technique was applied to account for these patients. Therefore, 45 patients were assessed at Month 9 (2 of them did not have any post-baseline diary data so that number is limited to 43 for all diary variables).

Physician Global Assessment – Response to Treatment.—Between 68% and 83% of patients showed at least a slight improvement (25%) in migraine at each of the month 1, 3, 6, and 9 assessments for both the onabotulinumtoxinA and topiramate groups (Fig. 3). Most patients in both groups reported moderate to marked improvements at all time points. No significant differences between the onabotulinumtoxinA and topiramate groups were noted, except for the percentage of patients reporting marked improvement at the month 9 assessment (27.3% vs 60.9% for the onabotulinumtoxinA and topiramate groups, respectively; $P = .0234$, chi-square). However, the final onabotulinumtoxinA/placebo injection occurred at month 3, while topiramate/oral placebo treatment continued through study end.

Headache/Migraine Days, Headache/Migraine-Free Days, Average Headache/Migraine Severity.—At baseline (day 0), patients in the onabotulinumtoxinA group reported 15.6 ± 7.0 HA/migraine days and patients in the topiramate group reported 15.5 ± 7.2 HA/migraine days. The number of HA/migraine days decreased for patients in both the onabotulinumtoxinA and topiramate groups, with no differences between groups noted (Fig. 4). At month 3, 10/26 (38.5%) and 5/22 (22.7%), month 6, 14/24 (58.3%) and 7/22 (31.8%), month 9, 9/22 (40.9%), and 9/21 (42.9%) patients in the onabotulinumtoxinA and topiramate groups, respectively, reported ≥50% reduction in HA/migraine days. HA/migraine-free days/30 days increased at months 3, 6, and 9 by 5.3 ± 4.7, 7.4 ± 5.7, and 5.2 ± 5.9 days from baseline for patients in the onabotulinumtoxinA group and by 4.2 ± 5.5, 5.3 ± 4.9, and 5.8 ± 6.5 days from baseline
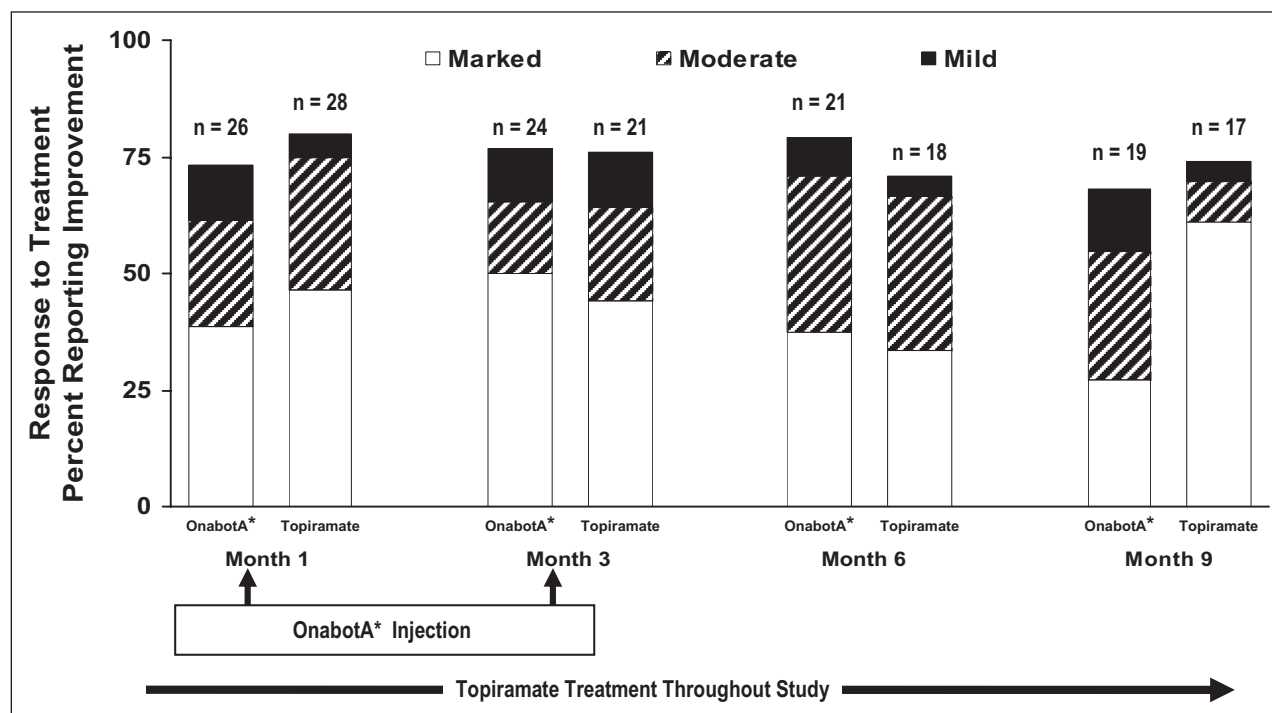

