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Acute treatment patterns in patients with migraine newly initiating a triptan

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Abstract

Background: Triptans are the most commonly used acute treatment for migraine. This study evaluated real-world treatment patterns following an initial triptan prescription to understand refill rates and use of non-triptan medications for the acute treatment of migraine.

Methods: Commercially-insured adult patients over 18 years of age with a triptan prescription between 1/1/2013 to 31/12/2013 were identified from the Optum Clinformatics™ Data Mart database, with date of the first triptan fill designated as index date. Inclusion was limited to those with no fills for a triptan in the 12 months prior to index date (i.e. new users or initiators of triptans) and continuous enrollment in the 12 months pre- and 24 months post-index date. Fills for index triptan, non-index triptan, and other acute treatments for migraine were assessed for up to 24 months post-index.

Results: Among 10,509 patients, 50.8% did not refill the initial triptan within 12 months and 43.6% did not refill within 24 months. In the 12 months post-index, 90.5% of patients used only one type of triptan, 8.4% used two different triptans, and 1.0% used three or more triptans. Among patients with and without a triptan refill, use of opioids (39% vs. 42%), non-steroidal anti-inflammatory drugs (22% vs. 22%), and butalbital-containing products (9% vs. 10%) were similar.

Conclusion: More than half of those who newly initiated a triptan did not refill their initial prescription, and less than 1 in 10 used two or more triptans within 12 months. High rates of non-triptan acute medication use were found over 12 and 24 months of follow-up, most commonly opioids.

Keywords

Triptan persistency, migraine medication, refill patterns, claims data

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Introduction

Migraine is a chronic neurological disease defined by often incapacitating neurological symptoms, such as headache pain, sensitivity to light and sound, and nausea. Migraine has a significant impact on health-related quality of life, disability, productivity losses, and health care costs (1,2,3). Acute treatments for migraine are taken during an attack with the goals of rapidly treating pain, restoring normal function, and minimizing the use of rescue medications (4,5). Acute treatments are divided into migraine-specific treatments, such as triptans and ergots, and non-specific treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, and caffeinated analgesic combinations (6). Emerging migraine-specific acute therapies include gepants (ubrogepant and rimegepant) and ditans (lasmiditan) (4).

Triptans, a class of migraine-specific acute treatments that act as selective serotonin receptor (5-HT1b/d) agonists, include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan (oral, nasal spray, injectable), and zolmitriptan (oral and nasal spray). Triptans have long been recommended by the American Academy of Neurology

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(AAN) as an initial therapy for the acute treatment of moderate or severe migraine attacks (5). Triptans are commonly used, with approximately half of those who receive any prescription acute medications for migraine reporting use of a triptan (7). Furthermore, the recent American Headache Society (AHS) Consensus Statement recommends the trial of at least two oral triptans prior to switching to a different medication class for acute treatment of migraine (4). Real-world studies have shown poor persistency and low refill rates for triptans both in the United States (8,9,10,11,12) and Europe (13,14,15,16). In an analysis of a large United States administrative claims dataset from 2001 to 2005, 54% of new triptan users did not refill their index triptan and 67% of this subgroup switched to a medication other than a triptan at the time of first refill (10). In addition, real-world studies have demonstrated that switching among triptans (i.e. use of a second triptan agent) is relatively uncommon, ranging between 9% and 14% (10,16). More commonly, triptan users who switched therapies turned to a different medication class such as NSAIDs, opioids, and barbiturates (10).

The current body of published research on real-world treatment patterns for acute treatment of migraine in the United States is limited. Prior studies are not generalizable given that the data come from small single managed care plans; much of the data are from more than a decade ago (8,9,10,11,12). Triptan treatment patterns may have changed over time as triptans became available as generics. Novel emerging acute treatments for migraine are being introduced in the United States. Therefore, there is a need to better understand recent treatment patterns of current acute treatments for migraine and assess the unmet need for emerging treatments. Furthermore, a more recent assessment of how triptans are used within the migraine population would be of great relevance in light of the new AHS Consensus Statement.

