Headache
© 2008 the Authors
Journal compilation © 2008 American Headache Society

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2008.01217.x
Published by Wiley Periodicals, Inc.

Harold G. Wolff Lecture Award Winner

Acute Migraine Medications and Evolution From Episodic to Chronic Migraine: A Longitudinal Population-Based Study

Marcelo E. Bigal, MD, PhD; Daniel Serrano, MA; Dawn Buse, PhD; Ann Scher, PhD;
Walter F. Stewart, PhD; Richard B. Lipton, MD

Background.—Though symptomatic medication overuse is believed to play a major role in progression from episodic to chronic or transformed migraine (TM), population-based longitudinal data on these agents are limited.

Objectives.—To assess the role of specific classes of acute medications in the development of TM in episodic migraine (EM) sufferers after adjusting for other risk factors for headache progression.

Methods.—As a part of the American Migraine Prevalence and Prevention study (AMPP), we initially surveyed a population sample of 120,000 individuals to identify a sample of migraineurs to be followed annually over 5 years. Using logistic and linear regression, we modeled the probability of transition from EM in 2005 to TM in 2006 in relation to medication use status at baseline. Adjustments were made for gender, headache frequency and severity, and prevention medication use.

Results.—Of 8219 individuals with EM in 2005, 209 (2.5%) had developed TM by 2006. Baseline headache frequency was a risk factor for TM. Using acetaminophen user as the reference group, individuals who used medications containing barbiturates (OR = 2.06, 95%CI = 1.3-3.1) or opiates (OR = 1.98, 95%CI = 1.4-2.2) were at increased risk of TM. A dose–response relationship was found for use of barbiturates. Use of triptans (OR = 1.25, 95%CI = 0.9-1.7) at baseline was not associated with prospective risk of TM. Overall, NSAIDs (OR = 0.85, 95%CI = 0.63-1.17) were not associated with TM. Indeed, NSAIDs were protective against transition to TM at low to moderate monthly headache days, but were associated with increased risk of transition to TM at high levels of monthly headache days.

Conclusion.—EM sufferers develop TM at the rate of 2.5% per year. Any use of barbiturates and opiates was associated with increased risk of TM after adjusting for covariates, while triptans were not. NSAIDs were protective or inducers depending on the headache frequency.

Key words: transformed migraine, medication overuse, chronic migraine, migraine progression

(*Headache* 2008;48:1157-1168)

From the Global Center for Scientific Affairs, Neuroscience, Merck Research Laboratories, Whitehouse Station, NJ (M.E. Bigal); Department of Neurology, Albert Einstein College of Medicine, Bronx, NY (M.E. Bigal and R.B. Lipton); Vedanta Research and The L.L. Thurstone Psychometric Laboratory, UNC-Chapel Hill, NC (D. Serrano); The Montefiore Headache Center, Bronx, NY (D. Buse and R.B. Lipton); Department of Preventive Medicine and Biometrics, Uniformed Services University, Bethesda, MD (A. Scher); The Center for Health Research, Danville, PA (W.F. Stewart); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA (R.B. Lipton).

Address all correspondence to M.E. Bigal, One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 08889-0100, USA.

Disclosure: This study was sponsored by the National Headache Foundation through a grant from Ortho-McNeil Neurologics, Inc., Titusville, NJ. Dr. Bigal is an employee of Merck Research Laboratories.

All authors included on a paper fulfill the criteria of authorship. All analyses conducted by Daniel Serrano. No one else fulfills criteria for authorship.

Migraine is a common and disabling disorder that may be divided into 2 broad groups based on the number of headache days.[1] If attacks occur less than 15 days per month the term episodic migraine (or simply migraine) is applied; when headaches occur on 15 or more days per month the terms chronic or transformed migraine (CM and TM) are used.[1,2] Since the revised definition of CM is relatively recent,[3] most clinical observation and longitudinal studies assessed the chronic form of migraine as a chronic daily headache that evolved from episodic migraine, a process often referred to as transformation.[4-6] Accordingly, herein we refer to TM instead of CM. In a single population study, the rate of transformation from episodic migraine to TM was around 3% per year,[4] while in specialty clinics, it is as high as 14% per year.[7] Identifying risk factors for migraine transition from an episodic into a chronic status is, therefore, a crucial step towards developing preventive strategies.[8]

Excessive symptomatic medication (SM) use has been proposed as a risk factor for migraine transformation. In headache centers, over 80% of patients with TM use acute medications on more days than not.[9-11] In the general population, the prevalence of TM with medication *overuse* (use of acute medications on more than 10 or 15 days per month, depending on the medication class) is around 1.5%.[4,5]

Although TM and CM are firmly associated, it is not clear whether acute medication use is a cause of migraine transformation, or if it arises as a consequence of accelerating headache frequency.[12,13] Distinguishing these alternative hypotheses is of importance. If SM is a risk factor for TM, strict dose limits are required for individuals with episodic migraine. If specific classes of medications are particularly associated with TM, limits should be reinforced for these classes. Alternatively, if SM is not a risk factor for TM, providers may be adding the burden of under-treatment to the burden of illness. Pain under-treatment, in addition to the burden imposed on the patient, may itself aggravate headache frequency.[14,15]

The American Migraine Prevalence and Prevention (AMPP) study provides an opportunity to explore the relationship between use of SM and migraine progression. The AMPP is a multi-year longitudinal population-based study where a cohort of headache sufferers were defined and are being followed over 5 waves of assessment.[16,17] One of the main objectives of the project is to establish the natural history and prognosis of migraine, as well as risk factors for TM. As a part of the surveys, complete information on prescribed and over-the-counter medication obtained in a specific year can be used to predict new onset TM in the following year.

Accordingly, herein we use data from the AMPP to address the following goals: (1) to provide longitudinal data exploring the relationship between SM use and TM; (2) to explore the relationship between TM and exposure to specific classes of medication (eg, opioids, barbiturates, triptans); (3) to assess the dose–response relationships between medication use and TM, after adjusting for headache frequency.