Fig 3.—Most patients reported improvement in migraine with onabotulinumtoxinA or topiramate. Marked improvement indicates at least a 75% improvement, moderate improvement indicates at least a 50% improvement, and mild improvement indicates at least a 25% improvement. *OnabotulinumtoxinA.
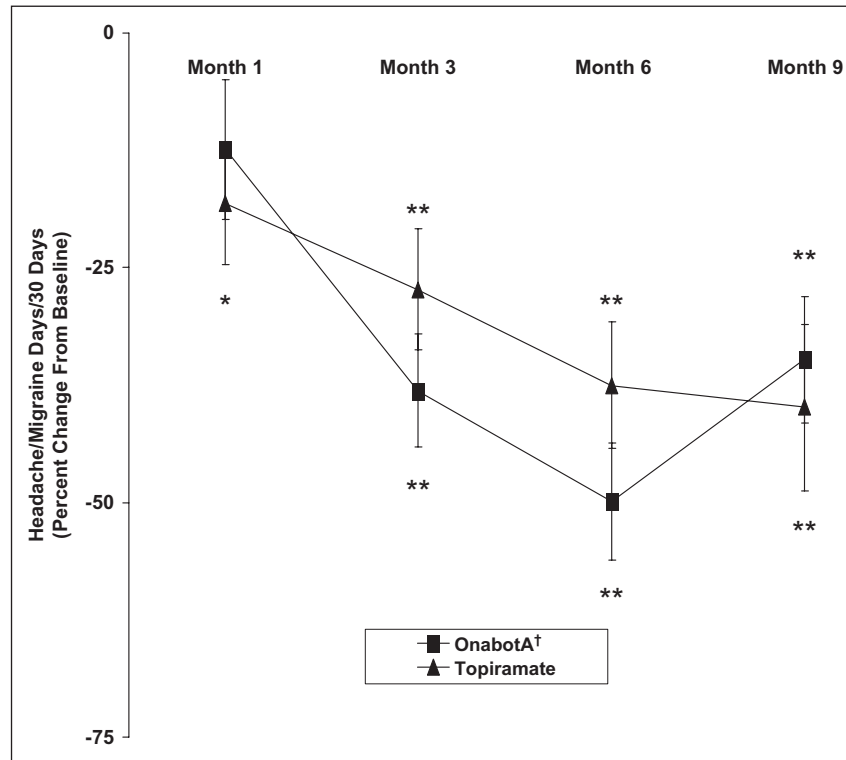
Fig 4.—HA/migraine days per 30 days decreased with onabotulinumtoxinA or topiramate. *P < .01 vs baseline, t-test; **P < .001 vs baseline, t-test. †OnabotulinumtoxinA. Data are reported as mean ± standard error (SE).