The objective of this study was to examine recent real-world patterns of acute treatments for migraine among patients newly initiating triptans using data from a large national insurer. This study examined triptan refill patterns including different triptan agents used and the use of non-triptan medications for the acute treatment of migraine over 12 months and 24 months of follow-up among patients newly initiating a triptan.

Methods

Data source

The study used medical, pharmacy, and enrollment information from the Optum Clinformatics™ Data Mart (CDM) with data spanning from 2012 to 2015. The Optum CDM is a database comprising administrative health claims for members of a large national insurer in the United States. Claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion in the CDM. The population covered in the CDM is geographically diverse, spanning all 50 states in the United States and is fairly representative of the United States insured population (17).

Study design and sample

This was a retrospective cohort analysis of new users (i.e. initiators) of a triptan. The sample included commercially insured patients aged 18 years or older with at least one prescription claim for a triptan with the date of the first claim during the identification window (01/01/2013–31/12/2013) assigned as index date (and the triptan on the first claim assigned as the index triptan agent). The triptans included almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan combinations, and zolmitriptan (5). Patients were excluded if they had claims for multiple triptan agent prescriptions on the index date. Patients were required to have continuous medical and pharmacy enrollment in the 12-month pre-index period and 24-month post-index period. All patients were required to have at least one medical claim with a migraine diagnosis (ICD-9-CM code 346.XX; corresponding ICD-10 codes G430–G436, G438, and G439) on the index date or in the 12-month pre-index period. Finally, patients were required to have no triptan claim in the 12-month pre-index period to qualify as new triptan users. A study design schematic is shown in Figure 1.

Outcomes

The first outcome of interest was the pattern of triptan refills. In the primary analysis, the main measure for this outcome was the number of refills for the index triptan over the 12-month and 24-month post-index periods. In the sensitivity analysis, we loosened the criteria to allow any (index or non-index) triptan fill to be included in the count of the number of triptan refills. In addition, we examined the number of triptan refills in the subgroup of those who received a quantity of four pills or less with their index triptan prescription.

The second outcome of interest was the use of multiple different triptan agents over the 12-month and 24-month post-index periods. Specifically, we measured the number of different triptan agents filled and the time to initiation of a second (different) triptan agent.

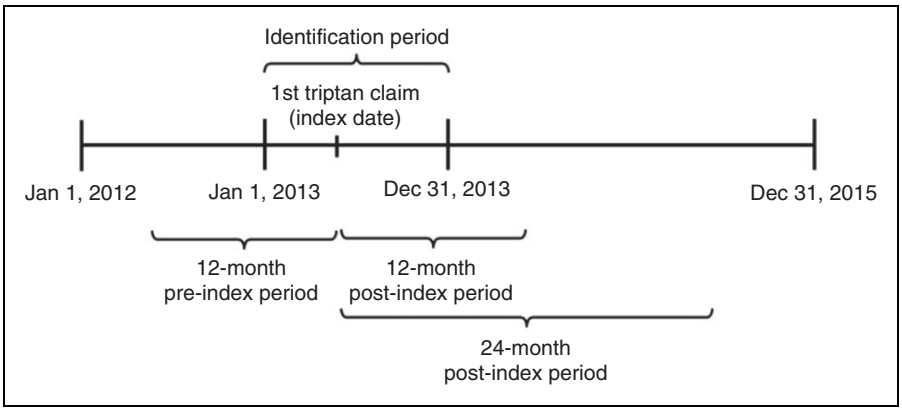

Figure 1. Study design.