METHODS

Study Population.—The AMPP is a longitudinal study of headache sufferers selected from a representative sample of the general population. Methods of the AMPP have been described in detail elsewhere[16-18] and the design is outlined in Figure 1. Briefly, the AMPP is composed of 2 major phases. In phase 1 (the screening phase) we used a validated self-administered screening questionnaire to identify a nationally representative sample of severe headache sufferers.[16-19] The screening questionnaire was mailed in 2004 to a stratified random sample of 120,000 U.S. households, drawn from a 600,000-household national panel maintained by the National Family Opinion, Inc. Of 162,576 individual respondents, 30,721 reported at least 1 severe headache in the previous year.[16]

In phase 2, we selected a random sample of 24,000 headache sufferers for a 5-year follow-up study.[17] The initial phase 2 questionnaire was used to determine headache diagnosis and to assess risk factors for headache progression. Episodic headache sufferers (<15 days of headache per month) were classified according to the Second Edition of the International Classification of Headache Disorders as having migraine, probable migraine, or tension-type headaches.[1] Individuals with chronic daily headaches (≥15 days of headache per month) were subdivided into

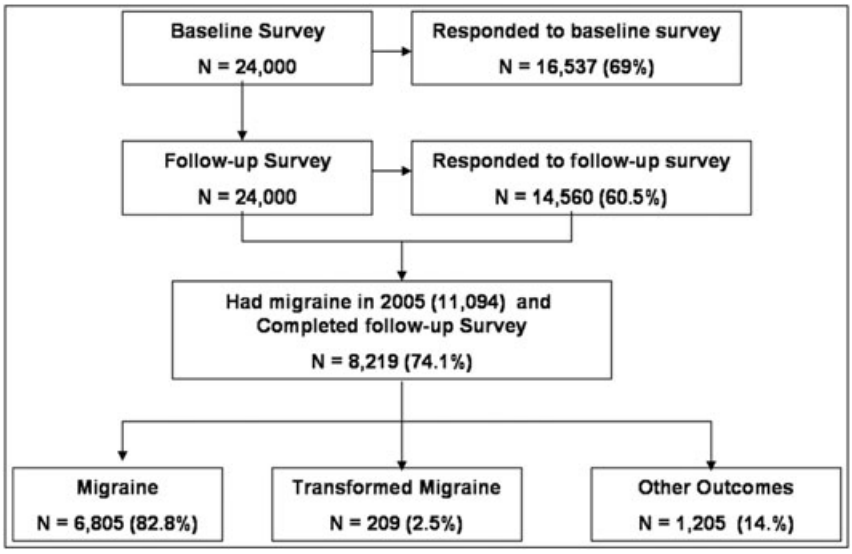

Fig 1.—Flow of the study.

TM and other chronic daily headaches. TM was classified according to the Silberstein-Lipton criteria.[2] The second phase 2 questionnaire was mailed in 2006 to all of the 2005 respondents reporting past year headache in 2005.

The sample for this report includes individuals with ICHD-2 defined episodic migraine in 2005 who completed the survey in 2006. We examined the relationship between use of analgesics reported in 2005, and headache outcomes in 2006 (see *Analyses*).

Description of the Survey.—The self-administered phase 2 questionnaire comprised 82 questions, assessing headache diagnosis, comorbidites, headache-related impact, health-related quality of life, demographics, and other information of interest (eg, height and weight, cutaneous allodynia, etc). The headache module consists of 21 questions for each of up to 3 headache types.[14-17] The survey had been previously shown to have a sensitivity of 100% and specificity of 82.3% for the diagnosis of migraine.[16] The questionnaire has a sensitivity of 93% and a specificity of 85% for the diagnosis of TM.[20]

Assessment of Acute Medication Use.—Respondents were provided a comprehensive list of acute and preventative medications used to treat headaches, listing both generic and brand name(s). Subjects identified medications they ever used for their head pain. For medications that were ever used, respondents reported the number of days of use per month. We specifically asked about each marketed triptan in all formulations, ergotamine compounds, 7 nonsteroidal anti-inflammatory drugs, 9 over-the-counter medications, 8 opioids, 2 butalbital-containing combinations (using several names), and medications containing isometheptene. Finally, subjects were asked to add other medications not listed in text fields.

For individuals using more than 1 type of acute medication, we first assessed the effects of the most frequently used medication. We then adjusted for multiple use (see *Analyses*). Using a similar strategy, we assessed medications of continuous use (eg, migraine preventives and medications used daily for other medical conditions). For migraine preventives, we presented a list with the name of medications and asked whether subjects were using or had used in the past year, dose, schedule, and duration of use.

Analyses.—All statistical analyses were conducted using the SAS system version 9.1.3. Descriptive statistics such as means, standard deviations (SDs), and percents were computed using the MEANS and FREQ Procedures. Statistical models were estimated using the GENMOD Procedure, a general procedure for estimating generalized linear models. Logistic regression was used for all modeling using the binomial likelihood with logistic link function.

The contrast of interest centered on the odds of transition to TM in 2006 from EM in 2005 (compared with those who continue to have episodic migraine in 2006) as a function of use of drug class (over-the-counter medications, anti-inflammatory medications, compounds with isometheptene, opiates, barbiturates, ergotamine compounds, and triptans). Because acetaminophen was the most frequently used acute treatment, and because its use was not associated with an increased risk of TM (see *Results*), all other drugs were compared with acetaminophen use (reference class).

Odds ratio (OR) estimates were adjusted for a continuous measure of baseline headache frequency, baseline prevention medication use, and headache severity (defined on a 0-10 scale). Separate analyses were conducted for men, women, and overall. ORs were computed using linear contrasts parameterized in the ESTIMATE statement. To illustrate the influence of baseline headache frequency on developing TM, we predicted the probability of incident TM as a function of 3 categories of headache frequency at baseline: low frequency headache (<5 days per month), intermediate frequency headache (5-9 days per month), and high frequency headache (10-14 days per month) and days per month of medication use for each class of drugs. The interaction between monthly headache frequency and monthly medication use days was examined for each drug class. The monthly frequency effect for each drug class was estimated separately. For drug classes in which the monthly drug use frequency by headache frequency interaction was not statistically significant, the interaction term was trimmed, but all main effects were retained. Predicted probabilities were generated from the resulting logistic regression models. To account for a gender effect, main effects for gender were added to the model, and gender-specific predicted probabilities were generated.

