Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine

S.D. Silberstein, MD
D.W. Dodick, MD
A.S. Lindblad, PhD
K. Holroyd, PhD
M. Harrington, MS
N.T. Mathew, MD
D. Hirtz, MD

Correspondence & reprint requests to Dr. Lindblad: alindblad@emmes.com

ABSTRACT

Objective: To assess the efficacy and safety of adding propranolol to topiramate in chronic migraine subjects inadequately controlled with topiramate alone.

Methods: This was a double-blind, placebo-controlled, randomized clinical trial conducted through the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, expected to randomize 250 chronic migraine subjects inadequately controlled (≥ 10 headaches/month) with topiramate (50–100 mg/day) to either propranolol LA (long acting) (240 mg/day) or placebo. Primary outcome was 28-day moderate to severe headache rate reduction at 6 months (weeks 16 to 24) compared with baseline (weeks –4 to 0).

Results: A planned interim analysis was performed after 48 sites randomized 171 subjects. The data and safety monitoring board recommended ending the trial after determining that it would be highly unlikely for the combination to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were randomized. No safety concerns were identified. At study closure, 191 subjects were randomized. The 6-month reduction in moderate to severe 28-day headache rate and total 28-day headache rate for combination therapy vs topiramate alone was not significantly different: 4.0 vs 4.5 days (moderate to severe 28-day headache rate; $p = 0.57$) and 6.2 vs 6.1 days (total 28-day headache rate; $p = 0.91$).

Conclusions: This study does not provide evidence that the addition of propranolol LA to topiramate adds benefit when chronic migraine is inadequately controlled with topiramate alone.

Classification of evidence: This study provides Class II evidence that propranolol LA, added to topiramate, is ineffective in chronic migraine patients who fail topiramate monotherapy. *Neurology*® 2012; 78:976–984

GLOSSARY

ANCOVA = analysis of covariance; **BDI** = Beck Depression Inventory; **CM** = chronic migraine; **CMTT** = Chronic Migraine Treatment Trial; **DSMB** = data and safety monitoring board; **IRB** = institutional review board; **ITT** = intent-to-treat; **MIDAS** = Migraine Disability Assessment; **MSQL** = Migraine Specific Quality of Life; **OR** = odds ratio.

Chronic migraine (CM) (previously termed transformed migraine or mixed headache) evolves from episodic migraine and affects about 2%–3% of adults.^{1,2} Given its prevalence, associated disability, and inadequacy of current management,^{3,4} CM, as defined by the International Headache Society,⁵ is a problem for practicing neurologists and represents a significant research need and treatment priority in clinical practice.

Topiramate is an effective, safe, and generally well-tolerated preventive treatment for episodic migraine, with efficacy observed within the first month of treatment. It also is one of the few preventive treatments for CM that has been studied in placebo-controlled, randomized trials with positive, statistically significant results.^{6–8} However, topiramate alone is not an entirely effective CM treatment for most patients; thus combinations of preventive medica-

Editorial, page 940

Supplemental data at www.neurology.org

Supplemental Data

CME

From Thomas Jefferson University (S.D.S.), Philadelphia, PA; Mayo Clinic (D.W.D.), Phoenix, AZ; The EMES Corporation (EMMES) (A.S.L., M.H.), Rockville, MD; Ohio University (K.H.), Athens, OH; Houston Headache Clinic (N.T.M.), Houston, TX; and National Institute of Neurological Disorders and Stroke (D.H.), Bethesda, MD.

Coinvestigators of the Chronic Migraine Treatment Trial Research Group are listed on the *Neurology*® Web site at www.neurology.org.

Study funding: Supported by NIH National Institute of Neurological Disorders and Stroke Contract HHSN265200523641C. Ortho-McNeil-Janssen Pharmaceuticals, Inc., donated the study-supplied topiramate used during the screening and randomization phases of this study.

Disclosure: Author disclosures are provided at the end of the article.

tions are often used. Based on a review of available options, propranolol hydrochloride, a nonselective β -blocker, was chosen as the second medication because it is a standard preventive medication for episodic migraine,⁹ represents a different class of medication, has a reasonable side effect profile, is approved by FDA for the prevention of episodic migraine, and has been used in combination with topiramate in an uncontrolled study.¹⁰

The Chronic Migraine Treatment Trial (CMTT) was designed as a double-blind, randomized, placebo-controlled trial to assess whether topiramate, combined with add-on propranolol, decreases the 28-day moderate to severe headache rate at 6 months compared with topiramate given with a placebo. It was conducted within the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration, a consortium of community practice-based and university neurologists and physicians.

