Comparative effectiveness of erenumab versus oral preventive medications among migraine patients: A US claims database study

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Abstract

Background: Erenumab, a fully human monoclonal antibody targeting the calcitonin gene-related peptide pathway, was developed specifically for preventive treatment of migraine.

Objective: To compare the real-world effectiveness of erenumab and non-specific oral migraine preventive medication (OMPM) on acute medication usage and healthcare resource utilization (HCRU) among migraine patients.

Methods: This retrospective US claims analysis included patients (18 years) diagnosed with migraine who initiated erenumab (May 01, 2018 and September 30, 2019) or OMPM (May 01, 2016 and October 31, 2017). Cohorts were matched 1:1 using the propensity score (PS) method with stratification. Acute medication usage, HCRU, and a composite endpoint of 1) outpatient visit with a migraine diagnosis and associated acute medication claim, 2) hospital admission with a primary migraine diagnosis, or 3) emergency room visit with a primary migraine diagnosis were assessed 6 months post-treatment initiation.

Results: Following PS matching, both cohorts included 2,343 patients. At 6 months, erenumab was associated with significantly less acute medication usage versus OMPM, including number of types of acute medications used, number of claims per person, and proportion of patients using acute medication. HCRU and number of composite events were also significantly lower among erenumab users.

Conclusion: Erenumab is more effective than OMPM at reducing acute medication usage and HCRU among migraine patients.

Trial registration: N/A.

Keywords
acute medication usage, burden, chronic migraine, emergency room, healthcare resource utilization

Introduction

Migraine is a common, complex, and long-term disabling neurological disease that imposes a significant burden on patients’ lives and on society.1-4 Migraine can either be categorized as episodic migraine (EM), defined as <15 headache days per month, or chronic migraine (CM), defined as ≥15 headaches days per month for more than 3 months, of which ≥8 days have features of migraine.5 Guidelines recommend the use of both acute and preventive therapy for the pharmacological management of migraine, with their use...
depending on the severity and frequency of attacks, as well as patient characteristics and preferences.\(^6\)

The main goal of acute medication is to rapidly restore function, with minimal recurrence and avoidance of side effects.\(^7\) However, in reality, older acute medications are often associated with limited efficacy, leading to an increased need for their use.\(^8\)–\(^13\) This, in turn, can lead to the development of medication overuse headache, to chronicification from EM to CM, to exacerbation or precipitation of comorbid medical and/or psychiatric conditions, and ultimately, to greater utilization of healthcare resources.\(^14\)–\(^18\)

Newer acute agents such as lasmiditan and gepants have become available in US since early 2020, which was beyond the study period of this retrospective study. In contrast, the goal of migraine preventive medication is to reduce the frequency, duration, and severity of attacks, the overall cost associated with migraine, and the use of acute medications, including migraine-specific medications. None of the currently available oral migraine preventive medications (OMPM, such as antihypertensives, anticonvulsants, or antidepressants), were developed specifically for migraine prevention, and many have limited to moderate efficacy, poor tolerability, or contraindications that may restrict their use.\(^19\)–\(^22\) Adherence and persistence to OMPM are poor among patients with migraine, mainly due to lack of efficacy and intolerable side effects, leading many to rely on acute medication for pain relief.\(^21\)–\(^23\)

On May 17, 2018, the United States (US) Food and Drug Administration (FDA) approved erenumab (erenumab-aooe in the US; Aimovig\(^R\)), a fully human monoclonal antibody (mAb) that targets the calcitonin gene-related peptide (CGRP) pathway.\(^24\) Erenumab, along with other mAbs in its class, namely galcanezumab, fremanezumab, and eptinezumab, was specifically designed for the preventive treatment of migraine, and its clinical efficacy and safety have been established in several clinical trials.\(^25\)–\(^26\) We previously demonstrated that 6 months of erenumab treatment was associated with reduced acute medication usage and healthcare resource utilization (HCRU) in a real-world setting.\(^27\) Furthermore, the magnitude of the reductions were generally higher in erenumab- than onabotulinumtoxinA-treated patients.\(^28\) The aim of this study was to compare the effectiveness of erenumab and OMPM on acute medication usage (triphtans, opioids, non-steroidal anti-inflammatory drugs [NSAIDs], and barbiturates) and HCRU among commercially insured patients with migraine in the US.

Methods

Data source

Data were extracted from the Optum’s de-identified Clininformatics\(^R\) Data Mart (CDM), which is a database of administrative health claims from beneficiaries of commercial and Medicare Advantage health plans in the US. Data are derived from claims submitted by providers and pharmacies to obtain payment for healthcare services rendered, track plan membership for premium billing, and track participating physicians who have contracts with health plans to provide services. Such data provide a key source of information for a variety of research efforts, including research related to healthcare costs and resource utilization, as well as quality and effectiveness.

Study design

This was a retrospective, treatment effectiveness, non-interventional, observational study. The aim of the study was to evaluate the real-world impact of erenumab and OMPM on acute medication usage and HCRU (including emergency room [ER] visits/inpatient visits, office visits, neurologist or headache specialist visits, and other outpatient visits) among patients with migraine 6 months after treatment initiation.