This study has been approved by the Albert Einstein College of Medicine Investigation Review Board.

RESULTS

Description of the Sample.—Of 24,000 headache sufferers surveyed in 2005, 16,573 returned complete questionnaires (69.0% response rate). In the 2006 follow-up, 14,540 returned the questionnaires (87.7% response rate). Table 1 contrasts the demographics of the target sample, and of responders in the baseline (2005) and follow-up (2006) surveys. In 2005, a total of 11,094 headache sufferers had migraine; 1491 had probable migraine, 1151 had severe episodic tension-type headache, 643 had TM, and 152 had other CDHs. A total of 2042 had unclassified headaches. In 2006, a total of 9494 respondents had migraine and 520 had TM (including both incident and prevalent cases).

The demographics of the 2006 sample were similar to the demographics of the 2005 respondents, and of the target sample. Responders did not differ from nonresponders on region of the Country, State, race, gender of the head of household, annual household income, and household size. Responders differed from nonresponders on age (OR = 0.76, 95% CI = 0.72-0.78) and gender (male vs female, OR = 0.72, 95% CI = 0.67-0.76). Responders did not differ from nonresponders as a function of headache frequency or severity (Table 2). Responders and nonresponders were not significantly different as a function of type of acute medication used in 2005 (Table 2).

Since we aimed to estimate the influence of acute medication use on the incidence of TM, we restricted our analyses to those individuals with episodic migraine in 2005 who completed the 2006 survey (n = 8219). Of these individuals, 6805 (82.8%) still had episodic migraine, and 209 (2.5%) had incident TM; 14.7% remitted or were assigned a different diagnosis in 2006 (eg, probable migraine or tension-type headache). Figure 1 displays the flow of our study.

Acute Medication Exposure.—In 2005, a total of 47.4% of the migraineurs used acetaminophen, for a mean of 8.8 days per month (SD = 10.1). Among those who persisted with episodic migraine in 2006, 43.2% of the migraineurs used it, for a mean of 6.4 (7.5) days per month. The combination of acetaminophen, aspirin, and caffeine was used by 33.9% of those who developed TM (mean of 9.9 days per month) and 32.2% of those maintaining episodic migraine (5.4 days per month). Nonsteroidal anti-inflammatory medications (NSAIDs) were used by 47.4% of the incident TM (mean of 16 days) and by

Table 1.—Demographic Features for the Target Sample and Respondent Sample in 2005 and 2006

	Target sample n = 24,000 n (%)	Complete responses in 2005 n = 16,577 n (%)	Complete responses in 2006 n = 14,450 n (%)
Gender			
Male	7077 (29.5%)	4053 (24.4%)	3585 (24.7%)
Female	16,923 (70.5)	12,524 (75.6)	10,955 (75.3%)
Race			
White	20,528 (85.5)	14,364 (86.6)	12,610 (86.7%)
Black	2021 (8.4)	1311 (7.9)	1162 (8.0%)
Asian, Pacific Islander	243 (1.0)	142 (0.8)	119 (0.8%)
American Indian	216 (0.9)	124 (0.7)	112 (0.8%)
Other	362 (1.5)	225 (1.3)	181 (1.2%)
Unknown/no answer	630 (2.6)	411 (2.5)	356 (2.4%)
Age			
18-24	1768 (7.4)	741 (4.5)	484 (3.3%)
25-34	4179 (17.4)	2478 (14.9)	1795 (12.3%)
35-44	5414 (22.6)	3693 (22.3)	3004 (20.7%)
45-54	6191 (25.8)	4616 (27.9)	4240 (29.2%)
55-64	3706 (15.4)	2977 (17.9)	2957 (20.3%)
65-74	1676 (6.9)	1321 (8.0)	1359 (9.3%)
75+	1066 (4.4)	751 (4.5)	701 (4.8%)
Region			
New England	1104 (4.6)	758 (4.6)	650 (4.5%)
Middle Atlantic	3313 (13.8)	2259 (13.6)	2005 (13.8%)
East North Central	3827 (15.9)	2682 (16.3)	2374 (16.3%)
West North Central	1696 (7.1)	1200 (7.2)	1104 (7.6%)
South Atlantic	4672 (19.5)	3213 (19.4)	2827 (19.4%)
East South Central	1824 (7.6)	1306 (7.9)	1167 (8.0%)
West South Central	2791 (11.6)	1904 (11.5)	1631 (11.2%)
Mountain	1550 (6.5)	1087 (6.6)	953 (6.6%)
Pacific	3223 (13.4)	2168 (13.0)	1829 (12.6%)
Urbanization			
<100,000	3883 (16.2)	2770 (16.7)	2429 (16.7%)
100,000-499,999	4174 (17.4)	2916 (17.6)	2560 (17.6%)
500,000-1,999,999	5772 (24.1)	3987 (24.0)	3435 (23.6%)
2,000,000+	10,171 (42.4)	6904 (41.7)	6116 (42.1%)
Household size			
1 member	4527 (18.9)	3129 (18.9)	2959 (20.4%)
2 members	7950 (33.1)	5680 (34.3)	5141 (35.4%)
3 members	4421 (18.4)	3045 (18.4)	2604 (17.9%)
4 members	4018 (16.7)	2706 (16.3)	2253 (15.5%)
5+ members	3084 (12.9)	2017 (12.2)	1579 (10.9%)
Family annual income			
<$22,500	6378 (26.6)	4267 (25.7)	3659 (25.2%)
$22,500-$39,999	4893 (20.4)	3312 (19.9)	2885 (19.8%)
$40,000-$59,999	4390 (18.3)	3094 (18.7)	2701 (18.6%)
$60,000-$89,999	4234 (17.6)	2993 (18.1)	2613 (18.0%)
$90,000+	4105 (17.1)	2911 (17.7)	2682 (18.4%)

51.6% of those that continued to have episodic migraine (8.9 days).