METHODS **Standard protocol approvals, registrations, and patient consents.** A steering committee designed the study and The EMMES Corporation (Rockville, MD) was the coordinating center responsible for data collection, quality monitoring, statistical analysis, and training and certification of seventy sites to enroll subjects following protocol approval by local institutional review boards (IRBs) (or a central IRB for sites without a local IRB). Each site obtained written informed consent from each subject enrolled. An independent data and safety monitoring board (DSMB; contributors appendix on the *Neurology*[®] Web site at www.neurology.org) reviewed and approved the protocol prior to enrollment and reviewed study progress for safety, efficacy, and quality throughout study conduct and the study was registered with clinicaltrials.gov prior to subject enrollment (NCT00772031).

Subjects. Subjects must have been age 18 years or older, had a history (at least 3 months) of CM as defined by the International Headache Society,⁵ and had been able to tolerate at least 50 mg of topiramate a day with no contraindications to taking topiramate or propranolol. Subjects must not have had an immediate intent to change usual acute headache medications or other treatments. Subjects with major depression or severe psychiatric disorder (Beck Depression Inventory [BDI] FastScreen score of 13 or greater) were excluded, as were those who had used other migraine preventive medications in the past 2 months or onabotulinumtoxinA injections within the past 3 months. Subjects must not have been using butalbital or opioids for 10 or more days per month. Subjects new to topiramate, not on a maximum tolerated dose, or unable to tolerate a higher dose but at their current dose (must have been at least 50 mg/day) for less than 3 months, entered into a 28-day topiramate titration phase before beginning their baseline diary. Subjects currently on a stable dose of topiramate for at least 3 months at a maximum tolerated dose of 50 mg/day up to 100 mg/day initiated the 28-day diary directly following screening.

Treatments. The Coordinating Center randomly assigned treatment to a subject ID with balanced allocation (1:1) using

random block sizes stratified by practice, medication overuse (as defined by the 2006 International Headache Society criteria⁵), and use of topiramate at screening. After baseline diary completion and eligibility verification, a Web-based enrollment system assigned the subject ID. Neither the subject nor the clinic staff was aware of the contents of the study medication assigned. Masking of propranolol was accomplished by the Drug Distribution Center located at the Veterans Affairs Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico, using overencapsulation with locking capsules, such that propranolol and placebo were indistinguishable. Study medication was given as follows: week 1: 1 capsule 60 mg LA propranolol or placebo PM; week 2: 1 capsule AM and 1 capsule PM; week 3: 1 capsule AM and 2 capsules PM; week 4: 2 capsules AM and 2 capsules PM; for a total dose of 240 mg LA propranolol or 4 capsules placebo per day as tolerated. At the end of 6 months, subjects titrated off study medications over 4 weeks.

Primary research question. Does adding propranolol LA (up to 240 mg/day) to chronic migraine subjects taking topiramate (up to 100 mg/day) reduce the mean 28-day moderate to severe headache rate (headaches of at least moderate intensity lasting 4 hours or more, or treated by triptans or ergots regardless of severity or duration) at 6 months compared to adding placebo to chronic migraine subjects taking topiramate (up to 100 mg/day)?

Secondary outcomes. Secondary objectives included comparisons between treatment arms in change from baseline in 28-day moderate to severe headache rates at 3 months; need for acute symptomatic medications at 6 months; change in 28-day total headache rate (headaches of any severity), and percent experiencing at least a 30% or 50% reduction in 28-day headache rate from baseline at 3 and 6 months; change from baseline in Migraine Disability Assessment (MIDAS) score and Migraine Specific Quality of Life (MSQL) at 3 and 6 months; change from baseline in BDI FastScreen score at 1, 3, and 6 months; and adverse event rates.

Follow-up. After randomization, subjects were to be seen in the clinic at 1, 3, and 6 months. Coordinators placed follow-up phone calls at 2 weeks during titration to check on subject status, biweekly through 8 weeks, and monthly thereafter, with a final call at week 28 following completion of study medication withdrawal. Calls were used to verify completion of headache diaries and use of medication and to screen for and record adverse events.

Statistical methods. The study was designed to enroll 250 subjects to provide at least 90% power to detect a 3-day difference and 87% power to detect a 2.5-day difference in 28-day moderate to severe headache rate reductions at 6 months, assuming a type I error rate of 0.05, a 2-sided test, a 10% loss to follow-up, and a SD of within-person change in days with headache of 6. Imbalances in baseline characteristics were tested using the 2-sample *t* test for continuous measures and contingency tables for generalized linear models for categorical variables. Binary outcomes were analyzed using covariate-adjusted logistic regression with subjects terminating the study early treated as failures.