The third outcome was the use of non-triptan acute migraine medications over the 12-month and 24-month post-index periods. Non-index acute migraine medications were AAN clinical guideline-listed acute medications grouped into five medication classes, namely, acetaminophen, butalbital combinations, ergots, NSAIDs, and opioids or opioid combinations (5). Specific doses and strengths were not considered separately. It should also be noted that the guideline listed medications under the acetaminophen and NSAID classes (e.g. aspirin, ibuprofen, naproxen) are also available over the counter and are unlikely to be captured completely in the prescription claims data. Whereas the guidelines captured all available agents in the medication classes of triptans, ergots, and butalbital combinations (all of which are available as prescription only drugs), the agents listed under the opioids and opioid combinations in the clinical guidelines are limited to a small subset of all available opioids. Since patients may have used non-guideline listed opioids, we expanded the measure of opioids to the use of any available opioid medication. Specifically, individual or combination prescriptions included the following agents: Buprenorphine (transdermal Butrans® only [Purdue Pharma LP, Stamford, CT]), butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, nalbuphine, opium alkaloids, oxycodone, oxymorphone, pentazocine, propoxyphene, tapentadol, and tramadol). Since opioids may be used for several other indications, we created a measure of migraine-related opioid prescriptions; we required the presence of at least one medical claim with a migraine diagnosis (ICD-9 code 346.XX) in the 15-day window that includes the opioid fill date and the 14 days prior to the fill date to be classified as a potentially migraine-related prescription, an approach previously taken by Katić et al. (10).

Analysis

Demographic and clinical characteristics were summarized descriptively. Results were presented for all study outcomes over 12-month and 24-month post-index periods. Logistic regressions examined the demographic, clinical, and treatment characteristics associated with the outcome of having no refills for the index triptan agent. Demographic variables included age, gender, region (Northeast, Midwest, South, West), and insurance plan type (EPO, POS, HMO, PPO, other). Clinical variables included the number of Elixhauser comorbidities (0, 1, 2–3, 4–5, 6+), an established comorbidity index consisting of 31 conditions which have been shown to impact health outcomes, and the presence of comorbidities commonly associated with migraine but not included in the Elixhauser comorbidities list (mood disorders, rhinitis, irritable bowel syndrome, pain, sleep disturbances, and epilepsy) (18,19). In addition, the presence of cardiovascular risk factors (diabetes, hypertension, obesity, ischemic heart disease, hyperlipidemia, cerebrovascular disease, peripheral vascular disease, congestive heart failure), presence of chronic migraine diagnosis, and number of claims with migraine diagnoses in the pre-index period were included. Finally, the regression models included variables for the type of index triptan (i.e. almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and sumatriptan combinations, or zolmitriptan).

Results

Of 94,858 adults with ≥1 triptan prescription claim during the identification window and continuous enrollment 12 months prior to index, 38,912 (41%) were designated as new triptan initiators based on no evidence of a triptan claim in the 12 months prior to index. A total of 10,509 patients met all inclusion

criteria and were included in the analysis (Figure 2). Baseline patient characteristics are summarized in Table 1. While 12.5% of the sample were between the ages of 18 and 24 years, about 35% were 45 years or older. Approximately 82% of the patients were female and a large proportion resided in the South (42.7%) and the Midwest (28.7%). The majority of patients (77.9%) were enrolled in a point-of-service type of insurance plan. Sumatriptan (64.4%) was the most commonly used triptan as index treatment followed by rizatriptan (18.1%), and eletriptan (9.1%).

The majority of patients (58.5%) received four pills or less in their first triptan prescription while 35.9% received five to 12 pills, and 5.6% received 13 or more pills. Figure 3 presents the number of index triptan refills in the 12-month and 24-month post-index periods. When examining the outcome of the number of index triptan refills, we found that half (50.8%) of the sample had no triptan refills over 12 months of follow-up. The percentage with no refills was slightly lower at 43.6% when follow-up was extended to 24 months. When the outcome was expanded to the number of any (index or non-index) triptan refills, approximately 46% of patients had no triptan refills over 12 months and 38% had no triptan refills over 24 months' follow-up. The results remained similar in the subgroup of patients who received a quantity of four pills or less for their index triptan, with a high proportion of patients having only one triptan fill over 12 months (44.5%) and 24 months (37.6%) of follow-up. Older age groups and persons prescribed eletriptan as the index agent had lower odds of not refilling the index triptan for both follow-up periods (12 months and 24 months) (Supplemental Table A1). Factors consistently associated with higher odds of not refilling the index triptan were male gender and presence of diabetes.

