Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine

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ABSTRACT

Objective: To test the hypothesis that ineffective acute treatment of episodic migraine (EM) is associated with an increased risk for the subsequent onset of chronic migraine (CM).

Methods: In the American Migraine Prevalence and Prevention Study, respondents with EM in 2006 who completed the Migraine Treatment Optimization Questionnaire (mTOQ-4) and provided outcome data in 2007 were eligible for analyses. The mTOQ-4 is a validated questionnaire that assesses treatment efficacy based on 4 aspects of response to acute treatment. Total mTOQ-4 scores were used to define categories of acute treatment response: very poor, poor, moderate, and maximum treatment efficacy. Logistic regression models were used to examine the dichotomous outcome of transition from EM in 2006 to CM in 2007 as a function of mTOQ-4 category, adjusting for covariates.

Results: Among 5,681 eligible study respondents with EM in 2006, 3.1% progressed to CM in 2007. Only 1.9% of the group with maximum treatment efficacy developed CM. Rates of new-onset CM increased in the moderate treatment efficacy (2.7%), poor treatment efficacy (4.4%), and very poor treatment efficacy (6.8%) groups. In the fully adjusted model, the very poor treatment efficacy group had a more than 2-fold increased risk of new-onset CM (odds ratio = 2.55, 95% confidence interval 1.42–4.61) compared to the maximum treatment efficacy group.

Conclusion: Inadequate acute treatment efficacy was associated with an increased risk of new-onset CM over the course of 1 year. Improving acute treatment outcomes might prevent new-onset CM, although reverse causality cannot be excluded. *Neurology*® 2015;84:688–695

GLOSSARY

AMPP = American Migraine Prevalence and Prevention; **ASC-12** = Allodynia Symptom Checklist-12; **CI** = confidence interval; **CM** = chronic migraine; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **EM** = episodic migraine; **ICHD-2** = *International Classification of Headache Disorders*, 2nd edition; **MIDAS** = Migraine Disability Assessment Scale; **mTOQ-4** = Migraine Treatment Optimization Questionnaire; **NSAID** = nonsteroidal anti-inflammatory drug; **OR** = odds ratio; **PHQ-9** = Patient Health Questionnaire–depression module.

Several risk factors are associated with the development of chronic migraine (CM) in persons with episodic migraine (EM), including headache frequency, headache-related disability, and certain acute treatments, particularly opioids and barbiturates.^{1,2} With more frequent migraine attacks, prolonged activation of neuronal networks involved in pain processing during attacks may lower the threshold for subsequent attacks through neuroplastic mechanisms.^{3,4} As an extension, we predict that poor acute treatment efficacy among individuals with EM, leading to longer periods of exposure to pain, might increase the risk of new-onset CM. We measured acute treatment efficacy with the Migraine Treatment Optimization Questionnaire (mTOQ-4)⁵ and assessed the relationship of mTOQ-4 scores in 2006 in persons with EM as a predictor of CM onset in 2007 controlling for covariates to test this hypothesis.

METHODS Study design. The American Migraine Prevalence and Prevention (AMPP) Study is a longitudinal, population-based study.^{6,7} Self-administered questionnaires were mailed to a stratified sample of 120,000 US households. Of 162,562 respondents, 28,261 reported experiencing “severe headache” in the preceding year and provided useable data. A random sample of 24,000 respondents age ≥18 years with severe headache were invited to participate in a longitudinal portion of the study where

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participants completed an annual self-administered questionnaire from 2005 to 2009. AMPP Study respondents who met modified International Classification of Headache Disorders, 2nd edition (ICHD-2) criteria⁸ for EM and completed the mTOQ-4 in 2006 and provided necessary data in 2007 were eligible for the current analyses.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Albert Einstein College of Medicine Institutional Review Board.