Treatment effects on mean change in moderate to severe 28-day headache rate, BDI, MIDAS, and MSQL scores were compared using an analysis of covariance (ANCOVA) model with adjustment for covariates including study site, baseline moderate to severe 28-day headache rate, topiramate use, medication overuse, and antidepressant medications use. The SAS[®] GENMOD procedure for generalized linear models was used with Tukey adjusted *p* values presented for the multiple MSQL

patient-reported outcome scales. The analysis of the primary endpoint was performed following the intent-to-treat (ITT) principle applied to all participants with outcome data available. Headache rates were imputed from available data for diaries with 6 or more entries. Secondary analyses included multiple imputation methods (using SAS[®] PROC MI using propensity score method and PROC MIANALYZE) for 28-day diaries with 23 or more missing diary entries. Tests for significant interactions (p value ≤ 0.10) between treatment and depression and strata values were performed. Safety analyses include the outcomes of all subjects who were exposed to the study treatment. Interim analysis was performed using an α spending function approach with O'Brien-Fleming boundaries¹¹ and an inefficacy analysis.¹² All p values presented are unadjusted for multiple comparisons unless otherwise specified.

Classification of evidence. This randomized, double-blind, placebo-controlled trial provides Class II evidence that propranolol LA (up to 240 mg/day), when added to topiramate (up to 100 mg/day), is unlikely to be effective in reducing the number of moderate to severe headaches at 6 months compared to topiramate (up to 100 mg/day) alone in a chronic migraine population without adequate relief on topiramate monotherapy (difference in mean moderate to severe headache reduction on placebo and topiramate [4.5 days] vs propranolol and topiramate [4.0 days] was 0.5 days [95% confidence interval -1.4 to 2.5]).

RESULTS The DSMB reviewed results from 171 (68% of planned sample size) randomized subjects (85 assigned to topiramate plus propranolol; 86 assigned to topiramate plus placebo) during a pre-planned interim analysis and determined that it would be highly unlikely for the combination (topiramate plus propranolol) to result in a significant reduction in 28-day headache rate compared with topiramate alone if all 250 subjects were enrolled. The DSMB recommended termination of enrollment. Between October 2008 and September 2010, 65 centers screened 627 subjects, randomized 191 subjects, and reported 6-month outcome data for 116 subjects.

The figure provides the disposition of study subjects. A total of 627 subjects signed an informed consent and initiated the screening period. Of these, 191 were randomized (95 placebo and 96 propranolol). A total of 116 subjects (61%) completed at least some component of 6 months of follow-up (64 propranolol and 52 placebo). Fifty subjects (26%) did not complete 6-month follow-up because they were lost or refused further follow-up (20 propranolol and 30 placebo), and 25 subjects (13%) had not completed the 6-month follow-up window at the time of study closure because the study was discontinued by the DSMB (12 propranolol and 13 placebo). Follow-up rates at 3 (6) months for those with the opportunity for follow-up were 81% and 70% (76% propranolol and 63% placebo), respectively.

Subject demographics and baseline medical and headache histories are summarized by randomized

treatment in table 1. Of the 191 randomized subjects, 85% are Caucasian, 10% are of Hispanic or Latino ethnicity, and 90% are female. The median age at randomization is 42 years (range 18–67 years). The average 28-day headache rate for the study population was 18 days, with 11 days meeting the definition of moderate to severe headache. Treatments are balanced by demographics (except Hispanic or Latino ethnicity, p value = 0.03) and medical and headache history. The baseline characteristics of the 166 subjects with the opportunity for 6-month follow-up (includes those randomized at least 6 months prior to study closure with some 6-month follow-up [n = 116] and those lost to follow-up [n = 50]) were similar to the entire randomized subject population (data not shown). For the subjects with the opportunity for 6-month follow-up, treatments were balanced by Hispanic or Latino ethnicity.

At 6 months, 29 subjects (25%) had permanently discontinued one or both of topiramate and study medication; 16 subjects (14%) had permanently discontinued their study medication (4 placebo and 12 propranolol), and 13 subjects (11%) had permanently discontinued both medications (figure). Subject reports during follow-up diary entries indicated 59% and 73% of subjects assigned to propranolol and 45% and 68% of subjects assigned to placebo had a greater than 80% adherence to topiramate (p value = 0.03) and study medications, respectively. The average dose of medications taken was 88 mg/day of topiramate, 177 mg/day of propranolol, and 205 mg/day of placebo. Median doses were 100 mg/day of topiramate, 236 mg/day of propranolol, and 240 mg/day of placebo with ranges in each spanning from 0 to the maximum dose.

Table 2 provides results from subject diaries. At 6 months, the mean reduction in moderate to severe 28-day headache rate for combination therapy (n = 63) vs topiramate alone (n = 48) was 4.0 vs 4.5 days (p = 0.57). The 6-month mean reduction in total 28-day headache rate was 6.2 vs 6.1 days (p = 0.91) for combination therapy and topiramate alone. The difference between propranolol vs placebo added to topiramate in mean reduction of moderate to severe 28-day headache rate was 0.5 days (95% confidence interval -1.4 to 2.5), thus excluding differences of -1.4 days or larger in favor of propranolol (data not shown in table 2).