for patients in the topiramate group, respectively ($P < .001$ for both groups vs baseline, t-test). The average severity of HA/migraine, measured on a 5-point scale, with 5 being severe and 1 being mild, decreased at months 3, 6, and 9 by 0.20 ± 0.46, 0.09 ± 0.50, 0.23 ± 0.49 points from a baseline of 2.87 ± 0.83 for patients receiving onabotulinumtoxinA ($P = .0466$ vs baseline at month 3, $P = .4023$ vs baseline at month 6, and $P = .0513$, borderline significance vs baseline at month 9, t-test) and by 0.37 ± 0.78, 0.50 ± 0.79, and 0.44 ± 0.77 points from a baseline of 2.82 ± 0.71 for patients receiving topiramate, respectively ($P = .0506$ borderline significance vs baseline at month 3, $P = .0128$ vs baseline at month 6, and $P = .03$ vs baseline at month 9, t-test).

Migraine Disability Assessment.—The MIDAS total scores at baseline (day 0) were 34.12 ± 28.93 and 56.03 ± 66.48 for patients in the onabotulinumtoxinA and topiramate groups, respectively. At month 3, MIDAS total scores decreased by 10.48 ± 24.09 for patients in the onabotulinumtoxinA group (borderline significance vs baseline;

$P = .0541$, t-test) and by 33.30 ± 53.06 for patients in the topiramate group ($P < .0001$, signed rank). Before treatment, 75.9% (22/29) in the onabotulinumtoxinA group and 76.7% (23/30) in the topiramate group recorded MIDAS total scores >21 (severe disability). At month 3, 26.1% (6/22) of patients in the onabotulinumtoxinA group and 35.0% (7/20) of patients in the topiramate group recorded scores >21. Further, 55.0% (11/22) of patients in the onabotulinumtoxinA group and 63.2% (12/20) of patients in the topiramate group reported ≥50% improvement in the MIDAS total score.

The improvements seen at month 3 were also seen at the month 6 assessment. At month 6, MIDAS total scores decreased by 11.34 ± 22.38 for patients in the onabotulinumtoxinA group ($P = .0046$ vs baseline, signed rank) and decreased significantly more, by 46.28 ± 75.66, for patients in the topiramate group ($P < .0001$ vs baseline, signed rank, and $P = .0086$ vs onabotulinumtoxinA, rank ANCOVA). At month 9, 81.3% of patients in the onabotulinumtoxinA group and 93.8% in the topiramate group showed at least a

25% improvement in the MIDAS total scores (no between-group differences were observed).

HIT-6.—Patients in both groups (93.3% and 90.0% in the onabotulinumtoxinA and topiramate groups, respectively) reported severe impact (HIT-6 scores >60) of migraine HA at baseline. Mean HIT-6 scores were 65.20 ± 5.08 and 65.73 ± 5.43 for patients in the onabotulinumtoxinA and topiramate groups, respectively, at baseline. At month 3, HIT-6 scores decreased similarly in patients in both groups (−3.46 ± 6.16; $P = .0114$ vs baseline, t-test and −6.70 ± 5.85; $P < .0001$ vs baseline, t-test in the onabotulinumtoxinA and topiramate groups, respectively). The percentage of patients reporting severe impact decreased to 66.7% and 60.0% in the onabotulinumtoxinA and topiramate groups, respectively. Decrease in the percentage of patients reporting severe impact was maintained in both groups at months 6 and 9. Improvements in mean HIT-6 scores were also maintained in both groups at months 6 and 9: −5.62 ± 6.41 and −3.47 ± 5.23 ($P = .0004$ and $P = .0097$ vs baseline, t-test) at 6 and 9 months, respectively, in the onabotulinumtoxinA group and −10.44 ± 7.07 and −8.76 ± 7.44 ($P < .0001$ and $P = .0002$ vs baseline, t-test; $P = .0283$ and $P = .0178$ vs onabotulinumtoxinA, t-test) at 6 and 9 months, respectively, in the topiramate group.