Diagnostic and treatment questions. The AMPP Study survey is a self-administered questionnaire assessing information necessary to assign a headache diagnosis among other data. The American Migraine Study/AMPP diagnostic module was used to assign headache diagnoses. This module has a sensitivity of 100% and specificity of 82% for a diagnosis of migraine,⁹ and a sensitivity of 91% and specificity of 80% for the diagnosis of CM based on ICHD-2 criteria.¹⁰ No significant changes occurred between the ICHD-2 and ICHD-3 beta¹¹ related to the criteria used for the diagnosis of migraine. Study criteria used for migraine are ICHD-3 beta criteria with the exception of criterion A (a lifetime history of ≥ 5 migraine attacks). To define CM, we used Silberstein-Lipton criteria,¹² which are essentially ICHD-3 beta criteria with the exception of criterion C, which stipulates that of the ≥ 15 days with headache, ≥ 8 are identified as migraine. This criterion is difficult to assess in a large, self-report data collection paradigm. It requires the use of daily diaries and physician interviews to accurately assess. However, analyses of this criterion in controlled clinical trials suggest that the majority of those who would meet criteria without criterion C also meet strict ICHD-3 beta criteria using criterion C.¹³

Self-reported data on acute and preventive medication use for headache were collected. Food and Drug Administration–approved or widely used acute medications for headache/migraine were listed by both generic and brand names. Respondents identified all medications they used to treat their “most severe type of headaches.” For analyses, medications were combined into classes: simple analgesics, combination analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans. Opioids and barbiturates were combined and analyzed as a single category.

Treatment efficacy. The mTOQ is a validated, self-administered questionnaire that assesses acute treatment in several areas including treatment efficacy. The original validation work was conducted on the 19-item mTOQ using dichotomous yes/no response options.⁵ We subsequently modified the response options to 4 frequency-based response options (never, rarely, $<$ half the time, and $\geq$ half the time) and selected 6 key questions. The ordinal 6-item version was included in the AMPP Study survey in 2006 and 2007. Additional validation work has been done on this version of the questionnaire.¹⁴ From the 6 items, we selected the 4 that best assessed treatment efficacy. We excluded tolerability because it did not assess a concept related to treatment efficacy and quick return to function due to redundancy with the other items. The mTOQ-4 items, response options, and scoring are shown in table e-1 on the *Neurology*[®] Web site at Neurology.org. Briefly, respondents were asked “Please answer the following questions about the medication(s) that you currently use to treat headaches.” Response options are scored as never (0), rarely (0), $<$ half the time (1), $\geq$ half the time (2). Sum scores range from 0 to 8 and were not normally distributed.¹⁴ We defined 4 categories of treatment efficacy: very poor treatment efficacy (0), poor treatment efficacy (1–5), moderate treatment efficacy (6–7), and maximum treatment efficacy (8). Cut scores were defined

based on clinical judgment and psychometric analysis. After selecting these cut scores, we performed sensitivity analyses with various cut scores and obtained fundamentally similar results (data available upon request).

Other variables. Sociodemographic data based on self-report included measures of age, sex, and annual household income (which was coded dichotomously with a cut point of $\geq \$50,000$).

Headache-related disability was assessed with the Migraine Disability Assessment Scale (MIDAS), a 5-item, self-administered questionnaire that assesses days of missed or substantially reduced activity due to headache in the preceding 3 months in 3 domains: schoolwork/paid employment, household work or chores, and nonwork (family, social, and leisure) activities.¹⁵ Sum scores were analyzed as a continuous variable. The number of headache days over the preceding 3 months was obtained from the MIDAS. Monthly headache days were determined by dividing that number by 3. Headache day frequency per month was coded dichotomously as ≤ 4 or ≥ 5 headache days per month.

Cutaneous allodynia was assessed using the Allodynia Symptom Checklist–12 (ASC-12).^{16,17} Sum scores on the ASC-12 range from 0 to 24 and are divided into no allodynia (< 3), mild allodynia (3–5), moderate allodynia (6–8), and severe allodynia (≥ 9).

Depression was assessed with the Patient Health Questionnaire–depression module (PHQ-9),¹⁸ a validated measure of major depressive disorder based on *DSM-IV* criteria.¹⁹ The PHQ-9 contains 9 items with 4 frequency response options (scored 0, 1, 2, and 3). Sum scores are divided into 4 categories: none/minimal (0–4), mild (5–9), moderate (10–14), moderate–severe (15–19), and severe (20–27). As per scoring instructions, a cut score of ≥ 10 was used to define the dichotomous depression variable.

