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RESEARCH SUBMISSION

Understanding the migraine treatment landscape prior to the introduction of calcitonin gene-related peptide inhibitors: Results from the Assessment of TolerabiliTy and Effectiveness in MigrAINe Patients using Preventive Treatment (ATTAIN) study

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Abstract

Background: Calcitonin gene-related peptide (CGRP) inhibitors were introduced in the United States (US) in 2018. To understand the changing patterns of preventive treatment following the introduction of these new agents, we must first characterize the patterns which preceded their introduction.

Objective: To characterize the burden, unmet need, and treatment patterns in patients with migraine initiating preventive migraine medications before the introduction of CGRP inhibitors in the US.

Methods: Between March 2016 and October 2017, we enrolled episodic (EM) and chronic migraine (CM) patients initiating or changing preventive treatment at primary care or neurology clinic visits in the US, in a real-world observational study using a prospective cohort design. At baseline and monthly thereafter for 6 months, we collected data from study sites and patients on migraine frequency, treatment modifications, migraine impact on functioning, and work productivity for a descriptive analysis of migraine patient experience and treatment patterns.

Results: From the sample of 234 completers, 118 had EM (50.4%) and 116 had CM (49.6%). Mean age at enrollment was 41 years (SD = 12) and mean age at first migraine diagnosis was 22 years (SD = 11). Most participants were females (*n* = 204/234; 87.2%) and white (*n* = 178/234; 76.1%). The majority (*n* = 164/234; 70.1%) had not used preventive migraine treatment in the 5 years prior to enrollment (treatment naïve). At baseline, mean monthly migraine days were 9.6 days (SD = 5.0) for the preventive treatment

Abbreviations: ATTAIN, Assessment of TolerabiliTy and Effectiveness in MigrAINe Patients using Preventive Treatment; CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; ER, emergency room; HIT-6™, Headache Impact Test; HRU, healthcare resource utilization; MIDAS, Migraine Disability Assessment; MFIQ, Migraine Functional Impact Questionnaire; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; WPAI, Work Productivity and Activity Impairment questionnaire.

naïve group and 12.4 days (SD = 7.0) for treatment experienced patients. The majority had severe Migraine Disability Assessment (Grade IV, total score ≥21), including 67.1% (*n* = 110/164) of the preventive treatment naïve and 77.1% (*n* = 54/70) of the preventive treatment experienced patients. Headache Impact Test total scores indicating severe impairment (score >59) occurred in 88.4% (*n* = 145/164) of the treatment naïve and 88.6% (*n* = 62/70) of treatment experienced patients. Mean work productivity loss as measured by the Work Productivity and Activity Impairment questionnaire in the subsample of employed patients was 53.3% loss. The most used acute medications at baseline were nonsteroidal anti-inflammatory agents (*n* = 124/234; 53.0%), acetaminophen-based products (*n* = 112/234; 47.9%), and triptans (*n* = 105/234; 44.9%). The most commonly initiated preventive treatments were topiramate (*n* = 100/234; 42.7%), tricyclic antidepressants (*n* = 39/234; 16.7%), beta-blockers (*n* = 26/234; 11.1%), and onabotulinumtoxinA (*n* = 24/234; 10.3%). Over the 6-month follow-up period, almost half of patients (*n* = 116/234, 49.6%) modified their preventive treatment and discontinued treatment (*n* = 88/312 total modifications; 28.2%) or modified their pattern of use by increasing, decreasing, or skipping doses (*n* = 224/312 total modifications; 71.8%), often without seeking medical advice. Avoiding side effects was the main reason reported among patients who discontinued (*n* = 52/88; 59.1%), decreased frequency or dose (*n* = 37/89; 41.6%), and skipped doses (*n* = 29/86; 33.7%). Perceived lack of efficacy was another frequent reason reported among those who discontinued (*n* = 20/88; 22.7%), decreased frequency or dose (*n* = 15/89; 16.9%), and skipped doses (*n* = 18/86; 20.9%). Despite initiation of preventive treatment and improvements observed in number of headache and migraine days, migraine patients continued to experience substantial disability, headache impact, and reduced productivity throughout the 6-month follow-up period.

Conclusions: Prior to 2018, the burden of migraine was high for patients initiating preventive treatments. Despite having more than 9 days of migraine per month on average, the majority (70.1%) of patients initiating prevention had been treatment naïve, indicating underuse of preventive treatments. The preventive treatments used in this study were poorly tolerated and were reported by patients to lack efficacy, resulting in suboptimal adherence. The high discontinuation rates suggest that the preventive medications being offered during the period of the study did not meet the treatment needs of patients. In addition, the decisions by about half of patients to alter their prescribed treatment plan without consulting their provider can pose substantial health risks. These findings pertain to the broad set of preventive treatments initiated in this study and do not support inferences about individual preventive treatments, due to limitations in sample size. These findings suggest the need for more effective and better tolerated preventive treatment options.

KEYWORDS
migraine, prevention, burden, observational, discontinuation, treatment adherence

INTRODUCTION

Migraine is a public health concern that affected 21.0% of women and 10.7% of men in the United States (US) over a 3-month period in 2018.[1] A targeted systematic review of population-based US government surveys from 1997 to 2015 found that migraine prevalence has remained relatively stable over the past 19 years, commonly affecting women, particularly those of childbearing age.[2,3] Individuals with migraine experience considerable burden, and patients report severe impairment during migraine attacks (53.7%).[4] Migraine-related disability impacts productivity at work, school, and functioning at home.[5] Impacts on family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress are also common among migraine patients.[6–8]

Despite the availability of preventive medications for migraine, their use is not widespread, adherence is suboptimal, and considerable unmet need remains.[4,9] All currently marketed preventive medications available prior to 2018 were developed for other indications. Research suggests that episodic (EM) and chronic migraine (CM) patients may be underdiagnosed and undertreated,[10,11] and they often switch medications due to suboptimal efficacy and/or lack of tolerability.[9] In a 2010 cross-sectional observational study, 53% of patients reported using preventive medications; those who were not using preventive medications cited side effects and lack of efficacy as justification for not utilizing preventive therapy (Second International Burden of Migraine Study).[12] Similar findings were obtained in a 2014 cross-sectional study, where >50% had a current prescription for preventive treatment, and of those who gave reasons for discontinuation or switching treatments, over 70% reported lack of efficacy and tolerability or safety issues.[9] The preventive treatments for migraine available prior to introduction of CGRP inhibitors have typically been associated with tolerability concerns[13] that lead patients to modify their prescribed treatment regimen, often without consulting a healthcare provider. Hepp et al.[14] found that only 25% of CM patients were still taking a newly prescribed oral preventive medication as prescribed after six months, and a discouraging 83% had discontinued these preventive medications by 1 year, suggesting major clinical futility. Treatment disruption and lack of adherence to preventive therapies may also lead to heighted need for healthcare resources, such as emergency room (ER) or hospital visits.[15] Healthcare resource utilization (HRU) and associated costs can be considerable for patients with migraine.[16–19] The recent introduction and relatively rapid uptake of calcitonin gene-related peptide (CGRP) pathway inhibitors for migraine prevention raises the hope of better efficacy, tolerability, and adherence, in comparison with widely used oral generic agents.[20] Understanding the course of patients recently initiated on new preventives, prior to the introduction of CGRP inhibitors, sets the stage for characterizing changes in the treatment landscape. Better understanding of the need for migraine treatment innovation and challenges with treatment options before the availability of CGRP inhibitors will inform healthcare providers about potential unmet needs that newly available treatment options may help to address. The Assessment of TolerabiliTy and Effectiveness in migrAINe Patients using Preventive Treatment (ATTAIN) study is a prospective study that was conducted to characterize the burden and treatment patterns in patients with migraine who were newly initiating preventive migraine medications prior to 2018. The objective of this paper is to assess the patterns of treatment and unmet need among patients with migraine to characterize the treatment landscape prior to the introduction of CGRP inhibitors.

METHODS

Study design

ATTAIN is a multicenter, non-interventional, 6-month observational web-based prospective cohort survey of EM and CM patients recently initiated on migraine preventive treatment recruited from 28 primary care or neurology clinics in the US. The study protocol was reviewed and approved by Ethical & Independent Review Services (E&I study number: 15151-01). Patients were screened for study eligibility by clinical sites either over the phone or in-person using medical records review and patient-report. No statistical power calculation was conducted prior to the start of the study. As described in the study protocol, the survey targeted enrollment of up to 300 EM and CM subjects into the study, with the aim of analyzing data from at least 250 completers (assuming an approximate 17% attrition rate). Screening and recruitment took place between March 2016 and October 2017 and enrolled a total of 301 EM and CM patients, 296 of whom were eligible (n = 5 were identified as ineligible subsequent to enrollment). Survey data were collected from study sites and enrolled patients at baseline and monthly thereafter for 6 months and data collection was completed in June 2018.