Migraine Impact Questionnaire.—Patient-reported QoL measures after treatment with onabotulinumtoxinA paralleled those seen after treatment with topiramate in most respects. Patients in both groups reported significant improvements from baseline in average HA pain at months 1 and 6, but not at months 3 and 9. HA pain decreased from baseline values of 6.87 ± 1.70 and 6.67 ± 1.77 by 1.15 ± 2.05 and 1.04 ± 2.05 at month 1 ($P < .01$ for both groups, t-test) and by 0.50 ± 1.10 and 1.30 ± 2.69 at month 6 ($P < .05$ for both groups; onabotulinumtoxinA, t-test; topiramate, signed rank) for the onabotulinumtoxinA and topiramate groups, respectively. Patients in both groups reported a decrease in the number of days worked with migraine HA at months 1, 3, and 6. Number of days worked with migraine symptoms decreased from baseline values of 21.24 ± 25.15 and 25.50 ± 29.59 by 14.24 ± 26.25 and 17.89 ± 25.26 days at month 1 for the onabotulinumtoxinA and topiramate groups, respectively ($P < .001$ for both

groups, signed rank). Decreases were sustained at similar levels in both groups through month 6 (data not shown). At month 9, the topiramate group showed a significant decrease in the number of days worked with migraine HA, but not the onabotulinumtoxinA group. Patients in both groups reported a decrease in the amount of money spent on nonprescription and prescription drugs for HA. At month 3, patients receiving onabotulinumtoxinA reported a significant decrease in money spent on both nonprescription (−24.04 ± 43.41, $P = .0036$, signed rank) and prescription (−68.65 ± 203.46, $P = .0205$, signed rank) drugs, while patients receiving topiramate reported a significant decrease in nonprescription drugs only (nonprescription: −62.00 ± 132.71, $P = .007$; prescription: −31.87 ± 121.68, $P = .0654$; signed rank). At month 6, patients receiving onabotulinumtoxinA did not report a significant decrease in money spent on prescription (−32.00 ± 151.52, $P = .3517$, signed rank) and nonprescription (−10.71 ± 80.07, $P = .0773$, signed rank) drugs, while patients receiving topiramate reported a significant decrease in both (nonprescription: −66.13 ± 148.04, $P = .0147$; prescription: (−52.74 ± 118.54, $P = .0378$; signed rank). Topiramate also showed a significant decrease in money spent on prescription (−67.24 ± 121.73, $P = .0066$, signed rank) and nonprescription (−69.15 ± 131.03, $P = .0106$, signed rank) medication at month 9, while onabotulinumtoxinA had a significant decrease in nonprescription medications only (nonprescription: −23.45 ± 41.16, $P = .0047$; prescription: −12.95 ± 49.00, $P = .1035$; signed rank). Based on the HA diary, days on HA medication were reduced significantly from baseline at months 3 (−4.33 ± 4.34, $P < .0001$, t-test), 6 (−6.06 ± 5.23, $P < .0001$, t-test), and 9 (−4.48 ± 5.90, $P = .0018$, t-test) in the onabotulinumtoxinA group and at months 1 (−2.15 ± 4.63, $P = .0231$, t-test), 3 (−2.53 ± 4.82, $P = .0226$, t-test), 6 (−4.06 ± 5.36, $P = .0019$, t-test), and 9 (−4.02 ± 6.68, $P = .0122$, t-test) in the topiramate group. At baseline, days on HA medication were 13.15 ± 6.34 in the onabotulinumtoxinA group and 10.76 ± 5.98 in the topiramate group.

Safety and Tolerability.—Patients with at least 1 postbaseline visit or reporting an AE were included in the safety analysis: 26 patients in the onabotulinum-

Table 1.—Summary of Adverse Events (AEs) (Most AEs Were Mild to Moderate With OnabotulinumtoxinA or Topiramate)

		OnabotulinumtoxinA	Topiramate
	N	26	29
All AEs	Events	93	133
	Patients	26	28
Drug-related AEs	Events	41 (44.1%)	87 (65.4%)
	Patients	18 (69.2%)	25 (86.2%)
Probable/possible drug-related AEs	Events	55 (59.1%)	103 (77.4%)
	Patients	22 (84.6%)	26 (89.7%)
Permanently discontinued due to AEs[†]	Patients	2 (7.7%)	7 (24.1%)