This study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) 2016, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,\(^29\) and with the ethical principles laid down in the Declaration of Helsinki. This study was exempt from Institutional Review Board approval since only de-identified patient records were used.

Study population

Patients eligible for inclusion in the erenumab cohort were selected from the Optum’s de-identified CDM database based on having \(\geq 1\) migraine diagnosis (ICD10 codes is available in Supplementary Table S1) during the identification period between May 01, 2017 and September 30, 2019, \(\geq 1\) prescription for erenumab between May 01, 2018 and September 30, 2019, and \(\geq 3\) erenumab doses in the 6-month post-index period, including the index date (Supplementary Figure S1). The index date refers to the first erenumab or OMPM claim during the identification period. Eligibility criteria for inclusion in the OMPM cohort included \(\geq 1\) migraine diagnosis between May 01, 2015 and April 30, 2018, and \(\geq 1\) prescription (minimum of 28 days’ supply) for any OMPM during the identification period between May 01, 2016 and October 31, 2017. All patients in both cohorts were required to be aged \(\geq 18\) years as of the index date and have continuous medical/pharmacy coverage in the 12-month pre-index and 6-month post-index periods.

Patients were excluded from the erenumab cohort if they used other non-erenumab anti-CGRP therapies during the 12-month pre-index period or 6-month post-index period. Patients were excluded from the OMPM cohort if they used any anti-CGRP therapy in the 12-month pre-index period or in the follow-up period until September 30, 2019. Patients were also excluded from the OMPM cohort if they used...
| | Pre-matched Erenumab N = 4679 | | Post-matched OMPM N = 75,861 | | SMD | Pre-matched Erenumab N = 2343 | | Post-matched OMPM N = 2343 | | SMD |
|---|---|---|---|---|---|---|---|
| Age at index date, mean (SD) | 50.2 (13.7) | 50.2 (15.7) | 0.00 | 49.7 (13.9) | 49.2 (14.4) | 0.03 |
| Female | 3959 (84.6) | 61,856 (81.5) | 0.08 | 2070 (88.4) | 2070 (88.4) | 0.00 |
| CM w/o aura | 2820 (60.3) | 7875 (10.4) | 1.22 | 935 (39.9) | 935 (39.9) | 0.00 |
| Neurologist/headache specialist | 3186 (68.1) | 19,709 (26.0) | 0.93 | 1659 (70.8) | 1659 (70.8) | 0.00 |
| General practitioner | 689 (14.7) | 40,083 (52.8) | 0.88 | 461 (19.7) | 461 (19.7) | 0.00 |
| Nurse/physician assistant | 421 (9.0) | 4549 (6.0) | 0.11 | 140 (6.0) | 140 (6.0) | 0.00 |
| Unknown/missing | 208 (4.4) | 3241 (4.3) | 0.01 | 38 (1.6) | 38 (1.6) | 0.00 |
| Other specialist | 94 (2.0) | 5117 (6.7) | 0.23 | 34 (1.5) | 34 (1.5) | 0.00 |
| Other HCP | 55 (1.2) | 902 (1.2) | 0.00 | 3 (0.1) | 3 (0.1) | 0.00 |
| Index physician specialty | 3186 (68.1) | 19,709 (26.0) | 0.93 | 1659 (70.8) | 1659 (70.8) | 0.00 |
| General practitioner | 689 (14.7) | 40,083 (52.8) | 0.88 | 461 (19.7) | 461 (19.7) | 0.00 |
| Nurse/physician assistant | 421 (9.0) | 4549 (6.0) | 0.11 | 140 (6.0) | 140 (6.0) | 0.00 |
| Unknown/missing | 208 (4.4) | 3241 (4.3) | 0.01 | 38 (1.6) | 38 (1.6) | 0.00 |
| Other specialist | 94 (2.0) | 5117 (6.7) | 0.23 | 34 (1.5) | 34 (1.5) | 0.00 |
| Other HCP | 55 (1.2) | 902 (1.2) | 0.00 | 3 (0.1) | 3 (0.1) | 0.00 |
| Region | 2316 (49.5) | 35,316 (46.6) | 0.06 | 1199 (51.2) | 1189 (50.8) | 0.01 |
| West | 978 (20.9) | 15,692 (20.7) | 0.01 | 435 (18.6) | 419 (17.9) | 0.02 |
| Midwest | 974 (20.8) | 18,749 (24.7) | 0.09 | 514 (21.9) | 499 (21.3) | 0.02 |
| Northeast | 411 (8.8) | 6014 (7.9) | 0.03 | 195 (8.3) | 233 (9.9) | 0.06 |
| Insurance type | 2401 (51.3) | 40,255 (53.1) | 0.04 | 1291 (55.1) | 1275 (54.4) | 0.01 |
| Other | 989 (21.1) | 15,625 (20.6) | 0.01 | 447 (19.1) | 414 (17.7) | 0.04 |
| Health maintenance organization | 768 (16.4) | 10,590 (14.0) | 0.07 | 333 (14.2) | 346 (14.8) | 0.02 |
| Exclusive provider organization | 333 (7.1) | 5610 (7.4) | 0.01 | 188 (8.0) | 206 (8.8) | 0.03 |
| Preferred provider organization | 188 (4.0) | 3781 (5.0) | 0.05 | 84 (3.6) | 102 (4.4) | 0.04 |