Analyses. Analyses were performed using SPSS version 22.0.0 (IBM, Armonk, NY; 2011). Descriptive statistics were generated for all variables and reported by the total sample and by treatment efficacy groups. Responses and rates of new-onset CM in 2007 among respondents with EM in 2006 are reported for each of the individual mTOQ-4 items. Dichotomous variables including sex, annual household income ($< \$50,000$ vs $\geq \$50,000$), cutaneous allodynia (< 3 vs ≥ 3), monthly headache day frequency (< 5 vs ≥ 5 days), acute medication use, and depression (< 10 vs ≥ 10) were modeled with binary logistic regression. Age was modeled with linear regression and MIDAS, which has a count distribution, was modeled with negative binomial regression. For all models, odds ratio (OR), unstandardized linear regression coefficient (B), or rate ratio and 95% confidence intervals (CIs) are provided. A p value of ≤ 0.05 was used to identify statistically significant effects.

Multivariate binary logistic regression analysis was used to assess the influence of acute treatment efficacy (mTOQ-4 treatment efficacy group) in 2006 on onset of CM in 2007 adjusting for sociodemographics, headache characteristics, headache-related disability, and acute treatment use. The reference group is all other headache status outcomes, which could include EM, no headache diagnosis, or another headache diagnosis. ORs and 95% CIs are provided. Regression models were run sequentially first adjusting for sociodemographics (age, sex, annual household income), then adding in additional covariates as follows: headache characteristics (cutaneous allodynia, headache day frequency per month, and headache-related disability), depression, and acute medication use by class (simple analgesics, combination analgesics, NSAIDs, triptans, and narcotic/barbiturates; adding medication classes one at a time, then all together in one model). Final

Table 1 Sociodemographic characteristics, headache features, and current acute headache medication use by level of treatment efficacy in the study sample

Statistical model/variable	Total sample, n = 5,681	Degree of treatment efficacy (mTOQ-4 category)			
		Maximum treatment efficacy (8), n = 1,648	Moderate treatment efficacy (4–7), n = 2,657	Poor treatment efficacy (1–3), n = 1,007	Very poor treatment efficacy (0), n = 369
Sociodemographics and headache day frequency					
Age, y, mean (SD) ^a	47.9 (12.5)	48.1 (12.6)	47.9 (12.5)	47.8 (12.3)	47.5 (13.2)
Sex, n (%) ^b					
Male	990 (17.4)	288 (17.5)	472 (17.8)	161 (16)	69 (18.7)
Female	4,691 (82.6)	1,360 (82.5)	2,185 (82.2)	846 (84.0)	300 (81.3)
Annual household income, n (%) ^c					
<\$50,000	2,991 (52.6)	780 (47.3)	1,414 (53.2)	569 (56.5)	228 (61.8)
≥\$50,000	2,690 (47.4)	868 (52.7)	1,243 (46.8) ^d	438 (43.5) ^d	141 (38.2) ^d
Headache-related disability (MIDAS score), mean (SD) ^b	9.42 (14.2)	6.8 (11.9)	9.0 (12.8) ^d	12.9 (17.1) ^d	14.4 (20.5) ^d
Cutaneous allodynia (ASC-12 score dichotomous ≥3), n (%) ^c					
Negative	2,247 (40.1)	839 (52)	1,016 (38.7)	278 (27.9)	114 (31.6)
Positive	3,353 (59.9)	774 (48)	1,612 (61.3) ^d	720 (72.1) ^d	247 (68.4) ^d
Headache days/month, n (%) ^c					
<5	4,421 (79.5)	1,333 (82.9)	2,065 (79.1)	758 (77.2)	265 (73.6)
≥5	1,137 (20.5)	274 (17.1)	544 (20.9) ^d	224 (22.8) ^d	95 (26.4) ^d
Depression (PHQ-9, dichotomous ≥10), n (%) ^c					
Negative	4,623 (82.1)	1,446 (88.1)	2,165 (82.3)	747 (75.1)	265 (72.6)
Positive	1,010 (17.9)	196 (11.9)	466 (17.7) ^d	248 (24.9) ^d	100 (27.4) ^d
Current reported acute headache pharmacologic treatment use by class (dichotomous) ^d					
Simple analgesic use, n (%) ^c					
No	2,928 (51.5)	968 (58.7)	1,340 (50.4)	460 (45.7)	160 (43.4)
Yes	2,753 (48.5)	680 (41.3)	1,317 (49.6) ^d	547 (54.3) ^d	209 (56.6) ^d
NSAID use, n (%) ^c					
No	3,058 (53.8)	976 (59.2)	1,382 (52)	509 (50.5)	191 (51.8)
Yes	2,623 (46.2)	672 (40.8)	1,275 (48) ^d	498 (49.5) ^d	178 (48.2) ^d
Triptan use, n (%) ^c					
No	4,406 (77.6)	1,174 (71.2)	2,067 (77.8)	840 (83.4)	325 (88.1)
Yes	1,275 (22.4)	474 (28.8)	590 (22.2) ^d	167 (16.6) ^d	44 (11.9) ^d
Combination analgesic use, n (%) ^c					
No	3,626 (63.8)	1,074 (65.2)	1,652 (62.2)	635 (63.1)	265 (71.8)
Yes	2,055 (36.2)	574 (34.8)	1,005 (37.8) ^d	372 (36.9)	104 (28.2) ^d
Opioids or barbiturates, n (%) ^c					
No	4,647 (81.8)	1,409 (85.5)	2,156 (81.1)	779 (77.4)	303 (82.1)
Yes	1,034 (18.2)	239 (14.5)	501 (18.9) ^d	228 (22.6) ^d	66 (17.9)