[†]Permanently discontinued treatment because of definite or probable drug-related AE.

toxinA group and 29 patients in the topiramate group were included (Table 1). One hundred percent (26/26) of patients in the onabotulinumtoxinA group and 96.6% (28/29) of patients in the topiramate group reported at least 1 AE; 69.2% (18/26) of patients in the onabotulinumtoxinA group and 86.2% (25/29) of patients in the topiramate group reported AEs that were definitively linked to study treatment; 7.7% (2/26) of patients in the onabotulinumtoxinA group and 24.1% (7/29) of patients in the topiramate group reported treatment-related AEs that required permanent discontinuation of study treatment. There was no significant difference in overall incidence of AEs between the groups.

Qualitative and quantitative differences in the types of AEs were noted (Table 2). Most definite and probable drug-related AEs in patients in the onabotulinumtoxinA group were characterized by weakness in muscle groups in the local vicinity of injection sites around the head and neck. Most definite and probable drug-related AEs in the patients in the topiramate group were characterized by systemic effects, such as cognitive deficits, paresthesias, and loss of appetite and/or weight loss. Patient-reported incidence and impact of AEs parallel the findings in Tables 1 and 2. The proportion of patients reporting eyelid droop was greater in the onabotulinumtoxinA vs the topiramate group at months 1, 3, and 6 (the

Table 2.—Treatment-Related Adverse Events (AEs)

Most Common AEs (≥3 events)				
	OnabotulinumtoxinA		Topiramate	
	Definite	Probable	Definite	Probable
Weakness in eyebrow/eyelids	13	0		
Weakness in forehead/neck	6	3		
Paresthesias	3	0	14	11
Pain in head	2	2		
Sleepiness/tiredness/fatigue/dizziness	2	1	3	1
Depression/mood disturbance			5	1
Appetite/weight loss			8	1
Cognitive deficits			15	0
Night sweats			2	1
Dry mouth/thirst			1	3
Blurred vision/vision problems			2	2

between-group comparison did not reach statistical significance at month 3). The proportion of patients reporting tingling (numbness), difficulty concentrating (memory difficulties), and dry mouth was greater in the topiramate group than in the onabotulinumtoxinA group at months 1, 3, and 6 (the between-group comparison of difficulty concentrating did not reach statistical significance at month 6).

DISCUSSION

The findings of this study demonstrate that the efficacy of onabotulinumtoxinA as a preventive treatment for CM was indistinguishable from topiramate in both degree and consistency of benefit over time. A high percentage of patients in both the onabotulinumtoxinA and topiramate groups showed response to treatment, with the majority showing moderate-to-marked response. Some differences, however, were noted between the groups at month 9 (Fig. 3). There was a decrease in the percentage of patients with marked improvement in the onabotulinumtoxinA group at month 9. This observation is as expected because studies in HA patients and patients receiving onabotulinumtoxinA for other indications, such as cervical dystonia, suggest that onabotulinumtoxinA beneficial effects typically subside after 8-16 weeks.[19,20,27] In this study, the effects of the final injection administered at month 3 may have subsided by month 9 (~24 weeks since the last onabotulinumtoxinA injection). Despite the diminished effects of the final onabotulinumtoxinA injection, no significant between-group differences were noted in the number of HA/migraine days per month parameter. Both treatments showed a decrease from baseline of 27-50% in the number of HA/migraine days per month at months 3, 6, and 9. In addition, more than 40% of patients in both groups reported ≥50% reduction in HA/migraine days at month 9 (Fig. 4), indicating that the duration of effect of the final onabotulinumtoxinA injection lasted beyond 16 weeks. However, the authors would like to emphasize the pilot nature of this study and the fact that this study could have only detected very large differences between the 2 regimens because the small sample size prevented any comparison from being significant.