(continued)
Different identification periods were used for the selection of eligible patients in the erenumab and OMPM cohorts due to the FDA approval and subsequent availability of CGRP pathway targeted therapies since May 2018 in the US. The development of CGRP pathway targeted therapies initiated a new era in the acute and preventive treatment of primary headache disorders.\(^{30,31}\) Thus, matching patients in the erenumab and OMPM cohorts to

| Table 1. (continued) | Pre-matched | Post-matched (1:1) |
|----------------------|-------------|-------------------|
| **Erenumab** | **OMPM** | **Erenumab** | **OMPM** |
| **N (%)** | **N = 4679** | **N = 75,861** | **SMD** | **N = 2343** | **N = 2343** | **SMD** |
| Number of acute drug classes used in 6-month pre-index | | | | | | |
| 0 | 1403 (30.0) | 44,870 (59.2) | 0.61 | 844 (36.0) | 829 (35.4) | 0.01 |
| 1 | 2217 (47.4) | 24,186 (31.9) | 0.32 | 1150 (49.1) | 1128 (48.1) | 0.02 |
| 2 | 805 (17.2) | 5585 (7.4) | 0.30 | 299 (12.8) | 320 (13.7) | 0.03 |
| 3+ | 254 (5.4) | 1218 (1.6) | 0.21 | 50 (2.1) | 66 (2.8) | 0.04 |
| Acute medication used in 6-month pre-index | | | | | | |
| Any acute medication use | 3202 (68.4) | 30,108 (39.7) | 0.60 | 1464 (62.5) | 1492 (63.7) | 0.02 |
| Triptans | 2522 (53.9) | 22,042 (29.1) | 0.52 | 1204 (51.4) | 1182 (50.5) | 0.02 |
| Opioids | 883 (18.9) | 8920 (11.8) | 0.20 | 290 (12.4) | 365 (15.6) | 0.09 |
| NSAIDs | 319 (6.8) | 1725 (2.3) | 0.22 | 115 (4.9) | 133 (5.7) | 0.03 |
| Barbiturates | 301 (6.4) | 2985 (3.9) | 0.11 | 121 (5.2) | 129 (5.5) | 0.02 |
| Number of claims for acute medication drugs in 6-month pre-index, mean (SD) | | | | | | |
| Any acute medication use | 3.02 (4.13) | 1.20 (2.61) | 0.53 | 2.51 (3.56) | 2.47 (3.95) | 0.01 |
| Triptans | 2.41 (3.80) | 0.93 (2.37) | 0.47 | 2.14 (3.42) | 2.06 (3.75) | 0.02 |
| Opioids | 0.38 (1.18) | 0.19 (0.78) | 0.18 | 0.22 (0.82) | 0.26 (0.80) | 0.05 |
| NSAIDs | 0.09 (0.38) | 0.03 (0.18) | 0.21 | 0.06 (0.26) | 0.07 (0.30) | 0.04 |
| Barbiturates | 0.09 (0.43) | 0.05 (0.29) | 0.12 | 0.06 (0.33) | 0.07 (0.37) | 0.03 |
| Proportion of patients who used health care resources in 12-month pre-index period | | | | | | |
| ER/inpatient visits | | | | | | |
| All-cause | 1614 (34.5) | 24,434 (32.2) | 0.05 | 683 (29.2) | 653 (27.9) | 0.03 |
| Migraine-specific | 318 (6.8) | 2753 (3.6) | 0.14 | 18 (0.77) | 18 (0.77) | 0.00 |
| Office visits | | | | | | |
| All-cause | 4534 (96.9) | 70,595 (93.1) | 0.18 | 2265 (96.7) | 2251 (96.1) | 0.03 |
| Migraine-specific | 4250 (90.8) | 43,814 (57.8) | 0.82 | 2089 (89.2) | 2089 (89.2) | 0.00 |
| Other outpatient visits | | | | | | |
| All-cause | 4288 (91.6) | 66,442 (87.6) | 0.13 | 2101 (89.7) | 2093 (89.3) | 0.01 |
| Migraine-specific | 1611 (34.4) | 16,389 (21.6) | 0.29 | 419 (17.9) | 419 (17.9) | 0.00 |
| Neurologist/headache specialist visits | | | | | | |
| All-cause | 3685 (78.8) | 26,645 (35.1) | 0.98 | 1721 (73.5) | 1706 (72.8) | 0.01 |
| Migraine-specific | 3410 (72.9) | 15,808 (20.8) | 1.22 | 1559 (66.5) | 1559 (66.5) | 0.00 |
| Number of claims for HCRU in 12-month pre-index period, mean (SD) | | | | | | |
| ER/inpatient visits | | | | | | |
| All-cause | 1.59 (4.32) | 1.40 (4.13) | 0.04 | 1.19 (3.43) | 1.09 (3.15) | 0.03 |
| Migraine-specific | 0.16 (0.86) | 0.06 (0.55) | 0.13 | 0.01 (0.23) | 0.01 (0.14) | 0.02 |
| Office visits | | | | | | |
| All-cause | 19.38 (16.1) | 12.80 (12.82) | 0.45 | 16.13 (13.91) | 15.53 (13.93) | 0.04 |
| Migraine-specific | 4.39 (4.52) | 1.17 (1.76) | 0.94 | 2.73 (2.19) | 2.74 (2.19) | 0.00 |
| Other outpatient visits | | | | | | |
| All-cause | 10.32 (15.61) | 8.12 (13.46) | 0.15 | 7.99 (11.64) | 8.01 (13.94) | 0.00 |
| Migraine-specific | 1.07 (4.31) | 0.38 (1.37) | 0.22 | 0.30 (0.96) | 0.30 (1.06) | 0.01 |
| Neurologist/headache specialist visits | | | | | | |
| All-cause | 3.68 (4.27) | 1.22 (2.69) | 0.69 | 2.87 (3.97) | 2.74 (3.28) | 0.03 |
| Migraine-specific | 2.33 (2.47) | 0.38 (0.97) | 1.04 | 1.59 (1.67) | 1.62 (1.75) | 0.02 |