The observational study inclusion and exclusion criteria were designed to facilitate enrollment of a real-world sample of patients with migraine initiating preventive therapy, representative of migraine patients in the US before 2018. The survey recruited patients based on convenience sampling from the patient pool at study sites who met eligibility criteria and agreed to participate. Patients were eligible if they were between 18 and 65 years of age and were no older than 50 when their migraines began. Diagnosis of migraine subtype (EM vs. CM) was based on medical records and/or clinician-confirmed patient report of migraine frequency. Clinicians classified patients as EM patients who had ≥4 and ≤14 headache days per month (of which >50% were migraine days) in each of the three months prior to screening; CM patients had ≥15 headache days per month (of which ≥8 were migraine days) in each of the 3 months prior to screening. Eligible patients had to initiate for the purpose of migraine treatment, a protocol specified migraine preventive medication (Table 1) within ±14 days of the baseline visit. Eligible preventive treatments were based on frequently used medications or medication classes. If a previous preventive medication was discontinued, that had to occur at least 30 days prior to the study baseline assessment. Patients were not eligible if they had a history of cluster headache or hemiplegic migraine, new daily persistent headache, hemicrania continua, fibromyalgia, or chronic pelvic pain syndrome, of if they required daily or as-needed use of anti-psychotic medications for any major psychiatric disorder.

Study measures

Enrolled patients made one study visit to the clinical site to provide written informed consent and complete enrollment procedures, including receiving their study web-portal log-in information. Patients completed a battery of measures online at baseline and monthly for 6 months. Clinicians completed baseline and end-of-study clinical assessments for each patient. All study measures were completed online on an electronic data capture system custom built for this study. The study measures and frequency of assessments are summarized in Table 2.

TABLE 1 Qualifying migraine preventive medications for ATTAIN study eligibility

Medication category
Divalproex sodium, sodium valproate
Topiramate
Gabapentin
Pregabalin
Memantine
Beta blockers (may include propranolol, atenolol, etc.)
Tricyclic antidepressants (may include amitriptyline, nortriptyline, etc.)
Selective serotonin and norepinephrine reuptake inhibitors (SSRI/SNRI) antidepressants (may include: venlafaxine, desvenlafaxine, duloxetine, milnacipran, etc.)
Flunarizine (not available in the US)
Verapamil
Lisinopril
Candesartan
Cyproheptadine
OnabotulinumtoxinA (CM only)[a]
Zonisamide

Note: Medications may not have an FDA-approved indication for use as a migraine preventive treatment, and therefore may represent off-label use encountered in clinical practice.

[a]OnabotulinumtoxinA was removed as a qualifying medication in March 2017.

Statistical analysis

Six-month longitudinal data for a sample of 234 study completers from the ATTAIN study were analyzed using SAS statistical software version 9.4 or higher (SAS Institute Inc., Cary, NC). Of the 301 subjects enrolled into the study, 296 were confirmed to be eligible based on inclusion/exclusion criteria. Among the 296 eligible enrolled patients, 79% were study completers, defined as patients who completed study assessments from baseline to Month 6. This was the primary analysis of ATTAIN data, and analyses were conducted as outlined in the statistical analysis plan (SAP) prepared prior to study completion. Study data were analyzed using a descriptive approach; the study was not designed to evaluate comparisons or determine statistical significance. Subgroup analyses by migraine subtype (EM or CM) and by preventive treatment history were also conducted (treatment naïve vs. treatment experienced), as prespecified in the SAP. Patients who had not received preventive migraine treatment in the 5 years or more prior to enrollment were classified as treatment naïve based on input from the sponsor and clinical experts. Descriptive statistics include mean, standard deviation (SD), range (for interval and ratio-level continuous variables), and frequencies (for nominal and ordered categorical variables). The Migraine Disability Assessment scale (MIDAS),[21–23] Headache Impact Test (HIT-6™),[24–27] Migraine Functional Impact Questionnaire (MFIQ),[28–30] and Work Productivity and Activity Impairment (WPAI) questionnaire[31] are existing patient-reported outcome measures and their reliability and validity have been established previously. These validated measures were scored according to developer scoring guidelines (Table 2). Numeric rating scales for migraine pain severity (0 = no pain at all, 10 = pain as bad as it can be) and migraine interference with usual activities (0 = did not interfere at all, 10 = interfered completely) were categorized as 0 = none, 1–3 = mild, 4–6 = moderate, 7–10 = severe.

RESULTS

Demographic and clinical characteristics

The analytical sample consisted of 234 patients who received a new preventive treatment at baseline and completed all of the follow-up assessments (Table 3), of which 164 (70.1%) patients were naïve to migraine preventive treatment, and 70 (29.9%) patients were experienced with preventive treatment in the 5 years prior to enrollment. Patients (n = 234) had a mean age of 41 years (SD = 12); 118 (50.4%) patients were diagnosed with EM (naïve: n = 92/118, 78.0%; experienced: n = 26/118, 22.0%), and 116 (49.6%) patients were diagnosed with CM (naïve: n = 72/116, 62.1%; experienced: n = 44/116, 37.9%). Most patients were females (n = 204/234; 87.2%), white (n = 178/234; 76.1%), and employed full time or part time (n = 151/234; 64.5%). African-American subjects were over-represented in the treatment naïve group (n = 50/164; 30.5%), suggesting a potential racial difference in treatment profiles.

At screening, treatment naïve patients had fewer headache and migraine days than treatment experienced patients (Table 3). Mean monthly migraine days in the 3 months prior to enrollment were 9.6 days (SD = 5.0) for treatment naïve and 12.4 days (SD = 7.0) for treatment experienced patients. At baseline, patients reported severe migraine pain severity (mean = 7.7 on a scale of 0–10, SD = 1.7) and severe levels of interference of migraine with usual activities (mean = 7.6 on a scale of 0–10, SD = 2.0).

Treatment patterns for preventive and acute medications for migraine

At baseline, the most frequently initiated migraine preventive treatments were topiramate (n = 100/234; 42.7%), followed by tricyclic antidepressants (n = 39/234; 16.7%), beta-blockers (n = 26/234; 11.1%), and onabotulinumtoxinA (n = 24/234; 10.3%). Topiramate was more common among treatment naïve patients, and onabotulinumtoxinA was more frequently initiated among treatment experienced patients (Figure 1).

At baseline, patients also reported high rates of acute medication use; non-steroidal anti-inflammatory drugs (NSAIDs) (n = 124/234; 53.0%), acetaminophen-based products (n = 112/234; 47.9%), and triptans (n = 105/234; 44.9%) were the three most frequently reported acute medications, followed

TABLE 2 Summary of ATTAIN study measures and assessment schedule

Study measure	Assessment schedule	Description
Clinician-completed		
Baseline clinical form	• Baseline	Migraine symptoms and treatment history reported through medical chart review
End of study clinical form	• End of study	
Patient-completed[a]		
Baseline assessment	• Baseline	Sociodemographics and migraine treatment history
MIDAS (score range: 0–270)	• Baseline • Month 3 • Month 6	Five-scored items assessing lost days over the past 3 months at work or school, household work or chores, or family, social and leisure activity Higher scores represent greater disability and disability level can be described in grades: • Grade I: Little or no disability (0–5) • Grade II: Mild disability (6–10) • Grade III: Moderate disability (11–20) • Grade IV: Severe disability (≥21)
HIT-6™ (score range: 36–78)	• Baseline • Months 1–6 (monthly)	Six items assessing headache impact in the past month. Higher scores represent greater impact and can be described as impact categories: • Minimal impact (<50) • Mild impact (50–55) • Moderate impact (56–59) • Severe impact (>59)
MFIQ (score range: 0–100)	• Baseline • Months 1–6 (monthly)	Twenty-six items measuring the impact of migraine over the past 7 days. Higher scores represent greater burden
WPAI (score range: 0%–100%)	• Baseline • Months 1–6 (monthly)	Six items assessing degree of productivity impairment at work in the past 7 days, including: • Absenteeism (work time missed) • Presenteeism (reduced on-the-job effectiveness) • Work productivity loss • Activity impairmentHigher percentages represent greater impairment and less productivity
Post-baseline assessment	• Months 1–6 (monthly)	• Headache and migraine frequency: number of days per month, reported monthly; symptoms • Migraine acute (rescue) medication use • HRU including hospitalizations, emergency room or urgent care visits (ER/UC), and use of diagnostic tests
Tolerability survey	• Months 1–6 (monthly)	Patient-reported, study-specific survey assessing migraine preventive treatment modifications, reasons for treatment modifications, and related patient experiences, on a monthly basis. Modifications included: • Stopped medication permanently • Decreased frequency or dose • Waited a day or more • Increased frequency or dose

Abbreviations: HIT-6™, Headache Impact Test™[24–27]; HRU, healthcare resource utilization; MFIQ, Migraine Functional Impact Questionnaire[28–30]; MIDAS, Migraine Disability Assessment[21–23]; WPAI, Work Productivity and Activity Impairment questionnaire.[31]

by opioids and opioid-containing products (n = 43/234; 18.4%) (Table 4). Over the 6-month follow-up period, patients continued to have substantial use of acute medications, despite initiation of a preventive medication. Approximately one-third of preventive treatment naïve patients reporting use of NSAIDs, triptans, or acetaminophen-based products per month, and approximately 10%–20% of treatment experienced patients reporting use of NSAIDs, triptans, or acetaminophen-based products per month. On average over the 6-month follow-up period, treatment naïve patients used an acute medication on 7.0 days (SD = 7.2) and treatment experienced patients on 7.5 days (SD = 7.3) per month.