Mean reductions of 2.2 and 1.6 moderate to severe 28-day headache rate (p = 0.48) and 4.0 and 3.2 total 28-day headache rate (p = 0.42) were reported at month 3 for propranolol (n = 70) and placebo (n = 65) respectively and were neither statistically nor clinically significant. There were no signif-

Figure Subject eligibility and follow-up for the Chronic Migraine Treatment Trial

*Three-month and 6-month follow-up is based on any required follow-up data provided (e.g., diary or questionnaires).

inant interactions between covariates and treatment detected. A larger baseline 28-day headache rate was, consistently, the only significant predictor of a larger decrease in follow-up 28-day headache rate ($\beta = -0.32$, $p < 0.001$, data not shown in table 2). There was also a significant site effect of moderate to severe 28-day headache and total 28-day headache at 3 months; however, adjustment for site did not alter the outcomes. Subjects who were using topiramate prior to screening experienced a similar decrease in 28-day headache rate as those not previously on topi-

ramate ($p = 0.31$), as did medication overusers ($p = 0.93$).

When headache outcome was analyzed as a percent reduction, subjects assigned to propranolol ($n = 84$) were 44% more likely (odds ratio [OR] = 1.44) to have a 30% or greater reduction in moderate to severe 28-day headache rate compared with subjects assigned to placebo ($n = 82$) at month 6. This difference did not reach statistical significance ($p = 0.27$). There was no difference in 50% or greater reductions (OR = 1.00; $p = 0.99$). Subjects assigned to pro-

Table 1 Summary of subject demographics by study treatment

Demographics	CMTT study treatment		
	Topiramate + propranolol	Topiramate + placebo	Total
Total	96	95	191
Enrollment age, y, median (min, max)	39 (18, 62)	42 (18, 67)	42 (18, 67)
% Female	87.5	92.6	90.1
% Caucasian	85.4	85.3	85.3
% Hispanic or Latino origin ^a	5.2	14.7	9.9
% Medication overuse, no topiramate ^b	17.7	24.2	20.9
% No medication overuse, no topiramate ^b	57.3	56.8	57.1
% Medication overuse, topiramate ^b	5.2	4.2	4.7
% No medication overuse, topiramate ^b	19.8	14.7	17.3
% Prior treatment for depression	10	15	13
BDI FastScreen Severity Score, n (%)			
Minimal	79 (82.3)	81 (85.3)	160 (83.8)
Mild	15 (15.6)	8 (8.4)	23 (12.0)
Moderate	2 (2.1)	6 (6.3)	8 (4.2)
Continuous headache, n (%)	49 (51)	46 (48)	95 (50)
Baseline 28-day headache rate, mean (SD)	18 (7)	18 (7)	18 (7)
Baseline moderate to severe 28-day headache rate, mean (SD)	12 (7)	11 (6)	11 (7)
MIDAS, mean (SD) ^c	18 (16)	18 (14)	18 (15)
MSQL domain: Role restrictive score, mean (SD)	55 (21)	57 (22)	56 (21)
MSQL domain: Role preventive score, mean (SD)	70 (21)	74 (19)	72 (20)
MSQL domain: Role emotional score, mean (SD)	60 (29)	61 (30)	61 (29)

Abbreviations: BDI = Beck Depression Inventory; CMTT = Chronic Migraine Treatment Trial; MIDAS = Migraine Disability Assessment; MSQL = Migraine Specific Quality of Life.

^a Significant difference between ethnicity and treatment ($p = 0.03$).

^b No topiramate: no prior use of topiramate, or less than 3-month use, or able to titrate higher. Topiramate: used a maximum tolerated stable dose of topiramate (50–100 mg/day) for at least 3 months prior to screening.

^c MIDAS scoring: 0–5 (grade I); 6–10 (grade II); 11–20 (grade III); and 21+ (grade IV).

pranolol were 47% more likely (OR = 1.44) to have a reduction in 28-day treated headache rate compared with subjects assigned to placebo, but this reduction in odds also did not reach statistical significance ($p = 0.24$). Imputation of 28-day headache rates for those who were lost to follow-up did not change the conclusions reported in table 2 and above for headache rate reduction or percentage reduction.

Table 3 summarizes the mean change in BDI score at months 1, 3, and 6 by treatment group and MSQL and MIDAS scores at month 3 and 6. An increase in change in BDI and MIDAS scores from baseline indicates a worsening, while an increase in MSQL indicates an improvement. There was a statistically significant but not clinically significant difference between treatments in mean change in BDI score at month 3 but not at month 6. There were no

statistically significant differences in mean change in MSQL or MIDAS scores by randomized treatment group for all domains at month 3. At month 6 there were no statistically significant differences in mean change in MIDAS, MSQL role restrictive, and MSQL emotional function domains. There was a significant interaction between randomized treatment and prior topiramate use (p value = 0.0002) for MSQL role prevention.