Data are n (%) unless otherwise stated.

ACE, angiotensin-converting enzyme inhibitor; CM, chronic migraine; CV, cardiovascular; ER, emergency room; HCP, healthcare practitioner; HCRU, healthcare resource utilization; NSAIDs, nonsteroidal anti-inflammatory drugs; OMPM, oral migraine preventive medication; OnabotA, onabotulinumtoxinA; SD, standard deviation; SMD, standardized mean difference.

onabotulinumtoxinA in the 12-month pre-index period or in the 6-month post-index period.

Different identification periods were used for the selection of eligible patients in the erenumab and OMPM cohorts due to the FDA approval and subsequent availability of CGRP pathway targeted therapies since May 2018 in the US. The development of CGRP pathway targeted therapies initiated a new era in the acute and preventive treatment of primary headache disorders.\(^{30,31}\) Thus, matching patients in the erenumab and OMPM cohorts to
ensure similarity of baseline disease severity becomes challenging after May 2018. To ensure the closest alignment as possible to clinical practice following the introduction of CGRP pathway targeted therapies, a period of 2 years prior to May 2018 was chosen to identify OMPM patients.

Data from the 12-month pre-index period for both the erenumab and OMPM cohorts were used to determine most baseline characteristics (e.g., preventive medication use and HCRU). Data from the 6-month pre-index period were used to determine baseline acute medication use.

Given that non-migraine specific acute and preventive medications are approved for other conditions, a claim associated with a migraine diagnosis was required. Use of non-migraine specific acute medication (NSAIDs, opioids, and barbiturates) required a migraine diagnosis on or before 7 days of the medication claim. Use of non-migraine specific preventive medication required a migraine diagnosis on or before 14 days of the medication claim, with a supply of ≥28 days. Patients identified for the OMPM cohort were allowed to have switched between classes of OMPM, which included anticonvulsants, antidepressants, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, and ergots (methysergide maleate; not commonly used for preventive treatment).

**Outcomes**

To evaluate the effectiveness of erenumab and OMPM on acute medication usage among patients with migraine in the US, the number of types of acute medication used at a specific class level (triptans, opioids, NSAIDs, and barbiturates) or at generic drug level, the number of claims per person for acute medication, and the proportion of patients using acute medication in the 6-month post-index period were assessed.

To evaluate the effectiveness of erenumab and OMPM on HCRU, the number of all-cause and migraine-specific ER/inpatient visits, office visits, neurologist or headache specialist visits, and other outpatient visits per person 6 months post-treatment initiation of erenumab or OMPM were assessed. The proportion of patients with all-cause and migraine-specific visits to healthcare providers 6 months post-treatment initiation of erenumab or OMPM was also evaluated.

An exploratory objective was to explore the composite endpoint of 1) outpatient visits with a diagnosis of migraine and an associated acute medication claim, 2) hospital admissions with a primary diagnosis for migraine, or 3) ER visits with a primary diagnosis for migraine. Any events that occurred ≤3 days apart were counted only once.