Patient-reported modifications to migraine preventive treatment

On a monthly basis, patients reported whether they had made any changes to their preventive medication since their last study assessment. The changes reported were unrelated to the recommended titration schedules directed by their prescribing provider. These proportions represent prevalence of medication changes in each 1-month epoch and are independent of prior changes. Beginning as early as Month 1, patients reported modifying how they took their prescribed migraine preventive treatment without consulting their provider. Nearly one-quarter

TABLE 3 Baseline patient demographic and clinical characteristics

Characteristics	Total (*N* = 234)	Preventive treatment history	
		Naïve[a] (*N* = 164)	Experienced[a] (*N* = 70)
Age (years), mean (SD)	41.1 (12.2)	41.2 (12.2)	40.8 (12.1)
Female, *n* (%)	204 (87.2%)	143 (87.2%)	61 (87.1%)
Race[b], *n* (%)			
White	178 (76.1%)	111 (67.7%)	67 (95.7%)
Black or African American	52 (22.2%)	50 (30.5%)	2 (2.9%)
Asian	4 (1.7%)	2 (1.2%)	2 (2.9%)
Native Hawaiian or other Pacific Islander	2 (0.9%)	1 (0.6%)	1 (1.4%)
American Indian or Alaska Native	3 (1.3%)	2 (1.2%)	1 (1.4%)
Other	9 (3.8%)	8 (4.9%)	1 (1.4%)
Employment status[b], *n* (%)			
Employed, full time or part-time	151 (64.5%)	101 (61.6%)	50 (71.4%)
Homemaker or student	45 (19.2%)	31 (18.9%)	14 (20.0%)
Retired or disabled	27 (11.5%)	23 (14.0%)	4 (5.7%)
Unemployed or other	28 (12.0%)	20 (12.2%)	8 (11.4%)
Migraine type[c], *n* (%)			
Episodic migraine	118 (50.4%)	92 (56.1%)	26 (37.1%)
Chronic migraine	116 (49.6%)	72 (43.9%)	44 (62.9%)
Age at first migraine diagnosis (years), mean (SD)	21.7 (11.1)	21.7 (10.3)	21.8 (12.5)
Migraine with aura[d], *n* (%)	102 (43.6%)	85 (51.8%)	17 (24.3%)
Migraine without aura[d], *n* (%)	153 (65.4%)	90 (54.9%)	63 (90.0%)
Menstrual migraine[e], *n* (%)	64 (33.3%)	50 (36.8%)	14 (25.0%)
Baseline monthly headache days[f], mean (SD)	15.1 (7.3)	13.9 (6.9)	17.9 (7.6)
Baseline monthly migraine days[f], mean (SD)	10.4 (5.8)	9.6 (5.0)	12.4 (7.0)

[a]Treatment naïve: Never taken migraine preventive medication or discontinued any previous medication >5 years ago; treatment experienced: discontinued any previous migraine preventive medication ≤5 years ago.

[b]Not mutually exclusive.

[c]Classified based on clinical site report.

[d]Clinical diagnosis of migraine with aura and/or migraine without aura, from clinical site report based on IHS criteria, documented in subject's medical records or confirmed by patient report.

[e]Premenopausal females only (*n* = 192).

[f]At screening, monthly average over 3 months pre-baseline.

(23.9%) of patients reported modifying their treatment at Month 1, and similar numbers of patients reported making changes during the subsequent months (Table 5). Over the 6-month follow-up period, almost half (*n* = 116/234; 49.6%) of the patients reported modifying how they took their preventive medication one or more times without medical advice. Modifications made were primarily discontinuing medication permanently (*n* = 88/312; 28.2%), decreasing frequency or dose (*n* = 89/312; 28.5%), or waiting a day or more to take medication (*n* = 86/312; 27.6%) (Figure 2). Patients in the sample reported on average 1.3 (SD = 1.8, range 0–7) modifications to treatment over 6 months. There was a slightly higher rate of medication changes in treatment naïve (mean = 1.4 changes, SD = 1.9) than in experienced patients (mean = 1.1 changes, SD = 1.5) over 6 months. Some patients also did not take preventive medications daily as prescribed; in the entire sample, on average, approximately 6–7 days were missed each month (Table 5). In addition, patients reported having continued high levels of migraine pain severity at Month 6, with moderate pain among treatment naïve patients (mean = 6.3, SD = 2.4, median = 7.0), and moderate to severe pain among treatment experienced patients (mean = 6.7, SD = 2.4, median = 8.0).

Reasons for modifications to migraine preventive treatment

When patients reported modifying the dosing regimens of their prescribed daily preventive medication without consulting their provider, they were asked for the most common reason for the change. Over the 6-month follow-up period, "side effects" was the main reason reported for discontinuation ("stopping medication permanently"; *n* = 52/88; 59.1%), "decreasing frequency or dose" (*n* = 37/89; 41.6%), and skipping doses ("waiting a day or more"; *n* = 29/86; 33.7%). Perceived lack of efficacy ("medication not effective") was

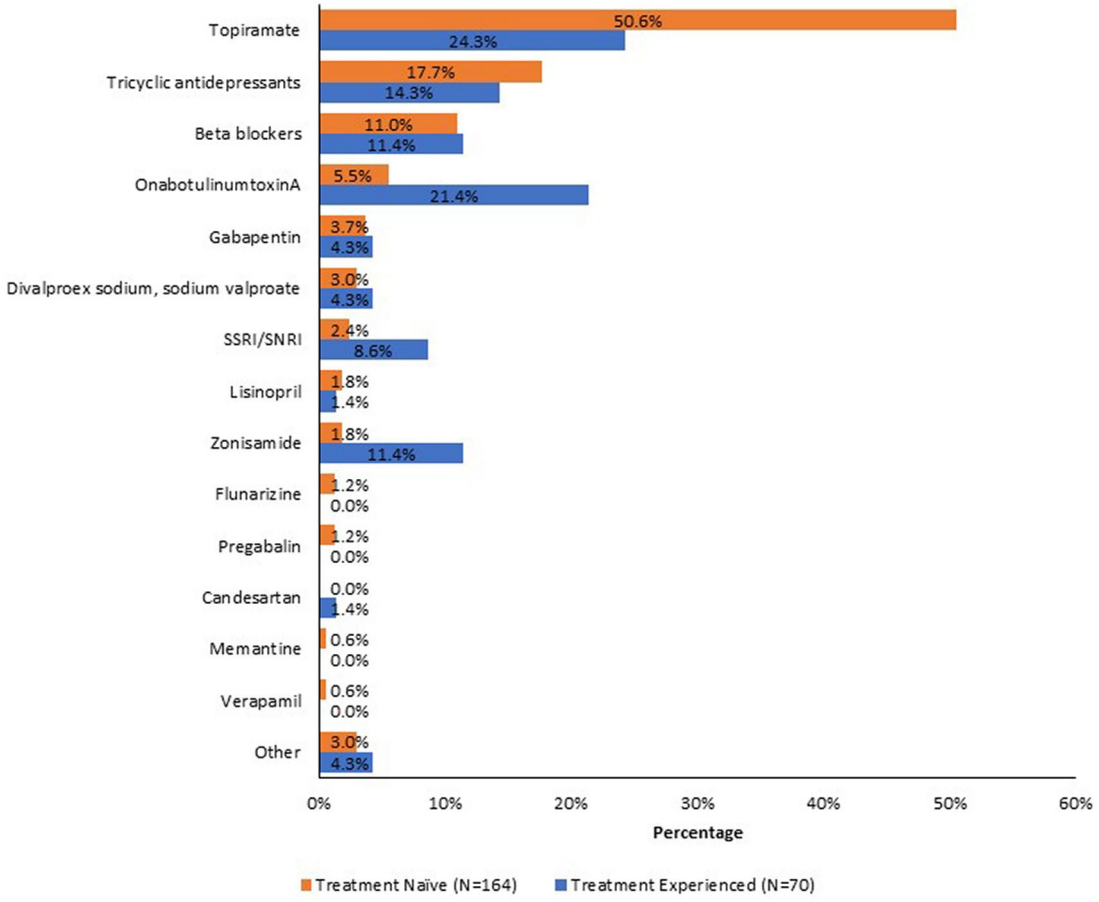

FIGURE 1 Treatment or treatment class initiated at baseline by treatment history. Treatment naïve: Never taken migraine preventive medication or discontinued any previous medication >5 years ago. Treatment experienced: Discontinued any previous migraine preventive medication ≤5 years ago. Medication percentages are reported within treatment history group and not mutually exclusive. SSRI/SNRI, selective serotonin and norepinephrine reuptake inhibitors [Color figure can be viewed at wileyonlinelibrary.com]

another frequent reason reported for discontinuation of preventive therapy (*n* = 20/88; 22.7%), along with decreasing frequency or dose (*n* = 15/89; 16.9%), and waiting to take medication (*n* = 18/86; 20.9%) (Figure 3). Perceived lack of efficacy ("The number of migraines I experienced stayed the same or increased") was also the most common reason given for "increasing frequency or dose" (*n* = 26/49; 53.1%).

Though patients often modified their preventive medication regimens, among those who continued to take medications, efficacy was often a reason. The most frequent reasons given by patients at Month 6 for continuing to take their preventive medications as prescribed were that the medication "decreases the number of migraines I have" (*n* = 125/232; 53.9%), "decreases the intensity/severity of migraines" (*n* = 90/232; 38.8%), "my doctor told me to take it" (*n* = 72/232; 31.0%), and "it improves my quality of life" (*n* = 65/232; 28.0%) (Table 5).