For prescribed medications, 24.9% of those with incident TM used triptans in 2005 (8.1 days), contrasted to 20.1% of the persistent migraineurs (5.3 days). Barbiturates were used by 12.9% (10.7 days) and 6.4% (6.6 days), opiates by 21.1% (9.9 days) and 11.5% (7.9 days).

Crude Analyses.—In unadjusted analyses, we compared incident TM vs persistent episodic migraine at

Table 2.—Comparison Between Responders and Nonresponders in 2006 Based on 2005 Data for Selected Variables

Variable	Odds ratio	Lower confidence limit	Upper confidence limit
Headache frequency	1.015	0.993	1.037
Headache severity (MIDAS score)	1.007	1.002	1.011
Use of over-the-counter	2.636	0.327	21.242
Use of NSAIDs	0.445	0.055	3.588
Use of triptans	0.949	0.807	1.117
Use of opiates	1.061	0.884	1.272
Use of barbiturates	0.926	0.712	1.204
Use of compounds with isometheptene	1.17	0.824	1.662
Use of compounds with ergotamine	1.097	0.67	1.794

follow-up, among individuals that had episodic migraine at baseline. Comparisons were done by class of medication, relative to acetaminophen use. Use of NSAIDs was not associated with incident TM in univariate analyses (OR = 0.85, 95% CI = 0.6-1.17). Similarly, use of a combination of acetaminophen, aspirin, and caffeine and other over-the-counter was not associated with increased incident of TM relative to acetaminophen use (Table 3).

Compounds containing barbiturates and opiates were associated with a twofold increased risk of TM in 2006 vs maintaining an episodic migraine status (barbiturates OR = 2.06, 95% CI = 1.3-3.1; opiates OR = 1.98, 95% CI = 1.4-2.8) (Table 3). Use of triptans relative to acetaminophen nonsignificantly increased the chances of transformation (OR = 1.25, 95% CI = 0.89-1.75). Compounds containing isometheptene and ergotamine were not associated with increased risk of TM relative to acetaminophen.

Adjusted Analyses.—To disentangle the influence of headache frequency and medication use we ran adjusted models including monthly headache days, preventive medication use as well as headache severity. The results are displayed in Table 4, overall and stratified by gender, using acetaminophen as a reference group.

In these adjusted analyses, those using barbiturates (OR = 1.73, 95% CI = 1.1-2.7) or opiates (OR = 1.4, 95% CI = 1.1-2.1) were at increased risk of incident TM compared with those using acetaminophen. Those using triptans (OR = 1.05, 95% CI = 0.8-1.6) or NSAIDs (OR = 0.97, 95% CI = 0.7-1.34) were not (Table 4). Results were similar for women and men, except that the risk of incident TM associated with use of opioids was higher in men (OR = 2.76) compared with women (OR = 1.28).

Critical Dose of Exposure.—To further explore the relationship between headache frequency and days of medication use, we included days of exposure to several classes of medication (mean days of use of the specific medication), as a function of trichotomized monthly headache frequency (0-4 days per month, 5-9 days per month, 10-14 days per month) as defined in the methods section. Independent of medication type, frequency of headaches at baseline influenced incident TM (Figs. 2-5). We also assessed the main effect of gender and of baseline headache frequency, as described in the methods (Table 5).

Odds of transition to TM increased with elevated monthly barbiturate exposure (OR = 1.25, 95% CI = 1.1-1.4) controlling for the effects of gender and monthly headache frequency. Controlling for monthly barbiturate use days and gender, the risk of TM was also influenced by headache frequency at baseline (OR = 2.3, 95% CI = 1.2-4.3). Gender did not influence transition (OR = 0.95, 95% CI = 0.2-3.8).

Figure 3 displays similar analyses for opiates. Even after controlling for monthly headache frequency and gender, opiate use predicted the incidence of TM (OR = 1.44, 95% CI = 1.1-1.8). There was a significant main effect of gender (OR = 2.82, 95% CI = 1.1-6.9) (Table 5). Elevated headache frequency at baseline was significantly associated with transition to TM (OR = 3.3, 95% CI = 2.1-5.2), even after controlling for monthly opiate use and gender.

Overall, controlling for headache frequency and gender, days of exposure to triptans did not increase the risk of TM (OR = 1.07, 95% CI = 0.89-1.29). Controlling for monthly triptan use days and gender, high frequency of headaches at baseline was associated with increased risk of transition to TM (OR = 4.3, 95% CI = 2.7-6.7) (Fig. 4, Table 5). The main effect of gender on the transition to TM indicated that risk of transition was greater in women than in men

Table 3.—Medication Use for Migraine in 2005 As a Predictor of Transformed Migraine in 2006 (Unadjusted Analyses)

	Headache status in 2006				
	Transformed migraine N = 209[†]		Episodic migraine N = 6805[‡]		
	N (%)	Mean monthly days of exposure in 2005 (SD)	N (%)	Mean monthly days of exposure in 2005 (SD)	Odds ratio for TM/CM (95% CI)
Acetaminophen[†]	99 (47.4%)	12.77 (10.13)	2943 (43.2%)	6.36 (7.52)	1 (reference)
Acetaminophen + aspirin + caffeine	71 (33.9%)	9.97 (8.09)	2195 (32.2%)	5.4 (6.68)	1.06 (0,79,1.42)
Nonsteroidal medications	99 (47.4%)	13.88 (10.77)	3502 (51.4%)	7.81 (8.35)	0.85 (0.63,1.17)
Other OTCs	9 (4.3%)	17.75 (11.74)	292 (4.3%)	9.87 (11.74)	0.97 (0.49,1.93)
Prescribed NSAIDs + OTCs	100 (47.8%)	16.01 (13.52)	3524 (51.8%)	7.8 (8.94)	0.85 (0.63-1.17)
Triptans	52 (24.9%)	6.8 (7.23)	1371 (20.1%)	4.8 (11.87)	1.25 (0.89,1.75)
Barbiturate compounds	27 (12.9%)	10.74 (6.73)	440 (6.4%)	6.55 (11.57)	2.06 (1.34,3.17)
Opiates	44 (21.1%)	9.91 (16.58)	779 (12.5%)	7.57 (12.63)	1.98 (1.38,2.83)
Isometheptene compounds	8 (3.8%)	8.63 (10.93)	242 (3.5%)	3.88 (7.64)	1.02 (0.50,2.111)
Ergotamine compounds	9 (4.3%)	8.63 (10.93)	277 (4.1%)	4.34 (9.77)	1.01 (0.51,2.01)

Data captured on the 2 most frequently used medications.
[†]Individuals with transformed migraine in 2006 who had episodic migraine in 2005.
[‡]Individuals with episodic migraine in 2006 who had episodic migraine in 2005.