**Statistical analysis**

Data analyses were performed using SAS® studio 3.8 (Copyright © 2018, SAS Institute Inc., Cary, NC). The erenumab and OMPM cohorts were matched 1:1 using the propensity score (PS) method with stratification. Stratification was performed based on gender, diagnosis of CM without aura, onabotulinumtoxinA use in the 12-month pre-index period, number of preventive drugs used during the 12-month pre-index period, index prescriber specialty, migraine-specific inpatient and ER visits in the 12-month
Greedy nearest neighbor matching with caliper $\frac{1}{2}$ = 0.05 was used. The variables for PS matching included age, gender, Charlson Comorbidity Index, insurance type, region, selected comorbidities (CM, insomnia, depression, CV, IBS, fibromyalgia), number of acute/preventative drug use by class (numerical), acute drug use by class (categorical), number of acute drugs (barbiturates, triptans, NSAIDS, opioids, antiemetics), all-cause inpatient or ER visit (binary), number of migraine-specific inpatient/ER visit, office visits, and others visits, and number of office visits to neurologists.CCI, Charlson Comorbidity Index; CI, confidence interval; CM, chronic migraine; CV, cardiovascular; ER, emergency room; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drug; OMPM, oral migraine preventive medication; OR, odds ratio; PS, propensity score.

Acute medication usage in the 6-month post-index period

At 6-month post-index period, the adjusted number of types of acute medications used (i.e. 0, 1, 2, 3+) was significantly lower in the erenumab cohort compared with the OMPM cohort (OR 0.70 [95% CI: 0.63, 0.79]; $p < 0.0001$) (Table 2).

The adjusted average number of claims per person for any acute medication was also significantly lower in the erenumab cohort in the 6-month post-index period (1.34 vs 1.70 in the OMPM cohort; RR 0.79 [95% CI: 0.74, 0.84]; $p < 0.0001$) (Figure 1), as was the adjusted proportion of patients who used any acute medication (68.2% vs 77.3%; OR 0.63 [95% CI: 0.55, 0.72]; $p < 0.0001$) (Figure 2). The adjusted average number of claims per person for triptans

Results

A total of 4679 erenumab patients met the entry criteria and were identified between May 01, 2017 and September 30, 2019; and 75,861 OMPM patients met the entry criteria and were identified between May 01, 2015 and April 30, 2018 from the Optum’s de-identified CDM database (Supplementary Figure S2). Following stratified PS matching, the number of patients included in the analyses was 2343 for each cohort.

Demographic and baseline clinical characteristics for the pre-matched and post-matched cohorts are shown in Table 1. In the post-matched data, 88.4% were female, 39.9% had a diagnosis of CM, and the mean age was 49 years. Most patients (70.8%) were prescribed erenumab or OMPM by a neurologist or headache specialist, while 19.7% received their prescription from a general practitioner. Greater than 60% of all patients in both cohorts used some form of acute medication to treat their migraine, with the most common being triptans and opioids. The baseline data were well matched with SMD below 0.1 for all covariates included on the PS model.

Acute medication usage in the 6-month post-index period

At 6-month post-index period, the adjusted number of types of acute medications used (i.e. 0, 1, 2, 3+) was significantly lower in the erenumab cohort compared with the OMPM cohort (OR 0.70 [95% CI: 0.63, 0.79]; $p < 0.0001$) (Table 2).

The adjusted average number of claims per person for any acute medication was also significantly lower in the erenumab cohort in the 6-month post-index period (1.34 vs 1.70 in the OMPM cohort; RR 0.79 [95% CI: 0.74, 0.84]; $p < 0.0001$) (Figure 1), as was the adjusted proportion of patients who used any acute medication (68.2% vs 77.3%; OR 0.63 [95% CI: 0.55, 0.72]; $p < 0.0001$) (Figure 2). The adjusted average number of claims per person for triptans
in the 6-month post-index period was lower in the erenumab cohort (0.87 vs 1.12 in the OMPM cohort; RR 0.78 [95% CI: 0.72, 0.84]; p < 0.0001) (Figure 1). Similarly, the adjusted proportion of patients who used triptans was lower in the erenumab cohort (52.7% vs 63.9% in the OMPM cohort; OR 0.63 [95% CI: 0.54, 0.74]; p < 0.0001) (Figure 2).

The adjusted average number of claims per person for opioids in the 6-month post-index period was lower in the erenumab cohort (0.13 vs 0.19 in the OMPM cohort; RR 0.68 [95% CI: 0.57, 0.80]; p < 0.0001) (Figure 1), as was the proportion of patients who used opioids (9.1% vs 14.3%; OR 0.60 [95% CI: 0.50, 0.72]; p < 0.0001) (Figure 2). The adjusted average number of claims per person for barbiturates in the 6-month post-index period was also lower in the erenumab cohort (0.04 vs 0.06 in the OMPM cohort; RR 0.75 [95% CI: 0.57, 0.99]; p = 0.0451) (Figure 1). Similarly, the proportion of patients who used barbiturates in the 6-month post-index period was lower in the erenumab cohort (3.5% vs 5.0% in the OMPM cohort; OR 0.69 [95% CI: 0.53, 0.91]; p = 0.0093) (Figure 2).

The number of claims per person for NSAIDs was not significantly different between the two cohorts, however, the proportion of patients who used NSAIDs in the 6-month post-index period was significantly lower in the erenumab cohort (2.6% vs 3.7% in the OMPM cohort; OR 0.71 [95% CI: 0.53, 0.95]; p = 0.0216) (Figure 2). The results for ergot use in the 6-month post-index period are not reported due to insufficient data.