Topiramate was the most common preventive medication initiated by patients at the start of this study (*n* = 100/234, 42.7%), and this subgroup of patients taking topiramate was examined in further detail. Over the 6-month follow-up period, the proportion of patients on topiramate who made one or more treatment modifications (*n* = 46/100; 46.0%) was similar to that of the overall sample (*n* = 116/234; 49.6%). Patients on topiramate reported an average of 1.3 modifications (SD = 1.8, range 0–7) modifications to treatment over 6 months. Over the 6-month follow-up period, 28.2% (*n* = 88) of the 312 total treatment modifications reported were patients who discontinued their preventive medication and 71.8% (*n* = 224/312) were patients who modified their pattern of use by increasing, decreasing, or skipping doses. Among patients on topiramate who made treatment modifications (*n* = 46), "side effects" was the most common reason given for "stopping medication permanently" (*n* = 25/36; 69.4%), "decreasing frequency or dose" (*n* = 13/35; 37.1%), and "waiting a day or more" (*n* = 13/39; 33.3%). Perceived efficacy ("I improved and did not feel the need to continue medication") was also a frequent reason given for decreasing frequency or dose (*n* = 8/35; 22.9%).

Headache and migraine days

At baseline, patients with EM and those who were classified as treatment naïve patients reported the lowest numbers of monthly headache and migraine days (Table 6). Patients with EM (mean = 6.6, SD = 3.4) and treatment naïve patients (mean = 8.5, SD = 4.8) reported having fewer migraine days than patients with

TABLE 4 Acute medication at baseline by preventive treatment history

Characteristics	Total (*N* = 234)	Preventive treatment history	
		Naïve[a] (*N* = 164)	Experienced[a] (*N* = 70)
Acute medication[b], *n* (%)			
Non-steroidal anti-inflammatories (NSAIDs)[c]	124 (53.0%)	90 (54.9%)	34 (48.6%)
Acetaminophen and Acetaminophen-based products	112 (47.9%)	79 (48.2%)	33 (47.1%)
Triptans[d]	105 (44.9%)	69 (42.1%)	36 (51.4%)
Opioids and opioid-containing products[e]	43 (18.4%)	32 (19.5%)	11 (15.7%)
Cox-2 inhibitors[f]	1 (0.4%)	1 (0.6%)	–
Ergots[g]	1 (0.4%)	1 (0.6%)	–
Other[h]	27 (11.5%)	15 (9.1%)	12 (17.1%)

[a]Treatment naïve: never taken migraine preventive medication or discontinued any previous medication >5 years ago; treatment experienced: discontinued any previous migraine preventive medication ≤5 years ago.

[b]Acute medications were defined as medications that were taken on an as needed (acute) basis by the patient to treat their migraine; medications were based on a list of triptans and ergot derivatives, pain relievers, anti-inflammatories, narcotics, and combination products.

[c]NSAIDs include aspirin, aspirin-based products, dexketoprofen, diclofenac, etodolac, ibuprofen, indomethacin, ketorolac, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, and tolfenamic acid.

[d]Triptans include almotriptan, eleptriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.

[e]Opioids and opioid-containing products include butorphanol, codeine, codeine-containing products, dihydrocodeine, dihydrocodeine-containing products, hydromorphone, hydrocodone-containing products, meperidine, morphine, oxycodone, oxycodone-containing products, tramadol, and tramadol-containing products.

[f]COX-2 inhibitors include celecoxib, etoricoxib, and parecoxib.

[g]Ergots include dihydroergotamine and ergotamine.

[h]Patient selected "other" if medication was not in the list provided.

CM (mean = 12.7, SD = 6.2) and treatment experienced patients (mean = 12.2, SD = 7.2). Patients on average reported experiencing fewer monthly headache days and monthly migraine days over the course of the study, with improvement observed at Month 3 and continuing to Month 6. At Month 6, overall reductions from baseline among completers were −5.7 headache days (SD = 7.7) and −3.7 migraine days (SD = 6.1). In the migraine type and treatment history subgroups, reductions in average monthly migraine days ranged from −2.1 days (SD = 3.8) among patients with EM to −5.3 days (SD = 7.4) in patients with CM; treatment naïve and experienced patients had reductions of approximately −5 days.

Patients reported having severe migraine pain at baseline, with similar ratings by migraine type and preventive treatment history groups (Table 6). Along with reductions in the number of headache and migraine days, patients experienced improvement from baseline to Months 3 and 6 in the severity of their migraine pain. On average, changes in pain ratings ranged from approximately 1- to 1.5-point reductions, indicating less intense pain during migraines.

Disability and impact of migraine

At baseline, the burden of migraine was considerable. Migraine patients experienced substantial disability throughout the study, particularly among patients with CM and treatment experienced patients. At baseline, migraine disability scores indicated severe disability (MIDAS Grade IV, score ≥ 21) in the majority of subjects with CM (*n* = 94/116; 81.0%), treatment naïve (*n* = 110/164; 67.1%), and treatment experienced patients (*n* = 54/70; 77.1%). Over half of patients with EM had severe disability (*n* = 70/118; 59.3%). Over the 6-month follow-up period, disability levels remained high despite initiation of preventive treatment, with approximately 30%–50% of patients continuing to report severe disability at Months 3 and 6 (Table 7). Changes from baseline to Month 3 and Month 6 reflected some reduction in disability scores, particularly at Month 6 among treatment experienced (mean change = −26.1, SD = 45.0) compared to treatment naïve patients (mean change = −18.6, SD = 39.8) (Figure 4).

Headache impact based on HIT-6™ also reflected severe impact of migraine throughout the study. HIT-6™ scores at baseline indicated severe impact of headaches on work and daily activities (HIT-6™ score >59) for nearly all patients (EM: *n* = 101/118, 85.6%; CM: *n* = 106/116, 91.4%; treatment naïve: *n* = 145/164, 88.4%; treatment experienced: *n* = 62/70, 88.6%). Over the 6-month follow-up period, the functional impact of headache remained high (HIT-6™ score >59 in *n* = 153/234; 65.4% of patients) despite initiation of preventive treatment, with severe impact more frequent among treatment experienced patients (*n* = 51/70; 72.9%) relative to patients with EM (*n* = 74/118; 62.7%) and CM (*n* = 79/116; 68.1%) and treatment naïve patients (*n* = 102/164; 62.2%) (Table 7). Changes in HIT-6™ score from baseline to Months 3 and 6 were modest (Figure 5).

Functional impacts of migraine in physical, social, and emotional aspects and daily activities were also observed using the MFIQ. Average MFIQ domain scores at baseline ranged from 51.4 for Social Function (SD = 27.3) and Usual Activities (SD = 25.6) to 57.3 (SD = 28.9) for Emotional Function in treatment naïve patients and 49.5 (SD = 26.3) for Usual Activities to 61.0 (SD = 29.1) for Emotional Function in treatment experienced patients. Baseline domain scores for patients with EM ranged from 46.8 (SD = 26.9) for Usual Activities to 54.6 (SD = 29.9) for Emotional Function and for patients with CM from 53.7 (SD = 26.1) for Social Function to 62.2 (SD = 27.4) for Emotional Function. Emotional function appeared to be particularly impacted by migraine. Over the 6-month follow-up period, migraine continued to impact multiple aspects of functioning despite initiation of preventive treatment, with higher impact scores among patients with CM and treatment experienced relative

TABLE 5 Treatment modifications made to preventive medications by month

	Month 1 (*n* = 226)	Month 2 (*n* = 229)	Month 3 (*n* = 229)	Month 4 (*n* = 227)	Month 5 (*n* = 219)	Month 6 (*n* = 232)
Number of patients with one or more modifications	*n* = 54 (23.9%)	*n* = 51 (22.3%)	*n* = 53 (23.1%)	*n* = 46 (20.3%)	*n* = 48 (21.9%)	*n* = 54 (23.3%)
Total number of modifications (events)	58	51	54	45	50	55
Did you ever change the way you took your daily preventive medication on purpose in any of the following ways without consulting your doctor?[a], *n* (%)						
Stopped medication permanently	13 (5.8%)	14 (6.1%)	14 (6.1%)	12 (5.3%)	15 (6.8%)	20 (8.6%)
Decreased frequency of medication taking or lowered dose	12 (5.3%)	15 (6.6%)	16 (7.0%)	16 (7.0%)	13 (5.9%)	18 (7.8%)
Waited a day or more	20 (8.8%)	15 (6.6%)	12 (5.2%)	13 (5.7%)	13 (5.9%)	13 (5.6%)
Increased frequency or dose	13 (5.8%)	7 (3.1%)	12 (5.2%)	4 (1.8%)	9 (4.1%)	4 (1.7%)
No change	172 (76.1%)	178 (77.7%)	176 (76.9%)	181 (79.7%)	171 (78.1%)	178 (76.7%)
I continue to take my daily preventive medication as prescribed because:[b], *n* (%)						
It decreases the number of migraines I have	102 (45.1%)	103 (45.0%)	120 (52.4%)	110 (48.5%)	119 (54.3%)	125 (53.9%)
It decreases the intensity/severity of my migraines	85 (37.6%)	99 (43.2%)	93 (40.6%)	95 (41.9%)	96 (43.8%)	90 (38.8%)
It helps me sleep	38 (16.8%)	37 (16.2%)	36 (15.7%)	41 (18.1%)	39 (17.8%)	37 (15.9%)
It improves my quality of life	54 (23.9%)	68 (29.7%)	63 (27.5%)	54 (23.8%)	71 (32.4%)	65 (28.0%)
I lose weight	4 (1.8%)	3 (1.3%)	4 (1.7%)	5 (2.2%)	4 (1.8%)	5 (2.2%)
My doctor told me to take it	78 (34.5%)	80 (34.9%)	72 (31.4%)	73 (32.2%)	71 (32.4%)	72 (31.0%)
It makes my acute treatment work better	20 (8.8%)	26 (11.4%)	19 (8.3%)	15 (6.6%)	19 (8.7%)	27 (11.6%)
Other reason	20 (8.8%)	17 (7.4%)	20 (8.7%)	19 (8.4%)	17 (7.8%)	24 (10.3%)
Number of days took preventive medication as prescribed in past 30 days						
Mean (SD)	23.4 (10.3)	22.1 (11.4)	21.7 (11.6)	22.0 (11.4)	22.7 (11.2)	20.8 (12.3)
Median (min–max)	30.0 (0–30)	29.5 (0–30)	29.0 (0–30)	29.0 (0–30)	30.0 (0–30)	29.0 (0–30)