There were no reported deaths. Twelve subjects (7% propranolol and 5% placebo) reported a serious adverse event including 1 case of depression (propranolol arm) and a wide range of other single events including gastrointestinal disorder, dehydration, paresthesia, syncope, insomnia, pregnancy, breast pain, pelvic pain, and surgical procedure. The number of subjects with a nonserious adverse event within selected system organ classes and preferred terms are summarized by study medication in table 4. More subjects assigned to propranolol vs placebo reported dizziness (14% vs 3%, respectively, p value = 0.01) and adverse events involving general disorders (28% vs 15%, respectively, p value = 0.04). Depression ($n = 5$) and fatigue ($n = 4$) were the most commonly cited reasons for medication discontinuation in the 29 subjects who reported medication discontinuation.

DISCUSSION We designed this study based on guidelines for studies of prophylactic treatment for CM.¹³ We found that the combination of topiramate with propranolol did not improve average days of moderate to severe headache or headache with any severity level over a 6-month period. We found a large decrease in 28-day headache rate in both the propranolol and placebo arms. Even subjects enrolled on a stable dose of topiramate had a 4- to 5-day reduction in moderate to severe 28-day headache rate, so it is unlikely there was a continuing impact of topiramate efficacy beyond the run-in and any carryover effect of topiramate would be expected to be balanced by treatment. This spontaneous improvement needs to be considered when interpreting results of single-arm trials where the subject serves as his or her own control. Open-label studies comparing headache frequency during treatment with topiramate 75–100 mg daily with baseline headache frequency (i.e., without a concurrent placebo group) reported 39%–90% reductions.^{14,15} Randomized placebo-controlled trials reported more modest reductions when compared to placebo.^{6,7,16,18}

Depression and fatigue have been associated with use of propranolol.¹⁹ No statistically significant changes in depression at 6 months were observed in our study. Fatigue incidence was borderline significant. Although the combination therapy appeared to be relatively well-tolerated compared with mono-

Table 2 Change in 28-day headache rate from baseline by treatment group^a

	No.	Propranolol		Placebo		p Value	
		No., mean	95% CI	No., mean	95% CI		
Change in 28-day headache rate from baseline by treatment group							
Moderate to severe headaches ^b							
Month 3	135	70, −2.2	−3.5, −0.9	65, −1.6	−2.8, −0.4	0.48	
Month 6	111	63, −4.0	−5.3, −2.6	48, −4.5	−5.9, −3.2	0.57	
Total 28-day ^b							
Month 3	135	70, −4.0	−5.5, −2.6	65, −3.2	−4.6, −1.9	0.42	
Month 6	111	63, −6.2	−7.9, −4.5	48, −6.1	−7.8., −4.4	0.91	
	No.	Total n	No. (%)	Total n	No. (%)	OR	95% CI
≥30% Reduction in 28-day moderate to severe headache rate ^c							
Month 3	173	86	31 (36.0)	87	26 (30.0)	1.21	0.62, 2.34
Month 6	166	84	37 (44.0)	82	28 (34.1)	1.44	0.75, 2.78
≥50% Reduction in 28-day moderate to severe headache rate ^c							
Month 3	173	86	23 (26.7)	87	22 (25.3)	0.95	0.47, 1.91
Month 6	166	84	26 (31.0)	82	23 (28.0)	1.00	0.50, 2.02
Any reduction in 28-day treated headache rate (regardless of headache severity) ^b							
Month 6	166	84	47 (56.0)	82	36 (43.9)	1.49	0.77, 2.90
	No.	No., mean	95% CI	No., mean	95% CI	p Value	
Mean change from baseline in moderate to severe 28-day headache rate by strata and treatment group at month 6 ^b							
Medication overuse, no topiramate ^d	27	15, −4.6	−7.3, −1.9	12, −4.7	−8.1, −1.4	0.80	
No medication overuse, no topiramate ^d	54	32, −3.3	−5.5, −1.2	22, −3.1	−5.2, −0.9		
Medication overuse, topiramate ^d	5	2, −7.8	−15.4, −0.2	3, −9.1	−16.7, −1.6		
No medication overuse, topiramate ^d	25	14, −3.7	−6.6, −0.8	11, −6.0	−9.3, −2.6		
Prior, stable topiramate use ^d	30	16, −4.6	−7.4, −1.8	14, −6.9	−9.7, −3.9	0.31	
No prior, stable topiramate ^d	81	47, −3.7	−5.4, −1.9	34, −3.5	−5.3, −1.8		
Medication overuse	32	17, −5.5	−8.0, −2.9	15, −5.9	−8.9, −2.9	0.93	
No medication overuse	79	46, −3.4	−5.0, −1.7	33, −4.0	−5.8, −2.2		

Abbreviations: CI = confidence interval; OR = odds ratio.