Abbreviations: ASC-12 = Allodynia Symptom Checklist-12; MIDAS = Migraine Disability Assessment Scale; mTOQ-4 = Migraine Treatment Optimization Questionnaire; NSAID = nonsteroidal anti-inflammatory drug; PHQ-9 = Patient Health Questionnaire–depression module.

Study sample is respondents who met criteria for episodic migraine in the 2006 American Migraine Prevalence and Prevention Study survey and provided necessary data in both 2006 and 2007 survey years.

^aLinear regression (age).

^bGeneral linear model: negative binomial distribution log link function (MIDAS).

^cBinary logistic regression (binary variables): respondents may be using more than one class of acute medication for headache.

^dStatistically significant difference relative to the maximum efficacy group.

models removed nonsignificant covariates including allodynia and depression. Medication use models by class are presented in table e-2.

RESULTS In 2006, we mailed 20,639 questionnaires and received 14,540 responses (70.4%). In 2007, 20,489 surveys were mailed and 14,069 surveys were returned (68.7%). There were 5,681 eligible respondents with EM who completed the mTOQ-4 in 2006 and provided necessary outcome data in 2007. The sample was predominantly female (82.6%), had a mean age of 47.9 years, and most participants reported an annual household income below \$50,000 (52.6%) (table 1).

Descriptive analyses showed that 369 respondents (6.5%) had very poor acute treatment efficacy, 1,007 (17.7%) had poor treatment efficacy, 2,657 (46.8%) had moderate treatment efficacy, and 1,648 (29.0%) had maximum treatment efficacy (table 1). Age and sex did not vary significantly across treatment efficacy groups. As treatment efficacy increased, the proportion of participants with annual household income <\$50,000 declined. In comparison to the group with maximal efficacy, the odds of being in the high-income groups were 0.79 (95% CI 0.70–0.89) for the moderate group, 0.69 (95% CI 0.59–0.81) for the poor group, and 0.56 (95% CI 0.44–0.70) for the very poor group (ORs not shown in table 1). MIDAS scores increased as treatment efficacy decreased from 6.8 for the maximum efficacy group to 14.4 for the very poor efficacy group. Compared to the maximum

treatment efficacy group, there were increases in reporting ≥ 5 headache days per month by moderate (OR 1.28, 95% CI 1.09–1.51), poor (OR 1.44, 95% CI 1.18–1.75), and very poor treatment efficacy (OR 1.74, 95% CI 1.33–2.28) groups.