[a]Not mutually exclusive; patients can report multiple changes each month, and changes can be made during more than 1 month.

[b]Not mutually exclusive; patients can select more than one reason; question was administered to all patients.

to patients with EM and treatment naïve patients (Table 7). Changes in MFIQ domain scores from baseline to Months 6 reflected modest improvement in functional impacts (Table 7).

Work productivity and impairment

Work productivity and activity impairment were evaluated using the WPAI. A larger proportion of treatment experienced (*n* = 50/70; 71.4%) compared to treatment naïve patients (*n* = 101/164; 61.6%) were employed full time or part time (Table 3). More patients with CM (*n* = 82/116; 70.7%) were employed than patients with EM (*n* = 69/118; 58.5%). Absenteeism (work time missed), presenteeism (reduced productivity while working), and work productivity loss (overall work impairment) were assessed in the subsample of employed patients (*n* = 151) and activity impairment was evaluated in the full sample (*n* = 234). At baseline among employed patients, mean work time missed (absenteeism) was 14.1%, mean reduced productivity while working (presenteeism) was 49.9%, and overall work productivity loss was 53.3%. Mean activity impairment across the sample at baseline was 57.0%. The WPAI showed that despite initiation of preventive treatment, there was considerable absenteeism, presenteeism, work productivity loss, and activity impairment in the sample surveyed over the 6-month follow-up period (Table 8). Substantial impairment was experienced by patients with EM and CM and treatment naïve and experienced patients, with over 40% impairment for work-related and non-work activities. Presenteeism was nominally higher among patients with CM (mean percent over 6 months: 44.6%) and treatment experienced patients (mean over 6 months: 43.2%) than among treatment naïve patients (mean over 6 months: 41.8%) and patients with EM (mean over 6 months: 40.0%). Work productivity loss was highest among patients with CM (mean over 6 months: 48.0%). Percentages of work productivity loss were similar among treatment experienced patients (mean over 6 months: 46.6%) and treatment naïve patients (mean over 6 months: 46.3%). Activity impairment was also considerable regardless of migraine

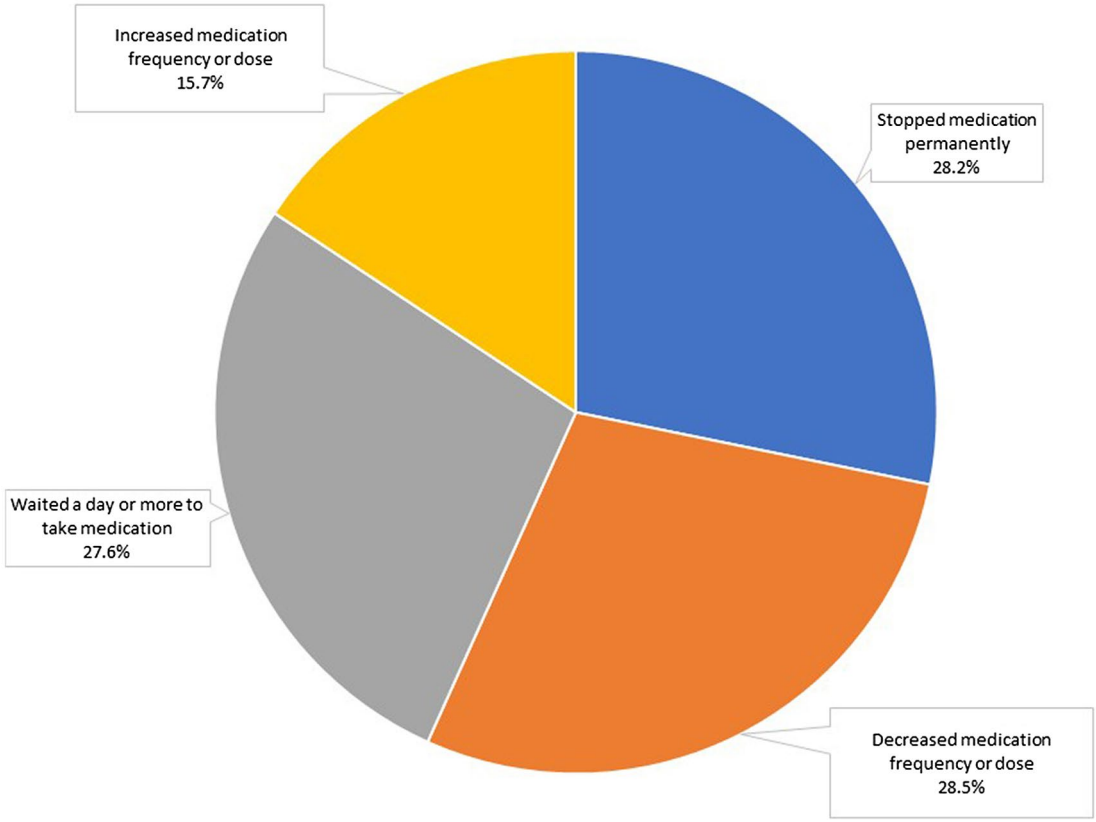

FIGURE 2 Types of treatment modifications to preventive medication over 6 months. *N* = 116 patients with one or more modifications on how they took their migraine preventive medication without consulting their provider; a cumulative total of 312 modifications among 116 patients were reported over 6 months (89 [28.5%] for decreased frequency or dose; 88 [28.2%] for discontinuation; 86 [27.6%] for waited a day or more; and 49 [15.7%] for increased frequency or dose) [Color figure can be viewed at wileyonlinelibrary.com]

type or treatment experience, with averages of 46.0% impairment for non-work activities among treatment naïve and 46.8% in treatment experienced patients and 43.2% among patients with EM and 49.3% in patients with CM. Changes from baseline to Month 6 in productivity and impairment were modest (Table 8).

DISCUSSION

This study demonstrated the substantial unmet need in patients with migraine that persisted despite the use of a preventive medication. This study was conducted prior to the approval of CGRP targeted monoclonal antibodies and was based on the standard of care available at the time of the study (including off-label use). After initiating preventive migraine medications, some improvements were observed in headache and migraine frequency, disability, and impacts of migraine on daily life and work productivity, reflecting efficacy of the available preventive medications. However, these modest improvements were associated with a high degree of patient-initiated treatment modifications and discontinuations that did not realize the full potential for improvements that would help to reduce migraines and their associated burdens. Most patients, regardless of migraine type or treatment history, continued to experience considerable burden and impacts of migraine on their functioning at work, school, and at home as indicated by scores on patient-reported measures MIDAS, HIT-6™, MFIQ, and WPAI. Despite initiation of preventive treatment, 40.9% (*n* = 95/234) of patients continued to experience severe disability due to migraine (MIDAS), and 65.4% (*n* = 153/234) experienced severe impact of headaches on function (HIT-6™). The impact of migraines on work productivity loss (46.4%) and usual activity impairment (46.2%) was also considerable (WPAI). Despite treatment with preventive medications available at the time of the study, levels of migraine pain were high and use of acute medications was substantial. This finding was not unexpected, as migraine patients on preventive medication often continue to use acute medications at a high rate. In addition, although NSAIDs, acetaminophen-based products, and triptans were the most frequently used acute medications at baseline, 18.4% (*n* = 43/234) of patients reported using opioids, which has implications in light of clinical guidelines for the appropriate use of opioid medications.