(OR = 2.9, 95% CI = 1.2-6.9), even after controlling for triptan use and headache frequency.

Finally, NSAIDs were protective against developing TM (OR = 0.31, 95% CI = 0.27-0.34). Even after inclusion of the interaction, the main effect of monthly headache days remained significant (OR = 0.23, 95% CI = 0.19-0.28). As revealed in the predicted probability plots, the significant interaction between monthly NSAID use days and monthly headache frequency (OR = 1.93, 95% CI = 1.82-2.06) suggested that increasing monthly NSAID use days were protective against transition to TM at low to moderate monthly headache days, but were associated with increased risk of transition to TM at high levels of monthly headache days. For NSAIDs, the main effect of gender indicated that women were at considerably greater risk of transition to TM than men (OR = 13.6, 95% CI = 9.3-19.9).

Table 4.—Association of Medication Use for Migraine in 2005 As a Predictor of Headache Status in 2006 Stratified by Gender

	Unadjusted women OR (95% CI)	Adjusted women OR (95% CI)	Unadjusted men OR (95% CI)	Adjusted men OR (95% CI)	Overall adjusted OR (95% CI)
Acetaminophen	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Acetaminophen + aspirin + caffeine	1.05 (0.76,1.46)	0.85 (0.60,1.21)	1.18 (0.62,2.25)	0.94 (0.46,1.89)	0.87 (0.64,1.19)
Nonsteroidal medications	0.88 (0.62,1.26)	0.97 (0.67,1.42)	0.73 (0.38,1.41)	0.93 (0.46,1.89)	0.97 (0.69,1.34)
Other over-the- counter	0.81 (0.35,1.87)	0.94 (0.40,2.21)	1.84 (0.55,6.19)	1.02 (0.26,4.04)	1.02 (0.50,2.06)
Prescribed meds + NSAIDs	0.88 (0.62,1.26)	0.97 (0.67,1.41)	0.85 (0.46,1.55)	0.93 (0.46,1.88)	0.96 (0.69,1.34)
Triptans	1.11 (0.76,1.63)	0.93 (0.62,1.40)	2.37 (1.20,4.71)	2.11 (0.97,4.63)	1.05 (0.73,1.50)
Barbiturate compounds	2.29 (1.44,3.64)	1.97 (1.21,3.23)	1.42 (0.43,4.72)	1.29 (0.38,4.37)	1.73 (1.10,2.73)
Opiates	1.74 (1.15,2.63)	1.28 (0.81,1.97)	3.48 (1.74,6.96)	2.76 (1.20,6.38)	1.44 (1.10,2.08)
Isometheptene compounds	0.94 (0.41,2.16)	0.85 (0.36,2.02)	1.64 (0.38,7.09)	1.60 (0.34,7.54)	0.93 (0.44,1.98)

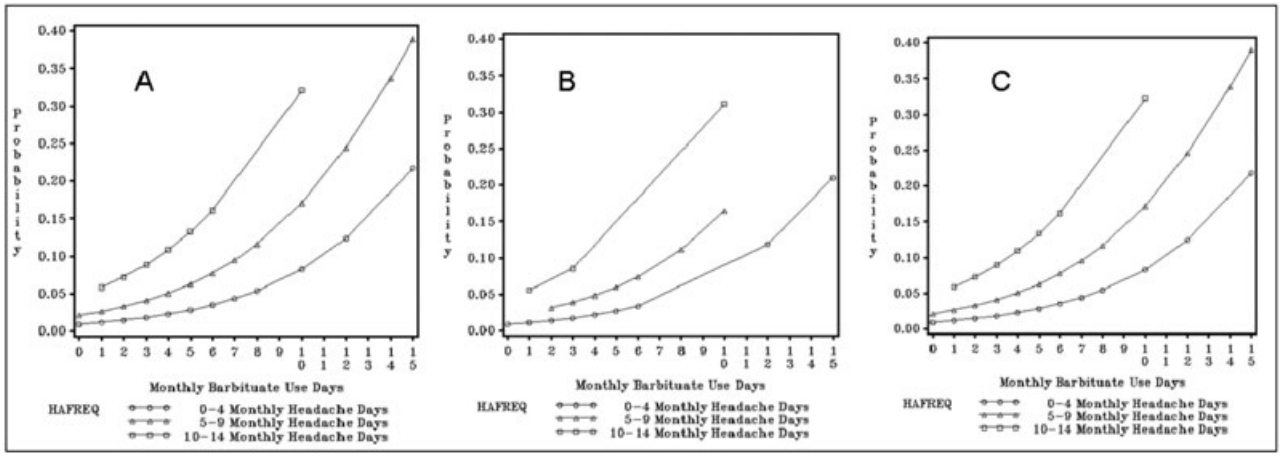

Fig 2.—Probability of developing transformed/chronic migraine in 2006 as a function of headache frequency and monthly barbiturate use in 2005 overall (A), in men (B), and women (C).