Respondents using simple analgesics or NSAIDs were less likely to be in the group with maximum treatment efficacy (table e-2). The pattern was reversed among triptan users, who were more likely to be in the group with maximum treatment efficacy. The odds of triptan use declined for the moderate (OR 0.71, 95% CI 0.61–0.81), poor (OR 0.49, 95% CI 0.40–0.60), and very poor treatment efficacy (OR 0.34, 95% CI 0.24–0.47) groups. Current usage of combination analgesic medications was not significantly different across treatment efficacy groups, and only the moderate (OR 1.37, 95% CI 1.16–1.62) and poor treatment efficacy groups (OR 1.73, 95% CI 1.41–2.11) showed significantly increased odds for narcotic/barbiturate medication use compared to the maximum treatment efficacy group.

Of 5,681 individuals with EM in 2006, 174 (3.1%) had new-onset CM, 4,451 (78.3%) remained EM, and 1,056 (18.6%) had other outcomes (e.g., no headache diagnosis, tension-type headache) in 2007. Rates of new-onset CM varied by response to individual mTOQ items (table 2). Higher-frequency responses (indicating greater treatment efficacy) were associated with lower rates of new-onset CM for all items. Of note, 4.4% of respondents who endorsed that they were never or rarely pain-free 2 hours after

Table 2 Response rates and headache frequency category (CM vs EM) in 2007 among persons with EM in 2006 by response to individual mTOQ-4 items in 2006

	Never/ rarely	Less than half the time	Half the time or more
1. After taking your migraine medication, are you pain-free within 2 hours for most attacks?			
EM respondents in 2006, n	1,445	1,669	2,567
CM in 2007, n (%)	63 (4.4)	49 (2.9)	62 (2.4)
2. Does one dose of your migraine medication usually relieve your headache and keep it away for at least 24 hours?			
EM respondents in 2006, n	1,484	1,467	2,730
CM in 2007, n (%)	79 (5.3)	41 (2.8)	54 (2.0)
3. Are you comfortable enough with your migraine medication to be able to plan your daily activities?			
EM respondents in 2006, n	671	1,224	3,786
CM in 2007, n (%)	36 (5.4)	40 (3.3)	98 (2.6)
4. After taking your migraine medication, do you feel in control of your migraines enough so that you feel there will be no disruption to your daily activities?			
EM respondents in 2006, n	1,095	1,684	2,902
CM in 2007, n (%)	53 (4.8)	50 (3.0)	71 (2.4)

Abbreviations: CM = chronic migraine; EM = episodic migraine; mTOQ-4 = Migraine Treatment Optimization Questionnaire.

taking their usual headache medications progressed to CM the following year compared with 2.4% of those who endorsed that they were pain-free half the time or more. Similarly, 5.3% of respondents who reported that their acute migraine medication never or rarely relived pain and kept it away for 24 hours progressed to CM the following year, compared with only 2.0% of those who reported sustained pain relief half the time or more. When analyzed by treatment efficacy group, only 1.9% of the maximum treatment efficacy group progressed to CM the following year, compared with 2.7% of moderate treatment efficacy, 4.4% of poor efficacy, and 6.8% of the very poor treatment efficacy group (figure).

Predictors of CM onset in multivariate models. We examined the relationship of treatment efficacy group membership to CM onset adjusting for covariates in a series of nested models (table 3; table e-2). When adjusted for sociodemographics (model 1), poor treatment efficacy (OR 2.17, 95% CI 1.36–3.44) and very poor treatment efficacy (OR 3.39, 95% CI 1.98–5.80) groups showed increased relative odds of CM onset. Variables including age

and sex were not associated with CM onset, but higher annual household income (>\$50,000) was associated with a reduced risk of CM onset (OR 0.49, 95% CI 0.36–0.69). When we added headache day frequency per month, cutaneous allodynia, and headache-related disability (MIDAS), allodynia was not a significant predictor of CM onset (OR 1.13, 95% CI 0.79–1.63) and was therefore trimmed from the model. We then added depression to the model and found that very poor treatment efficacy was associated with a 2.39-fold increased risk in CM onset (95% CI 1.33–4.28); however, the effect of depression was attenuated by headache-related disability and was not significant when MIDAS was included in the model. Depression was significant only when headache-related disability was removed from the model. The relative odds of CM onset related to a PHD-9 score of ≥ 10 was 1.46 (95% CI 1.02–2.09). Depression was not retained in the final model.