Although patients did experience some improvement using treatments that are non-specific to migraine, the course of treatment associated with patient self-medication adjustments was highly variable with many changes due to side effects that were undesirable or intolerable to the patient. Many of the patients who started on preventive

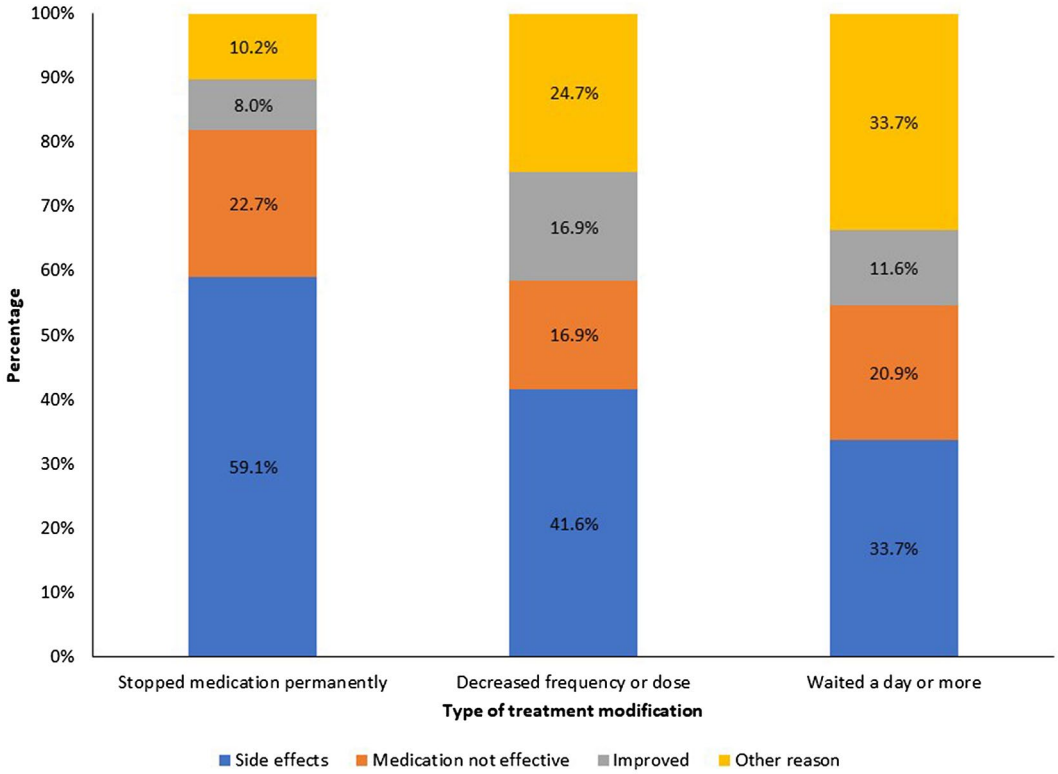

FIGURE 3 Main reasons for treatment modifications over 6 months. Other reasons for modification without consulting their provider may include cost/insurance, access, travel [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 6 Headache and migraine days over 6 months

		Migraine subtype[a]		Preventive treatment history	
Characteristics	**Total (*N* = 234)**	**EM (*N* = 118)**	**CM (*N* = 116)**	**Naïve[b] (*N* = 164)**	**Experienced[b] (*N* = 70)**
Monthly headache days[c], mean (SD)					
Baseline	14.7 (7.6)	10.0 (5.4)	19.5 (6.5)	13.3 (7.1)	18.0 (7.8)
Change from baseline to month 3	−4.7 (8.0)	−2.7 (6.7)	−6.7 (8.6)	−4.1 (7.8)	−6.2 (8.1)
Change from baseline to month 6	−5.7 (7.7)	−3.4 (6.4)	−8.1 (8.2)	−5.2 (7.2)	−6.9 (8.7)
Monthly migraine days[c], mean (SD)					
Baseline	9.6 (5.9)	6.6 (3.4)	12.7 (6.2)	8.5 (4.8)	12.2 (7.2)
Change from baseline to month 3	−2.8 (6.7)	−1.7 (4.8)	−3.8 (8.0)	−2.3 (6.5)	−3.9 (7.0)
Change from baseline to month 6	−3.7 (6.1)	−2.1 (3.8)	−5.3 (7.4)	−3.2 (5.7)	−4.9 (6.8)
Migraine pain severity[d], mean (SD)					
Baseline	7.7 (1.7)	7.6 (1.7)	7.9 (1.7)	7.7 (1.7)	7.8 (1.6)
Change from baseline to month 3	−1.3 (2.3)	−1.6 (2.3)	−1.0 (2.2)	−1.5 (2.5)	−0.9 (1.7)
Change from baseline to month 6	−1.4 (2.5)	−1.5 (2.5)	−1.2 (2.6)	−1.4 (2.5)	−1.2 (2.6)

[a]Classified based on clinical site report.

[b]Treatment naïve: never taken migraine preventive medication or discontinued any previous medication >5 years ago; treatment experienced: discontinued any previous migraine preventive medication ≤5 years ago.

[c]Number of monthly headache days and monthly migraine days based on patient report in response to the following questions: "In the past 30 days, on how many days did you experience a headache?" and "How many of these headache days were migraine headache days?"

[d]Rated as 0 = No pain at all to 10 = Pain as bad as it can be.

migraine therapies adjusted or discontinued their prescribed medication treatment plan without consulting their healthcare provider. Overall, approximately 50% of patients made treatment modifications (e.g., one or more in a 6-month period) without consulting their provider, including waiting a day or more to take medication, decreasing frequency or dose, or discontinuing preventive medication permanently. The primary

TABLE 7 Disability and impact of migraine over 6 months

Characteristics	Total (*N* = 234)	Migraine subtype[a]		Preventive treatment history	
		EM (*N* = 118)	CM (*N* = 116)	Naïve[b] (*N* = 164)	Experienced[b] (*N* = 70)
MIDAS grade at baseline[c], *n* (%)					
Grade I: Little or no disability (0–5)	25 (10.7%)	18 (15.3%)	7 (6.0%)	17 (10.4%)	8 (11.4%)
Grade II: Mild disability (6–10)	15 (6.4%)	10 (8.5%)	5 (4.3%)	13 (7.9%)	2 (2.9%)
Grade III: Moderate disability (11–20)	30 (12.8%)	20 (16.9%)	10 (8.6%)	24 (14.6%)	6 (8.6%)
Grade IV: Severe disability (≥21)	164 (70.1%)	70 (59.3%)	94 (81.0%)	110 (67.1%)	54 (77.1%)
MIDAS grade at month 3[d], *n* (%)					
Grade I: Little or no disability (0–5)	62 (27.1%)	38 (33.6%)	24 (20.7%)	48 (29.8%)	14 (20.6%)
Grade II: Mild disability (6–10)	22 (9.6%)	13 (11.5%)	9 (7.8%)	18 (11.2%)	4 (5.9%)
Grade III: Moderate disability (11–20)	34 (14.8%)	15 (13.3%)	19 (16.4%)	20 (12.4%)	14 (20.6%)
Grade IV: Severe disability (≥21)	111 (48.5%)	47 (41.6%)	64 (55.2%)	75 (46.6%)	36 (52.9%)
MIDAS grade at month 6[e], *n* (%)					
Grade I: Little or no disability (0–5)	66 (28.4%)	40 (34.2%)	26 (22.6%)	51 (31.3%)	15 (21.7%)
Grade II: Mild disability (6–10)	31 (13.4%)	20 (17.1%)	11 (9.6%)	23 (14.1%)	8 (11.6%)
Grade III: Moderate disability (11–20)	40 (17.2%)	22 (18.8%)	18 (15.7%)	29 (17.8%)	11 (15.9%)
Grade IV: Severe disability (≥21)	95 (40.9%)	35 (29.9%)	60 (52.2%)	60 (36.8%)	35 (50.7%)
HIT-6™ score categories at baseline[f], *n* (%)					
Minimal impact (<50)	2 (0.9%)	2 (1.7%)	0 (0.0%)	1 (0.6%)	1 (1.4%)
Mild impact (50–55)	7 (3.0%)	5 (4.2%)	2 (1.7%)	6 (3.7%)	1 (1.4%)
Moderate impact (56–59)	18 (7.7%)	10 (8.5%)	8 (6.9%)	12 (7.3%)	6 (8.6%)
Severe impact (>59)	207 (88.5%)	101 (85.6%)	106 (91.4%)	145 (88.4%)	62 (88.6%)
HIT-6™ score categories over months 1–6[f], *n* (%)					
Minimal impact (<50)	4 (1.7%)	4 (3.4%)	0 (0.0%)	2 (1.2%)	2 (2.9%)
Mild impact (50–55)	16 (6.8%)	11 (9.3%)	5 (4.3%)	12 (7.3%)	4 (5.7%)
Moderate impact (56–59)	61 (26.1%)	29 (24.6%)	32 (27.6%)	48 (29.3%)	13 (18.6%)
Severe impact (>59)	153 (65.4%)	74 (62.7%)	79 (68.1%)	102 (62.2%)	51 (72.9%)
MFIQ mean score at baseline, mean (SD)					
Physical function (0–100)	55.4 (25.6)	52.0 (27.6)	58.8 (23.0)	55.9 (26.0)	54.2 (24.7)
Usual activities (0–100)	50.9 (25.8)	46.8 (26.9)	55.0 (23.9)	51.4 (25.6)	49.5 (26.3)
Social function (0–100)	51.2 (27.1)	48.7 (28.0)	53.7 (26.1)	51.4 (27.3)	50.6 (27.1)
Emotional function (0–100)	58.4 (28.9)	54.6 (29.9)	62.2 (27.4)	57.3 (28.9)	61.0 (29.1)
Global item: overall impact on usual activities (0–100)	54.8 (28.0)	52.3 (29.4)	57.3 (26.4)	54.4 (28.2)	55.7 (27.6)
MFIQ mean score over months 1–6, mean (SD)					
Physical function (0–100)	44.0 (21.5)	40.3 (21.4)	47.8 (21.0)	43.4 (21.5)	45.4 (21.5)
Usual activities (0–100)	39.3 (21.6)	34.6 (20.1)	44.0 (22.0)	38.9 (21.3)	40.3 (22.4)
Social function (0–100)	40.5 (22.9)	36.1 (20.9)	45.1 (24.0)	39.5 (22.6)	42.9 (23.6)
Emotional function (0–100)	46.9 (25.2)	41.0 (23.5)	52.9 (25.5)	44.0 (24.6)	53.8 (25.3)
Global item: overall impact on usual activities (0–100)	42.6 (22.2)	38.2 (21.1)	47.0 (22.4)	41.6 (21.9)	44.8 (22.7)
MFIQ change from baseline to month 6, mean (SD)					
Physical function	−14.5 (30.6)	−14.3 (33.9)	−14.8 (26.9)	−15.8 (30.3)	−11.4 (31.3)
Usual activities	−15.1 (29.6)	−15.5 (31.5)	−14.7 (27.5)	−16.1 (29.0)	−12.8 (30.9)
Social function	−15.1 (32.8)	−17.7 (36.3)	−12.5 (28.6)	−15.8 (33.2)	−13.5 (32.0)
Emotional function	−15.5 (34.6)	−17.9 (36.3)	−13.1 (32.8)	−17.5 (34.3)	−10.8 (35.3)
Global item: Overall impact on usual activities	−16.6 (35.3)	−18.4 (36.9)	−14.7 (33.7)	−17.0 (36.3)	−15.4 (33.2)