In the 12 months post-index, 90.5% of all patients in our sample used only one type of triptan, 8.4% used two different triptan agents, and 1.0% used three or more different triptan agents (Figure 4). Rates were similar for 24 months post-index, with 86.1%, 12.0%, and 2.0% using one, two, and three or more triptan agents, respectively (Figure 4). Among patients who did not refill their index triptan, the proportion of patients filling two or more different triptan agents

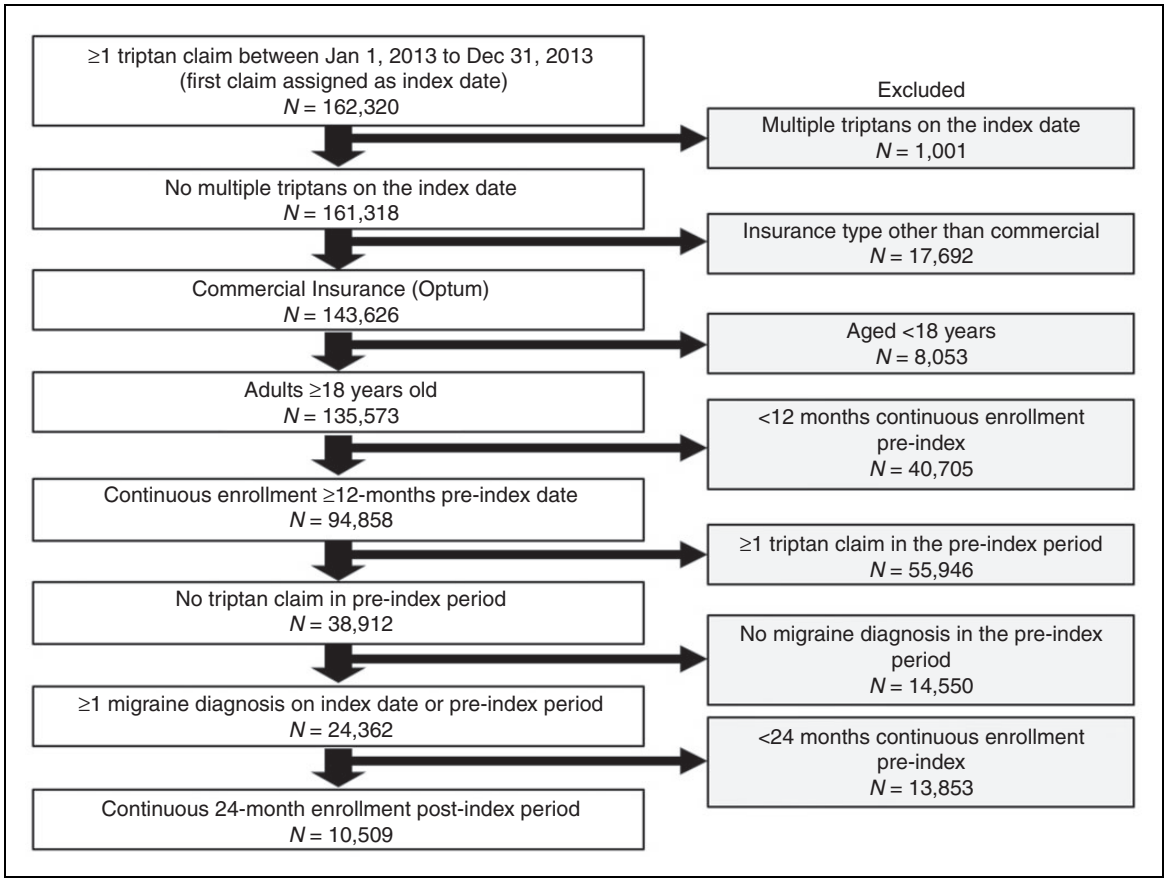

Figure 2. Sample selection.