Finally, we assessed the influence of current acute headache medication use by class (dichotomous). We added medication classes individually (table 3, table e-

Figure Rates and odds ratios of transition from EM to CM by treatment efficacy category in the fully adjusted model (model 3)

Total N of group	369	1,007	2,657	1,648
N who progressed	25	44	73	32
Maximum treatment efficacy group = reference				

CI = confidence interval; CM = chronic migraine; EM = episodic migraine; OR = odds ratio.

Table 3 Treatment efficacy as a predictor of CM onset: Binary logistic regression models adjusted for sociodemographics, headache characteristics, features, and acute headache medication use

Variables	Model 1: sociodemographics	Model 2: model 1 + headache days/month and headache-related disability	Model 3: model 2 + acute medication use (dichotomous) by class
Maximum treatment efficacy (8)	Reference		
Moderate treatment efficacy (4)	1.37 (0.9–2.09)	1.21 (0.77–1.88)	1.26 (0.81–1.97)
Poor treatment efficacy (1–3)	2.17 (1.36–3.44) ^a	1.61 (0.98–2.66)	1.69 (1.02–2.81) ^a
Very poor treatment efficacy (0)	3.39 (1.98–5.8) ^a	2.39 (1.33–4.28) ^a	2.55 (1.42–4.61) ^a
Age	1.00 (0.99–1.02)	1.01 (1.00–1.02)	1.01 (1–1.02)
Sex (ref: male)	1.38 (0.88–2.15)	1.30 (0.80–2.11)	1.24 (0.77–2)
Annual household income ≥\$50,000 (ref: >\$50,000)	0.49 (0.36–0.69) ^a	0.54 (0.38–0.78) ^a	0.54 (0.38–0.76) ^a
Monthly headache day frequency ≥5 days/month (ref: <5)		5.27 (3.71–7.49) ^a	5.12 (3.6–7.27) ^a
Headache-related disability (MIDAS)		1.01 (1.01–1.02) ^a	1.01 (1.01–1.02) ^a
Simple analgesics			1.01 (0.72–1.4)
NSAIDs			0.77 (0.55–1.08)
Triptans			1.03 (0.7–1.51)
Combination analgesics			1.17 (0.84–1.64)
Opioids or barbiturates			0.86 (0.57–1.3)

Abbreviations: CM = chronic migraine; MIDAS = Migraine Disability Assessment Scale; NSAID = nonsteroidal anti-inflammatory drug. Values shown are odds ratios with 95% confidence intervals (exponentiation of the B coefficient, lower–upper).

^a Significant.

2), then all classes combined (table e-2, model 3). None of the medication classes on their own were significantly associated with CM onset. In model 3, very poor treatment efficacy (OR 2.55, 95% CI 1.42–4.61) and poor treatment efficacy (OR 1.69, 95% CI 1.02–2.81) were significantly associated with CM onset after adjusting for sociodemographic variables, headache day frequency, headache-related disability, and acute medication use.

DISCUSSION These analyses demonstrate that among persons with EM, poor acute treatment efficacy at 1 year was associated with an increased risk of CM onset the next. In a model adjusted for sociodemographic features (table 3, model 1), individuals with poor treatment efficacy (OR 2.17) and very poor treatment efficacy (OR 3.39) were at significantly increased risk of CM onset in comparison to the group with maximum treatment efficacy. In a model adjusted for headache day frequency and disability (table 3; model 2), treatment efficacy was marginally significant (OR 1.61; 95% CI 0.98–2.66) and the OR for very poor treatment efficacy remained significant but was attenuated. With further adjustment for medication type, the odds of CM onset regained significance for poor treatment efficacy and were unchanged and significant for very poor treatment efficacy. As treatment efficacy declined, the odds of CM onset increased across a number of models.