[a]Classified based on clinical site report.

[b]Treatment naïve: never taken migraine preventive medication or discontinued any previous medication >5 years ago; treatment experienced: discontinued any previous migraine preventive medication ≤5 years ago.

[c]Past 3 months prior to baseline assessment.

[d]Past 3 months (months 1, 2, and 3), assessed at month 3.

[e]Past 3 months (months 4, 5, and 6), assessed at month 6.

[f]Based on categorization of mean HIT-6™ scores over months 1–6.

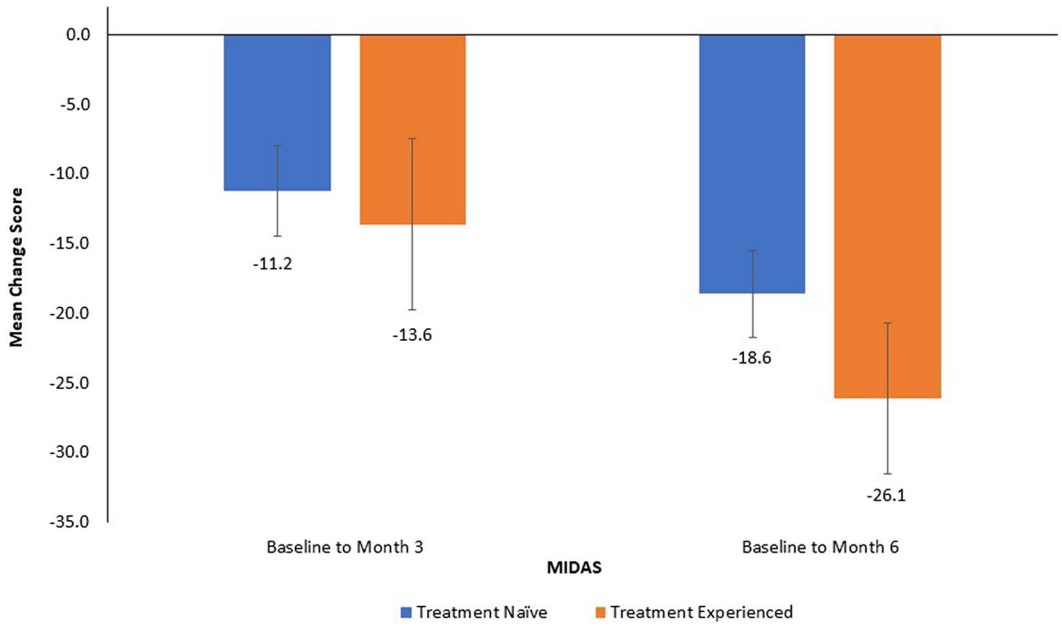

FIGURE 4 MIDAS mean change (±standard error) from baseline to months 3 and 6. Baseline MIDAS scores for Treatment naïve (mean = 48.2, SD = 2.6) and treatment experienced (mean = 55.1, SD = 47.6). Negative change score indicates reduced disability [Color figure can be viewed at wileyonlinelibrary.com]

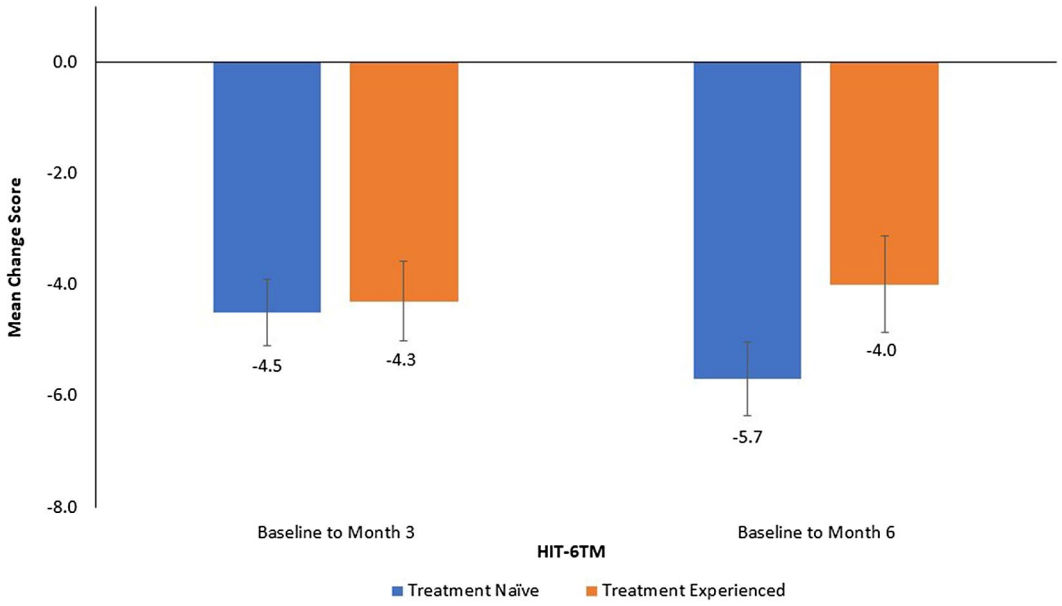

FIGURE 5 HIT-6™ mean change (±standard error) from baseline to months 3 and 6. Baseline HIT-6™ scores for Treatment naïve (mean = 66.1, SD = 6.1) and Treatment experienced (mean = 66.1, SD = 5.5). Negative change score indicates reduced impact [Color figure can be viewed at wileyonlinelibrary.com]

reasons given by patients for treatment modifications were side effects and perceived lack of efficacy of preventive treatments; these reasons were identified in both the overall sample of patients on a variety of preventive treatments, as well as within the subgroup of patients who initiated treatment with topiramate. Notably, there was a greater proportion of patients who discontinued topiramate due to side effects (n = 25/36; 69.4%), compared to the full sample of patients who discontinued any preventive treatment (n = 52/88; 59.1%). The slightly higher rate among the subgroup of patients taking topiramate may suggest the presence of tolerability issues that were related specifically to topiramate. An examination comparing the topiramate subgroup to the remaining patients taking other preventive medications could provide additional information about the relative effect of topiramate side effects in contrast to the other medications available at the time of the study.

High rates of patient-initiated changes in medication taking have implications for their outcomes. These findings based on patient

TABLE 8 Work Productivity and Activity Impairment (WPAI) over 6 months

Characteristics	Total (*N* = 234)	Migraine subtype[a]		Preventive treatment history	
		EM (*N* = 118)	CM (*N* = 116)	Naïve[b] (*N* = 164)	Experienced[b] (*N* = 70)
WPAI at baseline, mean percent (SD)					
Absenteeism[c]	14.1 (23.1)	15.3 (23.8)	13.1 (22.6)	15.4 (23.9)	11.7 (21.5)
Presenteeism[c]	49.9 (28.5)	48.0 (30.8)	51.6 (26.5)	50.7 (28.3)	48.5 (29.2)
Work productivity loss[c]	53.3 (29.8)	51.3 (32.6)	55.1 (27.3)	54.4 (30.3)	51.3 (29.2)
Activity impairment	57.0 (28.0)	55.2 (29.3)	58.9 (26.5)	58.4 (28.0)	53.7 (27.8)
WPAI over months 1–6, mean percent (SD)					
Absenteeism[c,d]	12.4 (17.4)	14.4 (19.4)	10.3 (14.9)	13.1 (17.0)	10.9 (18.3)
Presenteeism[c,d]	42.3 (24.3)	40.0 (25.1)	44.6 (23.5)	41.8 (24.8)	43.2 (23.5)
Work productivity loss[c,d]	46.4 (25.0)	44.7 (26.0)	48.0 (24.0)	46.3 (25.9)	46.6 (23.0)
Activity impairment[d]	46.2 (23.2)	43.2 (22.9)	49.3 (23.3)	46.0 (23.5)	46.8 (22.9)
WPAI change from baseline to month 6, mean percent (SD)					
Absenteeism[c]	−3.3 (24.6)	−1.5 (25.0)	−4.6 (24.5)	−3.0 (24.8)	−3.8 (24.6)
Presenteeism[c]	−12.9 (37.1)	−8.4 (38.1)	−16.4 (36.2)	−14.6 (35.8)	−10.2 (39.3)
Work productivity loss[c]	−12.0 (37.1)	−6.2 (37.5)	−16.5 (36.5)	−14.2 (36.2)	−8.6 (38.7)
Activity impairment	−14.4 (33.8)	−15.3 (36.0)	−13.5 (31.6)	−16.4 (33.7)	−9.7 (33.9)

[a]Classified based on clinical site report.