Sensitivity analysis of the IPTW model using the 1:3 randomized PS-matched data demonstrated similar findings for the number of types of acute medications used (Supplementary Table S2), number of claims per person for acute medication (Supplementary Figure S3), and for the proportion of patients who used acute medication (Supplementary Figure S4) in the 6-month post-index period.

### HCRU in the 6-month post-index period

By 6 months, the adjusted average number of migraine-specific office visits per person was significantly lower in the erenumab cohort (1.34 vs 1.62 in the OMPM cohort; 0.87 vs 1.12 in the OMPM cohort; RR 0.78 [95% CI: 0.72, 0.84]; p < 0.0001) (Figure 1). Similarly, the adjusted proportion of patients who used triptans was lower in the erenumab cohort (52.7% vs 63.9% in the OMPM cohort; OR 0.63 [95% CI: 0.54, 0.74]; p < 0.0001) (Figure 2).

### Table 2. Number of type of acute medications used in the 6-month post-index period.

|               | Erenumab N = 2343 | OMPM N = 2343 | OR (95% CI); P-value |
|---------------|-------------------|---------------|----------------------|
| Number of generic drugs used |                   |               |                      |
| 0             | 963 (41.1)        | 764 (32.6)    | 0.69 (0.62, 0.78); p < 0.0001 |
| 1             | 1091 (46.5)       | 1183 (50.5)   |                      |
| 2             | 221 (9.4)         | 298 (12.7)    |                      |
| 3+            | 68 (2.9)          | 97 (4.2)      |                      |
| Number of drug classes used |                   |               |                      |
| 0             | 961 (41.0)        | 770 (32.8)    | 0.70 (0.63, 0.79); p < 0.0001 |
| 1             | 1181 (50.4)       | 1297 (55.4)   |                      |
| 2             | 171 (7.3)         | 234 (10.0)    |                      |
| 3+            | 30 (1.3)          | 42 (1.8)      |                      |

A proportional odds model with PS-matched data with covariate adjustment was performed to assess the odds of having a higher number of different types of acute medication for both cohorts.

CI, confidence interval; OMPM, oral migraine preventive medication; OR, odds ratio.

![Figure 3](image_url)

**Figure 3.** Number of visits to healthcare providers in the 6-month post-index period. *1:1 PS-matched model did not converge (results from sensitivity analyses are shown). Negative binomial model with PS-matched data with covariate adjustment (age, gender; CCI, insurance type, region, selected comorbidities (CM, insomnia, depression, CV, IBS, fibromyalgia), number of acute/preventative drug use by class (numerical), number of acute drugs (barbiturates, triptans, NSAIDS, opioids, antiemetics), all-cause inpatient or ER visit (binary), number of migraine-specific inpatient/ER visit, office visits, and others visits, and number of office visits to neurologists. CCI, Charlson Comorbidity Index; CI, confidence interval; CM, chronic migraine; CV, cardiovascular; ER, emergency room; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drug; OMPM, oral migraine preventive medication; PS, propensity score; RR, rate ratio.
The adjusted average number of all-cause visits per person to a neurologist or headache specialist in the 6-month post-index period was lower in the erenumab cohort (1.21 vs 1.36 in the OMPM cohort; RR 0.89 [95% CI: 0.82, 0.96]; p = 0.0024), as was the adjusted number of migraine-specific visits per person to a neurologist or headache specialist (0.70 vs 0.91 in the OMPM cohort; RR 0.77 [95% CI: 0.72, 0.82]; p < 0.0001) (Figure 3). The proportion of patients with all-cause visits to a neurologist or headache specialist in the 6-month post-index period was also lower in the erenumab cohort (64.4% vs 68.5% in the OMPM cohort; OR 0.83 [95% CI: 0.73, 0.94]; p = 0.0043), as was the proportion of patients with migraine-specific visits to a neurologist or headache specialist (54.0% vs 58.3% in the OMPM cohort; OR 0.84 [95% CI: 0.74, 0.95]; p = 0.0054) (Figure 4).

The adjusted average number of all-cause other outpatient visits per person to a neurologist or headache specialist in the 6-month post-index period was lower in the erenumab cohort (3.15 vs 3.80 in the OMPM cohort; RR 0.83 [95% CI: 0.76, 0.91]; p < 0.0001), as was the number of migraine-specific other outpatient visits (0.18 vs 0.23 in the OMPM cohort; RR 0.78 [95% CI: 0.67, 0.91]; p = 0.0022) (Figure 3). Similarly, the proportion of patients with all-cause other outpatient visits was lower in the erenumab cohort (80.1% vs 82.3% in the OMPM cohort; OR 0.86 [95% CI: 0.75, 0.99]; p = 0.0412), as was the proportion of patients with migraine-specific other outpatient visits (11.5% vs 14.5%; OR 0.77 [95% CI: 0.65, 0.91]; p = 0.0021) (Figure 4).