This is the first randomized, controlled comparison of onabotulinumtoxinA with another preventive agent for CM. Placebo-controlled trials of onabotulinumtoxinA in migraine and CM have had mixed results in demonstrating benefit over placebo. Separation from placebo was not seen for onabotulinumtoxinA in the primary endpoints of change in HA-free days at the prespecified time point (180 days) in patients who did not have a previous response to placebo.[19,20] However, benefit was evident in secondary endpoints, such as the percentage of patients who experienced ≥50% response and the decrease from baseline in frequency of HA at the prespecified time point.

Although onabotulinumtoxinA and topiramate resulted in similar efficacy in this study, the 2 treatments resulted in different AE profiles. Most of the AEs seen with onabotulinumtoxinA were related to chemodenervation of muscles around the forehead and eyes, leading to eyelid and eyebrow droop or muscle weakness in the head and neck areas where the injections were made. Most of the AEs seen with topiramate treatment were central and peripheral nervous system effects, such as cognitive deficits and paresthesias. The overall discontinuation rate in this study was 36.7% in the onabotulinumtoxinA group and 43.3% in the topiramate group, with AEs being the primary reason for withdrawal in the topiramate group and lost to follow-up in the onabotulinumtoxinA group. Of note is the difference between treatment groups in discontinuation rates because of treatment-related AEs. Fewer than 10% of patients taking onabotulinumtoxinA withdrew from the study because of unacceptable treatment-related AEs, while more than 20% of patients taking topiramate withdrew for such reasons. A similar study by Blumenfeld and colleagues in patients with episodic or chronic migraine reported a favorable tolerability profile for onabotulinumtoxinA compared with divalproex sodium. A greater percentage of divalproex sodium-treated patients reported treatment-related AEs and discontinued the study because of AEs.[28] In a recent report pooling safety data on topiramate from 3 large 26-week randomized, controlled trials, paresthesias, cognitive symptoms, fatigue, and insomnia led to discontinuation in >3% of patients.[29]

Overall discontinuation rates for topiramate-treated patients in 2 pivotal episodic migraine trials ranged from 35% to 62%. AEs were the most frequently reported reason for withdrawal from study.[25,30] Controlled trials in the CM population have reported discontinuation rates of 25% to 44.2% in the topiramate group compared with 10% to 25% in the onabotulinumtoxinA group.[12,13,19,20] Insufficient tolerability and efficacy were the main reasons for withdrawal in the topiramate group, while lack of efficacy was the most commonly reported reason for withdrawal in the onabotulinumtoxinA group.[12,13,19,20]

In this study, the correlation between diary measures and subjective measures of migraine disability and impact (MIDAS and HIT-6) and QoL was variable. Although the decrease in HA days and response to treatment were consistently robust for both groups, MIDAS and HIT-6 scores did not parallel this consistency over the course of the study. A number of factors may have contributed to these findings: the relatively small population size and variable baseline values, especially for MIDAS, likely contributed to a lack of correlation in this study. Other studies have found stronger agreement between diary measures and subjective questionnaires, suggesting a correlation between decreases in days with HA or HA frequency and patients' perceptions of benefit from treatment.[31-33] Appropriately designed and administered large active-comparator studies should be able to overcome these shortcomings.

Various types of oral medications are used to prevent migraine, including β-blockers, antidepressants, antiepileptic agents, and calcium channel blockers.[11] The efficacy of these agents has been established in large, well-controlled clinical trials (reviewed in Silberstein et al[10]). Recent studies suggest beneficial effects on health-related QoL (HRQoL)[34,35] and resource utilization[36] as well. A recent study pooled HRQoL data from 3 large randomized, placebo-controlled trials of topiramate for prevention of migraine.[34] They found improvement in 3 domains of functionality: restriction of daily activities, prevention of daily activities, and emotional function.