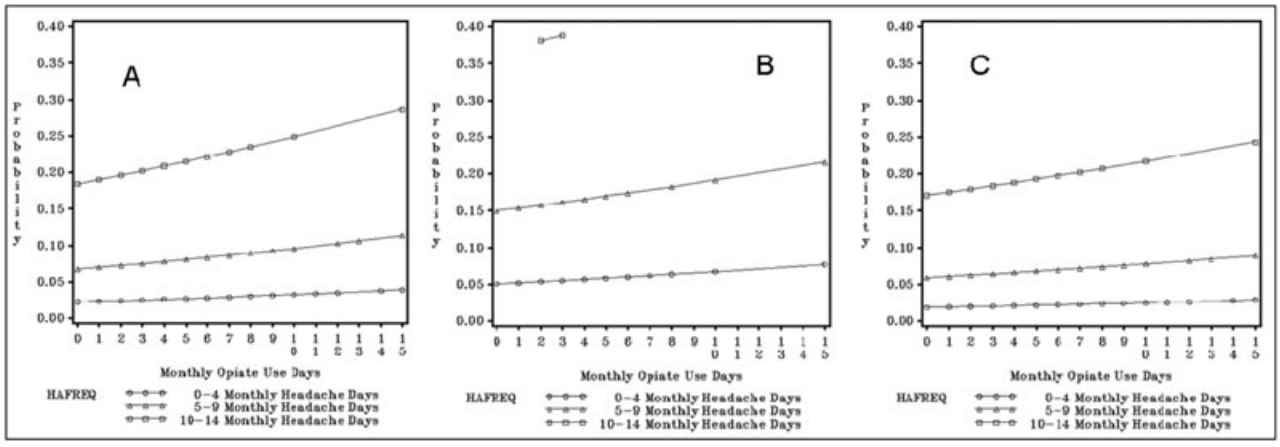

Fig 3.—Probability of developing transformed migraine in 2006 as a function of headache frequency and monthly opiate use in 2005 overall (A), in men (B), and women (C).

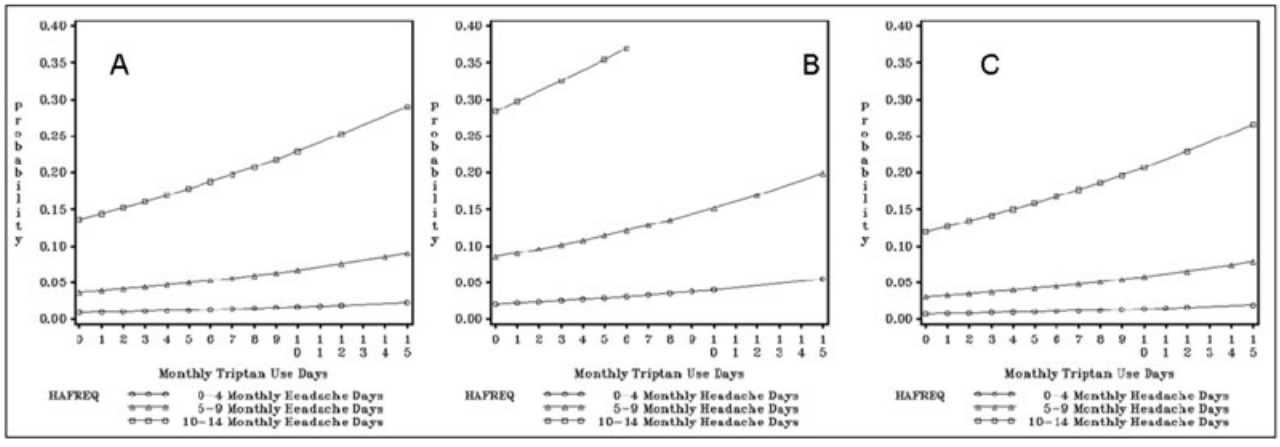

Fig 4.—Probability of developing transformed migraine in 2006 as a function of headache frequency and monthly triptan use in 2005 overall (A), in men (B), and women (C).

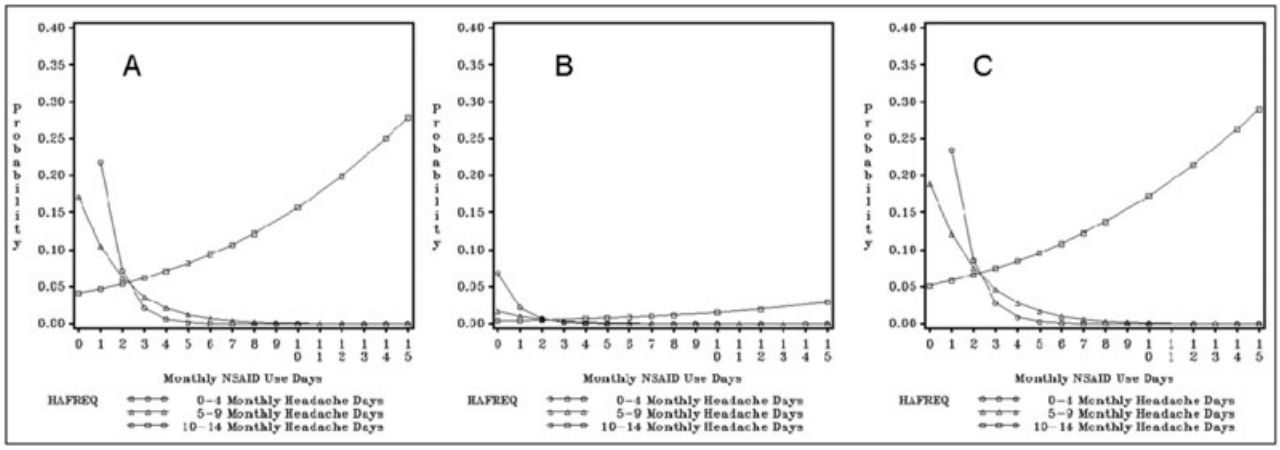

Fig 5.—Probability of developing transformed migraine in 2006 as a function of headache frequency and monthly use of anti-inflammatory medications in 2005 overall (A), in men (B), and women (C).