The adjusted average number of all-cause ER/inpatient visits in the 6-month post-index period was lower in the erenumab cohort (0.34 vs 0.43 in the OMPM cohort; RR 0.78 [95% CI: 0.64, 0.95]; p = 0.0153); however, the average number of migraine-specific ER/inpatient visits was similar for both cohorts (Figure 3). The proportion of patients with all-cause and migraine-specific ER/inpatient visits was also similar for both cohorts (Figure 4).

Sensitivity analysis of the IPTW model using the 1:3 randomized PS-matched data demonstrated similar findings for the number of all-cause and migraine-specific visits to healthcare providers (Supplementary Figure S5) and for the proportion of patients with all-cause and migraine-specific visits to healthcare providers (Supplementary Figure S6) in the 6-month post-index period.

**Composite endpoint**

As noted, the exploratory composite endpoint consisted of 1) outpatient visits with a diagnosis of migraine and an associated acute medication claim, 2) hospital admissions with a primary diagnosis for migraine, or 3) ER visits with a primary diagnosis for migraine. Patients in the erenumab cohort had a significantly lower number of composite events compared with the OMPM cohort (0.40 vs 0.57;
A lower proportion of patients with any of the three composite events was also observed in the erenumab cohort compared with the OMPM cohort (30.5% vs 40.7%; OR 0.64 [95% CI: 0.56, 0.73; \(p < 0.0001\)) (Figure 5(B)).

Sensitivity analysis of the IPTW model using the 1:3 randomized PS-matched data demonstrated similar findings for the number of composite events per person (Supplementary Figure S7A) and for the proportion of patients with a composite event (Supplementary Figure S7B) in the 6-month post-index period.

**Discussion**

This real-world effectiveness analysis suggests that over a period of 6 months, erenumab-treated patients had significantly decreased use of acute medication versus those treated with OMPM (RR 0.79; 95% CI: 0.74, 0.84; \(p < 0.0001\)). Erenumab-treated patients were also less likely to require different classes of acute medications after being treated with erenumab (RR 0.70 [95% CI: 0.63, 0.79]; \(p < 0.0001\)). All of the acute medication classes evaluated showed lower use in the erenumab group than the OMPM group. Importantly, this reduction was present for both opioid and barbiturate acute medication usage, however, it is important to note the limitations of the small number of patients treated with opioids and barbiturates. This reduced use can have profound medical, psychiatric, economic, and social implications, given the opioid crisis and the need to reduce chronic and repeated use of scheduled medications.

Furthermore, compared with the initiation of OMPM, the initiation of erenumab was associated with a lower HCRU relating to migraine-specific office visits (RR 0.83; 95% CI: 0.78, 0.87; \(p < 0.0001\)) and to a lower number of migraine-specific visits per person to a neurologist or headache specialist (RR 0.77 [95% CI: 0.72, 0.82]; \(p < 0.0001\)). In fact, this reduction of at least 23% in HCRU is considered a meaningful change especially given the widespread prevalence of migraine and the associated high rates of resource utilization.

Patients in the erenumab cohort had a significantly lower number of composite endpoints, that is, 1) outpatient visits with a diagnosis of migraine and associated acute medication claim, 2) hospital admissions with a primary diagnosis for migraine, or 3) ER visits with a primary diagnosis for migraine (0.40 vs 0.57; RR 0.71 [95% CI: 0.65, 0.77; \(p < 0.0001\)), which may be associated with a greater reduction in the frequency of migraine attacks or severity of attacks than in those treatment with OMPM, and which in turn could lead to an overall reduction in the burden of the disease in patients with migraine. A significant reduction of 29% in the number of the composite endpoint events shows the overall benefit of erenumab in the real world. A composite endpoint such as the one reported in this study may potentially be used as a proxy to evaluate migraine attacks, although further validation is needed.

The use of claims data is subject to several limitations. As Optum’s CDM is a US database, the results gained from claims analysis apply only to the insured population in the US, which may not be generalizable to the overall population, or to the international population. US claims data are dependent on professional International Classification of Diseases (ICD) coding, not the International Classification of Headache Disorders, 3rd Edition (ICHD-3) diagnosis, and therefore, some diagnoses may be missed, different professional types may have different coding patterns, and not all coding may be accurate. Further limitations of
prescription claims data are that over-the-counter (OTC) medications used to manage acute migraine attacks are missed, and a prescription does not always guarantee patient adherence. Patients receiving erenumab from the free drug program are also not captured in the Optum’s de-identified CDM database, thus, it is impossible to ascertain whether the first erenumab claim is truly indicative of the first time erenumab is used by a given patient. If used previously, the actual effectiveness might be larger than observed as baseline data may have been affected. In spite of these limitations, claims data are a valuable resource for exploratory analyses of a variety of health services research questions.

Given the widespread prevalence of migraine and the associated high rates of resource utilization, concerted efforts to reduce HCRU would help reduce burden upon the healthcare system. The personal, economic, and societal burden of migraine can be eased by optimizing acute care therapy and earlier initiation of effective preventive therapy. These findings suggest that erenumab, as a migraine preventive therapy, may reduce the holistic burden of the disease as well as overall cost in the real world.