Migraine prevention with oral daily medications presents a number of challenges affecting patient adherence and compliance with drug regimens. Factors such as high patient expectations; daily dosing regimens, dosage titration schedules, and the frequency of required medical follow-up; and the lack of an obvious relationship between drug taking and pain reduction can negatively affect adherence to drug regimens.[11,35] Effective use of onabotulinumtoxinA treatment for prevention of migraine may prove beneficial in avoiding some of the factors, such as daily dosing and troubling cognitive AEs, which affect patient adherence to treatment.

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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. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist*. 2006;12:204-213.
3. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: Burden, diagnosis, and satisfaction with treatment. *Neurology*. 2008;71:559-566.

4. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. *Headache*. 1987;27:102-106.

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. Headache Classification Committee: Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia*. 2006;26:742-746.

7. Mathew NT. The prophylactic treatment of chronic daily headache. *Headache*. 2006;46:1552-1564.

8. Bigal ME, Lipton RB, Tepper SJ, Rapoport AM, Sheftell FD. Primary chronic daily headache and its subtype in adolescents and adults. *Neurology*. 2004; 63:843-847.

9. 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.

10. Silberstein SD, Lipton RB. Chronic daily headache. *Curr Opin Neurol*. 2000;13:277-283.

11. 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.

12. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby P, on behalf of the TOPMAT-MIG-201 (TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2007;27:814-823.

13. Silberstein SD, Lipton RB, Dodick DW, et al., on behalf of the Topiramate Chronic Migraine Study Group. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache*. 2007;47:170-180.

14. Poewe W, Schelosky L, Kleedorfer B, Heinen F, Wagner M, Deuschl G. Treatment of spasmodic torticollis with local injections of botulinum toxin: One-year follow-up in 37 patients. *J Neurol*. 1992; 239:21-25.

15. Greene P, Kang U, Fahn S, Brin M, Moskowitz C, Flaster E. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology*. 1990;40:1213-1218.

16. Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet*. 1986;2:245-247.

17. Dunne JW, Heye N, Dunne SL. Treatment of chronic limb spasticity with botulinum toxin A. *J Neurol Neurosurg Psychiatry*. 1995;58:232-235.

18. Rivest J, Lees AJ, Marsden CD. Writer's cramp: Treatment with botulinum toxin injections. *Mov Disord*. 1991;6:55-59.

19. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C. 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. 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. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain*. 2004;107:125-133.

22. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache*. 2003;43(Suppl. 1): 9-15.

23. Aoki KR. Botulinum toxin: A successful therapeutic protein. *Curr Med Chem*. 2004;11:3085-3092.

24. Mathew NT, Schmitt J, Jacobs D, et al. Topiramate in migraine prevention (MIGR-001): Effect on migraine frequency. *Neurology*. 2003;60(Suppl. 1): A336. Abstract S42.001.

25. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: A randomized controlled trial. *JAMA*. 2004;291:965-973.

26. The International Classification of Headache Disorders. Headache Classification Subcommittee of the International Headache Society. *Cephalalgia*. 2004; 24(Suppl. 1):1-160.

27. Dauer WT, Burke RE, Greene P, Fahn S. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. *Brain*. 1998; 121:547-560.

28. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. *Headache*. 2008;48:210-220.

29. Lainez MJ, Freitag FG, Pfeil J, Ascher S, Olson WH, Schwalen S. Time course of adverse events most commonly associated with topiramate for migraine prevention. *Eur J Neurol*. 2007;14:900-906.

30. Silberstein SD, Neto W, Schmitt J, Jacobs D, for the MIGR-001 Study Group. Topiramate in migraine prevention: Results of a large controlled trial. *Arch Neurol*. 2004;61:490-495.

31. 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.

32. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: A preliminary study. *J Headache Pain*. 2003;4:146-151.

33. Aurora S, Gawel M, Brandes J, Pokta S, VanDenburgh AM. Botulinum toxin type A prophylactic treatment of episodic migraine: A randomized, double-blind, placebo-controlled exploratory study. *Headache*. 2007;47:486-499.

34. 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.

35. 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.

36. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache*. 2003;43:171-178.