^a Mean change in moderate to severe 28-day headaches and total 28-day headaches were calculated excluding those that had 3 months of follow-up and less than 6 completed diary days or 6 months of follow-up and less than 11 completed diary days. Participants lost to follow-up or who did not complete the minimum number of headache diary days were treated as failures for the 30%, 50%, and any reduction in headache days outcomes.

^b Model was adjusted for the following covariates: study site, baseline moderate to severe headaches, prior use of topiramate, medication overuse, and use of antidepressant.

^c Model adjusted for the following covariates: study site, baseline moderate to severe headaches, prior use of topiramate, medication overuse, ethnicity, and use of antidepressant.

^d No topiramate: no prior use of topiramate, or less than 3-month use, or able to titrate higher. Topiramate: used a maximum tolerated stable dose of topiramate (50–100 mg/day) for at least 3 months prior to screening.

therapy, the study was inadequately powered to determine expected safety in the general chronic migraine population.

The CMTT population was similar to the TOP-CHROME,⁶ the Topiramate Chronic Migraine Study,⁷ and PREEMPT^{16–18} study popula-

tions in severity of headaches, but not in the requirement that subjects have an inadequate response to topiramate. This factor presumably selected out easier-to-treat subjects. CMTT subjects began with an average of 18 headache days, 11 of which were moderate to severe, compared to TOP-

Table 3 Mean change in Beck Depression Inventory FastScreen score and MSQL domain scores and MIDAS scores by treatment group^{a,b}

		Propranolol		Placebo		
	No.	No., mean	95% CI	No., mean	95% CI	p Value
Beck Depression Inventory						
Month 1	157	79, −0.20	−0.61, 0.21	78, −0.40	−0.8, 0.02	0.30
Month 3	129	62, 0.66	0.2, 1.12	62, 0.19	−0.27, 0.66	0.04
Month 6	97	53, 0.3	−0.19, 0.80	44, 0.60	0.02, 1.19	0.23
MSQL domain: Role restrictive						
Month 3	129	67, 15.0	9.6, 20.4	62, 10.1	4.6, 15.6	0.12
Month 6 ^c	97	53, −0.72	−11.5, 10.1	62, −2.17	−13.4, 9.02	0.69
MSQL domain: Role prevention						
Month 3	129	67, 8.7	3.9, 13.6	62, 6.68	1.75, 11.6	0.47
Month 6: No prior, stable topiramate	71	40, 12.9	7.2, 18.5	31, 5.9	−0.18, 11.98	0.0002 for interaction
Month 6: Prior, stable topiramate	26	13, −11.5	−21.3, −1.7	13, 11.0	1.1, 20.9	
MSQL domain: Emotional function						
Month 3	129	67, 7.7	1.3, 14.0	62, 11.9	5.3, 18.5	0.25
Month 6	97	53, 8.9	2.2, 15.7	62, 9.8	2.4, 17.3	0.83
MIDAS						
Month 3 ^c	129	67, −1.98	−7.6, 3.6	62, −3.8	−9.1, 1.6	0.40
Month 6 ^c	97	53, −3.18	−10.4, 4.1	44, −3.46	−10.9, 4.0	0.91

Abbreviations: CI = confidence interval; MIDAS = Migraine Disability Assessment; MSQL = Migraine Specific Quality of Life.

^a Model adjusted for the following covariates: study site, baseline score, prior use of topiramate, medication overuse, and use of antidepressant.

^b Results include any participant randomized who had a non-missing score.

^c Model also included ethnicity.

CHROME, with an average of 15.5 migraine days, the Topiramate Chronic Migraine Study with 17 headache days, and the PREEMPT studies with 19.9 days. A 2.5-day reduction was observed in the topiramate arm of the TOP-CHROME study⁶ with no reduction in the placebo arm. In the Topiramate Chronic Migraine Study, headache days were reduced by 4.7 days with placebo and 6.4 days with topiramate over 12 weeks using a similar dosing regimen.⁷ The PREEMPT clinical trials also showed a substantial placebo effect in a population randomized to either onabotulinumtoxinA injections or placebo. The average reduction at 24 weeks in 28-day moderate to severe headache rate was 7.7 days for those assigned to onabotulinumtoxinA injections compared with 5.8 days for placebo.