DISCUSSION

Frequent use of analgesics is an important health problem and may be rapidly increasing in the population.[21] Research conducted by the National Institute of Drug abuse suggests that overuse of medications reached alarming levels for certain agents, especially opioid analgesics and stimulants, and that future research should focus on the identification of clinical practices aiming to the treatment of pain that minimize the risks of addiction or overuse, the development of guidelines for early detection and management of addiction, and the development of clinically effective agents that minimize the risks for abuse.[22]

Transformed migraine is associated with medication overuse in a number of clinic-based studies and in 2 population studies.[4,7,23-26] In a study that evaluated headache outcomes in individuals who underwent total colectomy for ulcerative colitis, of patients treated with daily opioids to control the bowel movements those with migraine were likely to develop TM.[24] A second study found that of patients treated with daily analgesics (62.5% used opiates) for medical conditions like rheumatoid arthritis, those with migraine developed TM at a higher-than-expected rate.[25] Similarly, of subjects with cluster headache taking daily analgesics, those with episodic migraine developed TM.[26] These clinic-based studies enrolled highly selected samples, were modest in size, and did not assess the influence of specific classes of medication. Data from the population partially support these clinic-based studies. In a longitudinal study, headache frequency predicted chronic daily headache after 1 year of follow-up.[4] A second

Table 5.—Odds Ratio and Fits Statistics for Overall Drug Use, Frequency of Use, Main Effect of Headache Frequency on the Effect of Exposure, and Main Effect of Gender on the Effect of Exposure

Exposure	Effect of exposure	Main effect of days of use OR (95% CI)	Main effect of headache frequency OR (95% CI)	Main effect of gender OR (95% CI)	Interaction of monthly use days and monthly headache days OR (95% CI)
Barbiturates	1.73 (1.10,2.73)	1.25 (1.13-1.38)	2.29 (1.21,4.35)	0.95 (0.24,3.81)	Trimmed
Opiates	1.44 (1.10,2.08)	1.03 (0.93,1.14)	3.29 (2.06,5.26)	2.82 (1.15,6.90)	Trimmed
Triptans	1.05 (0.73,1.50)	1.07 (0.97,1.17)	4.26 (2.69,6.73)	2.92 (1.23,6.92)	Trimmed
NSAIDs	0.97 (0.69,1.34)	0.31 (0.27,0.34)	0.23 (0.19,0.28)	13.58 (9.26,19.92)	1.93 (1.82,2.06)

population-based study showed that TM was much more likely in those with analgesic exposure 10 years earlier (OR = 7.5, 95% CI = 6.6-8.5).[23] This large study is limited by the lack of baseline information on headache status.

Our study supports and expands these previous results. Our findings may be summarized as follows: (1) Among individuals with episodic migraine, the average annual incidence of TM is 2.5%. This estimate is in close agreement with a prior population-based longitudinal study.[5] (2) Both frequency of headaches and use of specific classes of acute medication are independently associated with the development of TM (see Table 5). (3) Within a class of acute treatments, the influence of drug is modified by frequency of use (Table 5 and Figs. 2-4) as well as headache frequency. (4) The influence of drug remains after adjusting for baseline headache characteristics. (5) Relationships of medication type and frequency of use to gender and headache frequency are complex. Use of opiates and barbiturates is associated with an overall increased risk of TM, at any frequency of use. Although triptan use days did not significantly predict transition to TM, controlling for monthly triptan use days, monthly headache days and gender were both significant predictors of transition to TM. NSAID use was associated with a decreased risk of TM, but only in those with low or intermediate frequency of headaches. (6) Gender seems to influence the transition to TM.

High frequency of headaches at baseline has been associated with an increased risk of chronic daily headache. In the Frequent Headache Epidemiology Study, the risk increased in a nonlinear manner with baseline headache frequency; elevated risk for chronic daily headache primarily occurred in subjects who experienced 3 or more headaches per month.[3] It has been speculated that repetitive activation of trigeminovascular neurons as a function of migraine pain leads to repetitive activation of modulatory pain pathways involving the periaquedutal gray (PAG) area, which is fundamental for the endogenous modulation of pain.[27] Repetitive activation of the PAG may, in turn, lead to impairment of neuronal function at this area with further predisposition to migraine.[28,29]

We also found that specific medications (barbiturates and opioids) are associated with incident TM, and now considered putative mechanisms. As choice of medication is presumably related to headache severity as well as patient characteristics or comorbidities, it is possible that choice of medication is a marker, rather than a cause, of TM incidence. However, our data suggest that headache severity is not a strong driver of these results given that the relationship persisted after adjusting for baseline headache severity. As the relationship between use of barbiturates or opioids and incident TM was evident for even minimal use (see predicted probability plots), it may be that this class of medication is a marker for a multi-pain phenotype that is associated with a poorer prognosis. Specifically designed clinical studies are needed to test this hypothesis. Second, we note that frequency of medication use *per se*, after adjusting for frequency of headache, did not predict the incidence of TM. If frequency of medication use, independent of class, accounted for the risk of TM, combinations containing acetaminophen, as well as NSAIDs, would be more strongly associated with TM, since they were used more frequently than bartiburates and opioids (Table 4).

Of particular interest is the fact that increased monthly NSAID use days protected against TM in migraineurs with less than 10-14 headache days per month. The protective effect of NSAIDs for the development of TM has not been previously described or investigated. NSAIDs have been reported to protect against other neurologic diseases including Alzheimer's disease and Parkinson's disease.[30-32] For other neurological diseases, chronic inflammation seems to induce activation of glia, with consequent liberation of free radicals and other neurotoxic substances.[30-32] The release of inflammatory mediators is of importance not only in migraine pain, but also in the sensitization of trigeminal neurons. It has been suggested that individuals with central sensitization respond poorly to tritpans but not to NSAIDs.[33,34] Perhaps drugs that directly address migraine-related inflammation may prevent or reverse central sensitization and the risk of TM. In individuals with high frequency of attacks, central sensitization is frequently present even between the

attacks[17] and, accordingly, the NSAIDs would not be protective.