Prior work has not examined the relationship of acute treatment efficacy to CM onset in longitudinal observational studies of persons with EM. Cross-sectional studies suggest that acute treatment is less effective in CM than in EM. The present report shows that as acute treatment efficacy declines, the risk of CM onset increases in graded fashion. If this effect is causal, more effective acute treatments may reduce the risk of new onset of CM. Alternatives to the causal hypothesis, including reverse causality, were explored. Perhaps poor acute treatment efficacy is not a predictor of new-onset CM, but a marker for severe disease. In other words, people with frequent or severe migraine may be at increased risk for new-onset CM because of the severity of their illness which is, in turn, associated with poor acute treatment response. To address this possibility, we adjusted for headache days per month and headache-related disability. These adjustments attenuated the relative odds of CM onset though results remained statistically significant for the very poor treatment efficacy group (OR 2.55, 95% CI 1.42–4.61) and for the poor treatment efficacy group (OR 1.69, 95% CI 1.02–2.81). If headache frequency and disability are viewed as confounders, these findings suggest that above and beyond the effects of headache frequency and headache-related disability, poor treatment efficacy is associated with CM onset.

Alternatively, migraine frequency and disability could mediate the influence of poor efficacy on the risk of CM onset. Under this hypothesis, acute treatment failure leads to more frequent attacks and greater disability, which contribute to the risk of CM onset. If so, adjusting for disability and headache days may represent an overadjustment because these covariates are in the causal pathway. Resolving these alternative mechanisms is difficult in an observational study but may be possible in a randomized trial.

Cutaneous allodynia was associated with treatment efficacy and headache frequency but was not an independent predictor of CM onset in models that included treatment efficacy, headache frequency, and disability. Depression was significantly associated with CM onset in models that did not include headache-related disability, but depression lost significance as a predictor in models adjusted for disability. Perhaps poor treatment efficacy leads to disability and then depression through a mechanism of noncontingent punishment or learned helplessness.²⁰ Effective acute treatment may enhance self-efficacy, promote an internal locus of control, and reduce the risk of depression.^{21,22}

Acute medication use was associated with degree of treatment efficacy. Respondents who used NSAIDs and simple analgesics were less likely to be in the high treatment efficacy categories while persons who used triptans were more likely to be in favorable treatment efficacy categories. Inferences about comparative effectiveness require head-to-head clinical trials. Our concern is not comparative effectiveness but confounding. Controlling for acute treatment category one at a time or together in a single model did not substantially change the risk of new-onset CM as a function of treatment efficacy. In prior work, opioid and barbiturate use were associated with increased risk of CM onset in models that considered dose (i.e., days of use).¹

This study has several limitations, many arising from its observational nature and reliance on self-reported data. The primary independent variable in this study is the mTOQ-4, a self-report questionnaire that asks respondents to rate various attributes of their usual acute headache treatments. This method is limited by subjective self-report and recall bias. However, the items included in the mTOQ-4 have been shown to have high test-retest reliability and validity. While we used validated measures when possible, the mTOQ-4 has not been validated as a stand-alone measure. We examined all 6 items from the validated mTOQ-6 and also found that the sum score predicted the transition from EM to CM (data available upon request). However, we chose 4 items, eliminating a redundant efficacy item and a tolerability item, for the sake of simplicity. Strengths of this study

include the large, representative sample of the US population and the use of a variety of validated measures.

Our findings suggest that among persons with EM, those with ineffective acute treatment are at increased risk for CM onset while those with more effective acute treatment have better outcomes over 1 year of follow-up. These findings also support the hypothesis that the total duration of activation of the nociceptive system may be in the causal pathway that leads from EM to CM. Future work should assess the influence of improving acute treatment on long-term migraine outcomes.

AUTHOR CONTRIBUTIONS

Dr. Lipton: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination, obtaining funding. Dr. Fanning: drafting/revising the manuscript for content, analysis or interpretation of data, statistical analysis. Dr. Serrano: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision or coordination. Dr. Reed: drafting/revising the manuscript for content, study concept or design, acquisition of data, study supervision or coordination, obtaining funding. Dr. Cady: drafting/revising the manuscript for content, study concept or design, obtaining funding. Dr. Buse: drafting/revising the manuscript for content, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination, obtaining funding.

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DISCLOSURE

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