Clinical implications

- Treatment with erenumab is associated with significantly less acute medication usage compared with oral migraine preventive medication, including the number of types of acute medications used, the number of claims per person for acute medications, and the proportion of patients using acute medications.
- More reduction in triptan, opioid, and barbiturate use in the erenumab group compared with conventional, non-specific oral migraine prevention should have favorable medical, psychiatric, economic, and social implications.
- Healthcare resource utilization is meaningfully reduced in patients treated with erenumab compared with oral migraine preventive medication.
- Erenumab treatment may be associated with less frequent migraine attacks compared with oral migraine preventive medication, as assessed using a composite endpoint (outpatient visits with a diagnosis of migraine and an associated acute medication claim; hospital admissions with a primary diagnosis for migraine; or ER visits with a primary diagnosis for migraine) as a proxy to evaluate migraine attacks.
- These findings suggest that erenumab, as a migraine preventive therapy, may reduce the holistic burden of the disease as well as overall cost in the real world.

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Availability of data and materials

Raw data were generated by Optum, Inc. and are subject to their data security and privacy protocols. Derived data supporting the findings of this study are available from the corresponding author [JF] on reasonable request.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

References

1. Buse DC, Rupnow MF and Lipton RB. Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life. Mayo Clin Proc 2009; 84: 422–435.
2. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My migraine voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain* 2018; 19: 115.

3. Bonafede M, Sapra S, Shah N, et al. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache* 2018; 58: 700–714.

4. Diseases GBD and Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1204–1222.

5. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.

6. American Headache Society. The American headache society position statement on integrating new migraine treatments into clinical practice. *Headache* 2019; 59: 1–18.

7. Ong JJY and De Felice M. Migraine treatment: current acute medications and their potential mechanisms of action. *Neurotherapeutics* 2018; 15: 274–290.

8. Marmura MJ, Silberstein SD and Schwedt TJ. The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies. *Headache* 2015; 55(1): 3–20.

9. Lipton RB, Buse DC, Serrano D, et al. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2013; 53(8): 1300–1311.

10. Buse DC, Serrano D, Reed ML, et al. Adding additional acute medications to a triptan regimen for migraine and observed changes in headache-related disability: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2015; 55(6): 825–839.

11. Serrano D, Buse DC, Kori SH, et al. Effects of switching acute treatment on disability in migraine patients using triptans. *Headache* 2013; 53(9): 1415–1429.

12. Holland S, Fanning KM, Serrano D, et al. Rates and reasons for discontinuation of triptans and opioids in episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *J Neurol Sci* 2013; 326(1–2): 10–17.

13. Serrano D, Buse DC, Manack Adams A, et al. Acute treatment optimization in episodic and chronic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2015; 55(4): 502–518.

14. Leroux E, Buchanan A, Lombard L, et al. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. *Adv Ther* 2020; 37: 4765–4796.

15. Schwedt TJ, Alam A, Reed ML, et al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. *J Headache Pain* 2018; 19: 38.

16. Bigal ME, Rapoport AM, Sheffell FD, et al. Transformed migraine and medication overuse in a tertiary headache centre—clinical characteristics and treatment outcomes. *Cephalalgia* 2004; 24: 483–490.

17. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008; 48: 1157–1168.

18. Silberstein SD, Lee L, Gandhi K, et al. Health care resource utilization and migraine disability along the migraine continuum among patients treated for migraine. *Headache* 2018; 58: 1579–1592.

19. Estemalik E and Tepper S. Preventive treatment in migraine and the new US guidelines. *Neuropsychiatr Dis Treat* 2013; 9: 709–720.

20. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache* 2013; 53: 644–655.

21. Hepp Z, Dodick DW, Varon SF, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. *Cephalalgia* 2017; 37: 470–485.

22. Hepp Z, Dodick DW, Varon SF, et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia* 2015; 35: 478–488.

23. Berger A, Bloudek LM, Varon SF, et al. Adherence with migraine prophylaxis in clinical practice. *Pain Pract* 2012; 12: 541–549.

24. AIMOVIG™. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761077s000lbl.pdf. (accessed 1 July 2021)

25. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017; 377: 2123–2132.

26. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017; 16: 425–434.

27. Tepper SJ, Fang J, Vo P, et al. Impact of erenumab on acute medication usage and health care resource utilization among migraine patients: a US claims database study. *J Headache Pain* 2021; 22(1): 27.

28. Tepper SJ, Fang J, Zhou L, et al. Effectiveness of erenumab and onabotulinumtoxinA on acute medication usage and health care resource utilization as migraine prevention in the United States. *J Manag Care Spec Pharm* 2021; 1–14. Online ahead of print. DOI: 10.18553/jmcp.2021.21060.

29. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014; 12: 1500–1524.

30. Vilkes M, Spingos KC and Rapoport AM. A new era in headache treatment. *Neurology* 2018; 39(Suppl 1): 47–58.

31. Tepper SJ. Anti-Calcitonin Gene-Related Peptide (CGRP) therapies: update on a previous review after the American headache society 60th scientific meeting, San Francisco, June 2018. *Headache* 2018; 58(Suppl 3): 276–290.