Caution is required in interpreting our data. First, our definition of migraine and TM was based on a questionnaire and not an in-person clinical assessment. Though our questionnaires were well validated and have sensitivity and specificity some degree of diagnostic error is likely.[16,20] It is unlikely that it could account for our strikingly positive findings, however. Second, our definition of TM follows the Silberstein and Lipton criteria,[2] instead of the revised criteria of the International Classification of Headache Disorders (ICHD-2R) for CM which would be difficult to implement in a large population study.[3] We have shown that of individuals with TM, 93% meet CM-R criteria so classification error is likely to be low. Third, medication use was self-reported. This strategy has been widely used, and data from self-reported use of substances are used for government statistics.[35] Since we used a report of medication use 1 year to predict headache type the next recall bias is unlikely. We plan to further refine our methods by conducting studies in the population, while using pharmacy claims and electronic health records to customize and validate the medication consumption data. Finally, despite our sample size, since TM is a relatively rare event, we had only 209 incident TM cases limiting our power for some multivariate models. Strengths of this study include the large representative sample of migraine sufferers, the longitudinal follow-up, and the depth of exposure and outcome data. As we continue to follow the cohort we will assess persistence and remission of TM and the influence of medications and other risk factors on these transitions.

These findings have potential implications for clinical practice. We suggest that use of opiates and barbiturates should be limited and well monitored in migraineurs. We also suggest particular caution in using opiates to treat migraine in men. Caution is also advised in individuals with high frequency of headaches using any medication.

REFERENCES

1. Headache Classification. Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. 2nd edn. *Cephalalgia*. 2004;24(Suppl. 1):1-160.
2. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: Field trial of revised IHS criteria. *Neurology*. 1996;47:871-875.
3. Classification H, Olesen J, Bousser MG, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia*. 2006;26:742-746.
4. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106:81-89.
5. Castillo J, Muñoz P, Guitera V, Pascual J. Epidemiology of chronic daily headache in the general population. *Headache*. 1999;39:190-196.
6. Silberstein SD, Silberstein JR. Chronic daily headache: Long-term prognosis following inpatient treatment with repetitive IV DHE. *Headache*. 1992;32: 439-445.
7. 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.
8. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression (or for chronic daily headaches)—clinical lessons. *Headache*. 2006;46 (Suppl. 3):S144-S146.
9. Mathew NT. Drug-induced headache. *Neurol Clin*. 1990;8:903-912.
10. Bigal ME, Rapoport AM, Sheftell FD, et al. Transformed migraine and medication overuse in a tertiary headache centre—clinical characteristics and treatment outcomes. *Cephalalgia*. 2004;24:483-490.
11. Rapoport A, Stang P, Gutterman DL, et al. Analgesic rebound headache in clinical practice: Data from a physician survey. *Headache*. 1996;36:14-19.
12. Dodick DW. Debate: Analgesic overuse is a cause, not consequence, of chronic daily headache. Analgesic overuse is not a cause of chronic daily headache. *Headache*. 2002;42:547-554.
13. Tepper SJ. Debate: Analgesic overuse is a cause, not consequence, of chronic daily headache. Analgesic overuse is a cause of chronic daily headache. *Headache*. 2002;42:543-547.
14. Sarchielli P, Di Filippo M, Nardi K, Calabresi P. Sensitization, glutamate, and the link between migraine and fibromyalgia. *Curr Pain Headache Rep*. 2007;11:343-351.

15. Rome HP Jr, Rome JD. Limbically augmented pain syndrome (LAPS): Kindling, corticolimbic sensitization, and the convergence of affective and sensory symptoms in chronic pain disorders. *Pain Med*. 2000;1:7-23.
16. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.
17. Lipton RB, Bigal ME, Burstein R, et al. Cutaneous allodynia in the migraine population. *Ann Neurol*. 2008;63:148-158.
18. Bigal ME, Tsang A, Loder E, Serrano D, Reed ML, Lipton RB. Body mass index and episodic headaches: A population-based study. *Arch Intern Med*. 2007;167:1964-1970.
19. Silberstein S, Loder E, Diamond S, et al. Probable migraine in the United States: results of the American Migraine Prevalence and Prevention (AMPP) study. *Cephalalgia*. 2007;27:220-234.
20. Liebestein M, Bigal ME, Sheftell FD, et al. Validation of the chronic daily headache questionnaire. *Neurology*. 2007;68(Suppl. 1):369.
21. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug Alcohol Depend*. 2006; 81:103-107.
22. Compton WM, Stein JB, Robertson EB, Pintello D, Pringle B, Volkow ND. Charting a course for health services research at the National Institute on drug abuse. *J Subst Abuse Treat*. 2005;29:167-172.
23. Zwart JA, Dyb G, Hagen K, et al. Analgesic overuse among subjects with headache, neck, and low-back pain. *Neurology*. 2004;62:1540-1544.
24. Wilkinson SM, Becker WJ, Heine JA. Opiate use to control bowel motility may induce chronic daily headache in patients with migraine. *Headache*. 2001;41:303-309.
25. Bahra A, Walsh M, Menon S, Goadsby PJ. Does chronic daily headache arise de novo in association with regular use of analgesics? *Headache*. 2003;43: 179-190.
26. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. *Neurology*. 2006;67: 109-113.
27. Welch KMA, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: Cause or the burden of illness? *Headache*. 2001;41:629-637.
28. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*. 2000;123:1703-1709.
29. Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. *Headache*. 2008;48:7-15.
30. McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. *Mov Disord*. 2008;23:474-483.
31. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. *Neurology*. 2007;69:1836-1842.
32. Weggen S, Rogers M, Eriksen J. NSAIDs: Small molecules for prevention of Alzheimer's disease or precursors for future drug development? *Trends Pharmacol Sci*. 2007;28:536-543. [Epub 2007 Sep 27].
33. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: A race against the development of cutaneous allodynia. *Ann Neurol*. 2004;55:19-26.
34. Jakubowski M, Levy D, Kainz V, Zhang XC, Kosaras B, Burstein R. Sensitization of central trigeminovascular neurons: Blockade by intravenous naproxen infusion. *Neuroscience*. 2007;148:573-583. [Epub 2007 Jul 25].
35. Center for Disease Control and Prevention. *Substance Abuse*. Available at: http://www.cdc.gov/correctionalhealth/specialtopics.htm. Accessed December 16, 2007.