[b]Treatment naïve: never taken migraine preventive medication or discontinued any previous medication >5 years ago; treatment experienced: discontinued any previous migraine preventive medication ≤5 years ago.

[c]Based on subset of patients who reported being currently employed full time or part time.

[d]Based on mean WPAI scores assessed at months 1 through 6.

adjustments to their medications may not reflect the outcomes of those who are able to successfully persist on their current medication regimens. First, the high rate of self-adjustment indicates that patients have problems with poor tolerability and lack of efficacy with preventive medications prescribed prior to 2018. Second, altering medication without medical input is potentially dangerous. For example, prescribing instructions warn that abrupt discontinuation of topiramate can cause withdrawal seizures even in those patients without epilepsy,[1] and abrupt discontinuation of beta-blockers can cause withdrawal cardiac arrhythmias.[2] If patients are unable to adhere to a preventive therapy and dose titration schedule due to the experience of side effects, they are unlikely to achieve a therapeutic dose or remain on the treatment for a sufficient length of time that would result in favorable efficacy.

STRENGTHS AND LIMITATIONS

This study aimed to investigate the burden of migraine, treatment patterns, and factors that are involved in treatment modifications. Recruitment of patients who were newly initiating migraine preventive therapy and study eligible medications based on standard of care at the time of the study (including off-label use) ensured that a variety of medications were included and reflected real-world treatment patterns. Although lack of effectiveness or adverse events (AEs) were expected to be the key reasons for treatment modification or discontinuation, other non-medication factors outside of those asked about in this survey (e.g., cost and insurance-related issues) may be involved in treatment decisions and contributed to patient changes in therapy. The relatively large patient sample size (*N* = 301 enrolled) and prospective data collection over a 6-month follow-up period enabled capture of detailed data from patients on a monthly basis across a variety of different aspects of migraine impact.

The observational and real-world design of ATTAIN and recruitment of patients from primary care and Neurology sites ensured that patients in this study were similar to migraine patients using migraine prophylactic treatment in clinical practice settings throughout the US. These findings pertain to the broad set of preventive treatments initiated in this study and do not support inferences about individual preventive treatments, due to limitations in sample sizes. There is some potential for sample selection bias due to convenience sampling of study patients from US sites and survey administration having been limited to US English. The study completers examined in this analysis may have had better outcomes than those who dropped out prior to Month 6. The definition of treatment naïve as no use or discontinued previous medication more than 5 years ago as opposed to no lifetime use may have impacted findings. The sample size was also insufficient to stratify patients by migraine type and treatment history to compare four unique groups. The findings from this study may have limited generalizability to non-English-speaking populations

or other countries and may not represent the full continuum of severity levels, including those with low headache and migraine frequencies, and migraine patient experiences with treatment failure.

CONCLUSION

Before the availability of CGRP inhibitors, and despite the use of then available preventive medications, the burden of migraine remained high for patients with migraine. Patients in this study reported more than 9 migraine days per month, but the majority were considered treatment naïve, indicating a critical need for preventive options in this population. Preventive treatments that were used were poorly tolerated and reported by patients to lack efficacy, resulting in suboptimal adherence to treatment. Patient adherence is important to achieving optimal outcomes; however, poor tolerability of standard oral therapies has often been an impediment to consistent use of preventive medications, limiting the potential for positive long-term outcomes.

Approximately half of the patients in this study altered their preventive medications without supervision or consultation, generally due to lack of efficacy or AEs. This suggests that there was limited therapeutic value for the non-specific medications available for migraine prevention prior to 2018. The self-adjustment of these medications also poses the potential for serious health effects, such as withdrawal seizures from abrupt discontinuation or precipitous lowering of anti-epilepsy drug dosing, or withdrawal arrhythmias from acute stopping of a beta-blocker.

Recent regulatory approvals for CGRP biologics, a new class of migraine preventive drugs, provide an additional treatment option with favorable efficacy and side effect profile with substantially lower discontinuation rates in clinical trials compared to other available oral preventive therapies. The rapidity of onset and favorable tolerability of CGRP biologics are attributes that promise to address the considerable limitations of previously available oral preventive options for migraine.[32] With clear limitations in previously available migraine preventives, it is easy to understand why both patients and physicians require innovation in treatment options.

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CONFLICT OF INTEREST

A.K. Kawata, S. Shaffer, and T.K. Wilcox are employees of Evidera. Evidera received financial support from Amgen Inc. in connection with the implementation of the observational study and development of this manuscript. J.-L. Poon was an employee of Evidera at the time this study was conducted and is currently an employee and shareholder of Eli Lilly and Company. N. Shah, S. Sapra, and S. Shah are employees and shareholders of Amgen Inc. S.J. Tepper has received research grants for research (no personal compensation) from Allergan, Amgen, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, and Zosano; served as a consultant and/or on advisory boards (honoraria) for Aeon, Align Strategies, Allergan/Abbvie, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CRG, Currax, Decision Resources, DeepBench, Eli Lilly, Equinox, ExpertConnect, GLG, Guidepoint Global, Healthcare Consultancy Group, Health Science Communications, HMP Communications, Impel, Lundbeck, M3 Global Research, Magellan Rx Management, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevale, SAI MedPartners, Satsuma, Slingshot Insights, Spherix Global Insights, Sudler and Hennessey, Synapse Medical Communications, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, and Zosano; receives a salary from Dartmouth-Hitchcock Medical Center, American Headache Society, and Thomas Jefferson University and received CME honoraria from American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital, Ontario, Canada, Headache Cooperative of New England, Henry Ford Hospital, Detroit, Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians' Education Resource, Rockpointe, ScientiaCME, and WebMD/Medscape. David W. Dodick reports the following conflicts: Personal fees: Amgen, Association of Translational Medicine, University Health Network, Daniel Edelman Inc., Autonomic Technologies, Axsome, Allergan, Alder BioPharmaceuticals, Biohaven, Charleston Laboratories, Dr Reddy's Laboratories/Promius, Electrocore LLC, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Sun Pharma (India), Theranica, Teva, Vedanta, WL Gore, Nocira, PSL Group Services, XoC, Zosano, ZP Opco, Foresite Capital, Oppenheimer; Upjohn (Division of Pfizer), Pieris, Revance, Equinox, Salvia, Amzak Health. CME fees or royalty payments: HealthLogix, Medicom Worldwide, MedLogix Communications, Mednet, Miller Medical, PeerView, WebMD Health/Medscape, Chameleon, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket, Global Scientific Communications, Global Life Sciences, Global Access Meetings, UpToDate (Elsevier), Oxford University Press, Cambridge University Press, Wolters Kluwer Health; Stock options: Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, GBS/Nocira, Matterhorn/Ontologics, King-Devick Technologies; Consulting without fee: Aural Analytics, Healint, Second Opinion/Mobile Health, Epien; Board of Directors: Epien, Matterhorn/Ontologics, King-Devick Technologies. Patent: 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis without fee; Research funding: American Migraine Foundation, US Department of Defense, PCORI, Henry Jackson Foundation; Professional society fees or reimbursement for travel: American Academy of Neurology, American Brain

Foundation, American Headache Society, American Migraine Foundation, International Headache Society, Canadian Headache Society. R.B. Lipton is the Edwin S. Lowe Professor of Neurology at the Albert Einstein College of Medicine in New York. He receives research support from the NIH, the FDA, Migraine Research Foundation and the National Headache Foundation. He serves on the editorial board of Neurology, senior advisor to Headache, and associate editor to Cephalalgia. He has reviewed for the NIA and NINDS, holds stock options in Biohaven Holdings; serves as consultant, advisory board member, has received honoraria from or conducted studies funded by American Academy of Neurology, Abbvie/Allergan, American Headache Society, Amgen, Biohaven, Dr. Reddy's (Promius), Electrocore, Eli Lilly, Equinox, GlaxoSmithKline, Lundbeck (Alder), Merck, Pernix, Pfizer, Supernus, Teva, Vector, Vedanta. He receives royalties from Wolff's Headache 7th and 8th Edition, Oxford Press University, 2009, Wiley and Informa.

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ENDNOTES

[1] Topamax prescribing instructions, section 5.8: "In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including TOPAMAX®, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. [see Clinical Studies (14)]. In situations where rapid withdrawal of TOPAMAX® is medically required, appropriate monitoring is recommended."

[2] Inderal prescribing instructions, page 16: "It may be advisable to withdraw the drug gradually over a period of several weeks."

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