Our 6-month follow-up rate of 76% for propranolol and 63% for placebo is similar or higher than 6-month follow-up rates reported by trials of topiramate vs placebo in previous studies which ranged from 55.2% to 75%.^{7,8} Our study tested the combination therapy of topiramate and propranolol against topiramate alone. A prior study testing low-dose topiramate vs propranolol demonstrated that both

low-dose topiramate and propranolol significantly reduced migraine headaches.²⁰ Although this study did not include a placebo comparator, other placebo-controlled trials have shown propranolol and topiramate each as efficacious monotherapy in people with migraine.⁹

The CMTT was performed in a large cohort of practices that were part of the National Institute of Neurological Disorders and Stroke Clinical Research Collaboration. The study was designed to answer an important question in clinical practice and was able to do so while minimizing the exposure of subjects to combination therapy. The results from this study suggest the combination of topiramate with propranolol does not provide clinically relevant benefit over topiramate alone in a CM population.

AUTHOR CONTRIBUTIONS

Dr. Silberstein: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Dodick: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Lindblad: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical

Table 4 Number of subjects with nonserious adverse events by treatment

System organ class	Preferred term	Propranolol (n = 96), n (%)	Placebo (n = 95), n (%)	Total (n = 191), n (%)	p Value
Total	At least one adverse event	59 (61)	50 (53)	109 (57)	0.39
Nervous system disorders	Any	36 (38)	23 (24)	59 (31)	0.09
Selected preferred terms	Amnesia	3 (3)	0 (0)	3 (2)	1.0
	Aphasia	2 (2)	0 (0)	2 (1)	1.0
	Dizziness	13 (14)	3 (3)	16 (8)	0.01
	Memory impairment	6 (6)	8 (8)	14 (7)	0.59
	Mental impairment	12 (13)	7 (7)	19 (10)	0.25
	Paraesthesia	12 (13)	10 (11)	22 (12)	0.67
Psychiatric disorders	Any	11 (11)	13 (14)	24 (13)	0.68
Selected preferred terms	Abnormal dreams	1 (1)	0 (0)	1 (1)	1.0
	Anxiety	3 (3)	0 (0)	3 (2)	1.0
	Depression	8 (8)	3 (3)	11 (6)	0.13
	Insomnia	2 (2)	7 (7)	9 (5)	0.18
Vascular disorders	Any	5 (5)	3 (3)	8 (4)	0.73
Selected preferred terms	Hypotension	3 (3)	0 (0)	3 (2)	1.0
	Peripheral coldness	2 (2)	0 (0)	2 (1)	1.0
General disorders and administration site conditions	Any	27 (28)	14 (15)	41 (21)	0.04
Selected preferred terms	Fatigue	22 (23)	11 (12)	33 (17)	0.06

analysis, study supervision, obtaining funding. Dr. Holroyd: drafting/ revising the manuscript, study concept or design, analysis or interpretation of data. M. Harrington: analysis or interpretation of data, statistical analysis. Dr. Mathew: study concept or design, analysis or interpretation of data, acquisition of data. Dr. Hirtz: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

DISCLOSURE

Dr. Silberstein serves on scientific advisory boards for AGA Medical Corporation, Allergan, Inc., Amgen, Boston Scientific, CAPNIA, Coherex Medical, CoLucid Pharmaceuticals, CyDex Pharmaceuticals, Inc., GlaxoSmithKline, Eli Lilly and Company, MAP Pharmaceuticals, Inc., Medtronic, Inc., Merck Serono, Minster Pharmaceuticals plc, Neuralieve Inc., the NIH/NINDS, NuPathe Inc., Pfizer Inc, St. Jude Medical, and Valeant Pharmaceuticals International; serves on the editorial boards of *Cephalalgia* and *Current Pain and Headache Reports*; serves on the speakers' bureaus for Endo Pharmaceuticals, GlaxoSmithKline, and Merck Serono; serves as a consultant for Amgen, Novartis, Opti-Nose, and Sepracor Inc.; receives publishing royalties for *Wolff's Headache, 8th edition* (Oxford University Press, 2009) and *Handbook of Headache* (Cambridge University Press, 2010); his employer receives research support from AGA, Allergan, Boston Scientific, CAPNIA, Coherex, Endo, GlaxoSmithKline, Lilly, MAP, Medtronic, Merck, the NIH/NINDS, NuPathe, St. Jude Medical, Valeant, and Zogenix, Inc.; and receives research support from the American Headache Society and the International Headache Society. Dr. Dodick serves on scientific advisory boards and as a consultant for Allergan, Inc., Pfizer Inc., Novartis, Merck Serono, NuPath Inc., Nautilus, Coherex Medical, Boston Scientific, Medtronic, Inc., GlaxoSmithKline, CoLucid Pharmaceuticals, Autonomic Technologies, Eli Lilly and Company, Miller Medical, Neuralieve Inc., NeurAxon, Inc., St. Jude Medical, Inc., Zogenix, Inc., CogniMed Inc., MAP Pharmaceu-

tics, Inc., Lundbeck Inc., IMPAX Laboratories, Inc., and the NIH/NINDS; has received funding for travel or speaker honoraria from CogniMed Inc., Miller Medical, and Annenberg Center for Health Sciences; serves as Editor-in-Chief of *Cephalalgia*, Editor-in-Chief and on the editorial boards of *The Neurologist*, *Lancet Neurology*, and *Postgraduate Medicine*; and has served as Editor-in-Chief of *Headache Currents* and as an Associate Editor of *Headache*; receives publishing royalties for *Wolff's Headache, 8th edition* (Oxford University Press, 2009) and *Handbook of Headache* (Cambridge University Press, 2010); and receives research support from Boston Scientific, Medtronic, Inc., Advanced Neurostimulation Systems, St. Jude Medical, Inc., and the NIH/NINDS. Dr. Lindblad receives salary from and is part owner of The EMMES Corporation, a Coordinating Center for clinical trials. Dr. Holroyd has served as a consultant for Endo Pharmaceuticals and Takeda Pharmaceutical Company Limited and received research support from Endo Pharmaceuticals and the NIH. M. Harrington receives salary from The EMMES Corporation, a Coordinating Center for clinical trials. Dr. Mathew has served on scientific advisory boards for Allergan, Inc., GlaxoSmithKline, and Nautilus; has served on speakers' bureaus for and received speaker honoraria from GlaxoSmithKline, Nautilus, Allergan, Inc.; and has received research support from Merck Serono, AstraZeneca, Pfizer Inc, and Endo Pharmaceuticals. Dr. Hirtz reports no disclosures.

Received March 29, 2011. Accepted in final form September 7, 2011.

REFERENCES

1. Dodick D. Clinical practice: chronic daily headache. *N Engl J Med* 2006;354:158–165.
2. Friedank-Mueschenborn E, Fox AW. Cusums to measure chronic daily headache. *Headache* 2006;46:110–114.
3. Stovener LJ, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27:193–210.
4. Coeytaux RR, Linville JC. Chronic daily headache in a primary care population: prevalence and headache impact test scores. *Headache* 2007;47:7–12.
5. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26:742–746.
6. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, for 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.
7. Silberstein SD, Lipton RB, Dodick DW, et al, Topiramate Chronic Migraine Study Group. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2007;47:170–180.
8. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003;23:820–824.
9. 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.
10. Pascual J, Rivas MT, Leira R. Testing the combination beta-blocker plus topiramate in refractory migraine. *Acta Neurol Scand* 2007;115:81–83.
11. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–556.
12. Freidlin BF, Korn EL, Gray R. A general inefficacy monitoring rule for randomized clinical trials. *Clinical Trials* 2010;7:197–208.

13. Silberstein S, Tfelt-Hansen P, Dodick D, et al, for the Task Force of the International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia* 2008;28:484–495.
14. Bartolini M, Silvestrini M, Taffi R, et al. Efficacy of topiramate and valproate in chronic migraine. *Clin Neuroparmacol* 2005;28:277–279.
15. Rothrock JF, Parada VA, Drinkard R, Zweifler RM, Key KF. Predictors of a negative response to topiramate therapy in patients with chronic migraine. *Headache* 2005;45:932–935.
16. Diener HC, Dodick DW, Aurora SK, et al, PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30:804–814.
17. Aurora SK, Dodick DW, Turkel CC, et al, PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30:793–803.
18. Dodick DW, Turkel CC, DeGryse RE, et al, PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010;50:921–936.
19. Ko DT, Herbert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;288:351–357.
20. Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. *Acta Neurol Scand* 2008;118:301–305.

AAN Webinars: Help for Your Practice, CME for Your Career

The American Academy of Neurology offers cost-effective Practice Management Webinars that can be attended live or through convenient recordings after the event. AAN members can benefit from *two free sessions* and save 25 percent on all regular webinars! Plus, registrants can earn 1.5 valuable CME credits for each webinar. For more information and to register, visit www.aan.com/view/pmweb today!

Online Now	Decoding the 2012 Physician Fee Schedule: Changes that Impact Neurology (FREE to AAN members!)
Online Now	EHR Implementation: What You Need to Know from A-Z
Online Now	CPT Coding for Neurodiagnostic Procedures Made Easy
April 12	Incentive Programs and Penalties: What Do They Mean for My Practice? (FREE to AAN members!)
May 16	Ready, Set, Payment: Using Certified EHRs for Meaningful Use Payments
June 12	The ABCs of Coding
July 17	E/M: Minimize Mistakes, Maximize Reimbursement
September 18	Thriving in the Face of an Audit
October 16	ICD-10: Are You Prepared?
November 6	Coding Accurately for Stroke and Critical Care