Table 1. Demographic and clinical characteristics.

	Total n = 10,509	No refill of index triptan* n = 4587	≥1 Refill of index triptan* n = 5922
Age (years)			
18–24	1312 (12.5)	727 (15.8)	585 (9.9)
25–34	2256 (21.5)	1115 (24.3)	1141 (19.3)
35–44	3280 (31.2)	1357 (29.6)	1923 (32.5)
45–64	3562 (33.9)	1349 (29.4)	2213 (37.4)
65+	99 (0.94)	39 (0.9)	60 (1.0)
Gender			
Female	8576 (81.6)	3670 (80.0)	4906 (82.8)
Male	1927 (18.3)	915 (19.9)	1012 (17.1)
Unknown	6 (0.01)	2 (0.0)	4 (0.1)
Chronic migraine diagnosis	636 (6.1)	256 (5.6)	380 (6.4)
Claims with migraine diagnosis, mean (SD)	1.25 (2.27)	1.12 (2.13)	1.35 (2.40)
Region			
Northeast	794 (7.6)	358 (7.8)	436 (7.4)
Midwest	3011 (28.7)	1249 (27.2)	1762 (29.8)
South	4483 (42.7)	2019 (44.0)	2464 (41.6)
West	2204 (21.0)	952 (20.8)	1252 (21.1)
Unknown	17 (0.2)	9 (0.2)	8 (0.1)
Plan type			
POS	8188 (77.9)	3569 (77.8)	4619 (78.0)
EPO	1007 (9.6)	454 (9.9)	553 (9.3)
HMO	965 (9.2)	415 (9.0)	550 (9.3)
PPO	254 (2.4)	107 (2.3)	147 (2.5)
Other	95 (0.9)	42 (0.9)	53 (0.9)
Elixhauser comorbidity count			
0	4406 (41.9)	2025 (44.1)	2381 (40.2)
1	3008 (28.6)	1285 (28.0)	1723 (29.1)
2–3	2316 (22.0)	967 (21.1)	1349 (22.8)
4–5	589 (5.6)	235 (5.1)	354 (6.0)
6+	190 (1.8)	75 (1.6)	115 (1.9)
Migraine-related comorbidities			
Pain	2739 (26.1)	1134 (24.7)	1605 (27.1)
Mood disorders	2337 (22.2)	944 (20.6)	1393 (23.5)
Rhinitis	1887 (18.0)	829 (18.1)	1058 (17.9)
Sleep disturbances	1185 (11.3)	483 (10.5)	702 (11.9)
IBS	391 (3.7)	155 (3.4)	236 (4.0)
Epilepsy	177 (1.7)	75 (1.6)	102 (1.7)
Cardiovascular disease-related comorbidities			
Hyperlipidemia	2170 (20.6)	895 (19.5)	1275 (21.5)
Hypertension	1918 (18.3)	808 (17.6)	1110 (18.7)
Obesity	893 (8.5)	381 (8.3)	512 (8.6)
Diabetes	524 (5.0)	242 (5.3)	282 (4.8)
Cerebrovascular disease	309 (2.9)	145 (3.2)	164 (2.8)
Ischemic heart disease	199 (1.9)	82 (1.8)	117 (2.0)
Peripheral vascular disease	118 (1.1)	48 (1.0)	70 (1.2)
Congestive heart failure	27 (0.3)	9 (0.2)	18 (0.3)

Note: All data are n (%) unless otherwise indicated.

*Refill of index triptan within 24 months of index fill date.

IBS: irritable bowel syndrome; EPO: exclusive provider organization; HMO: health maintenance organization; POS: point of service; PPO: preferred provider organization.

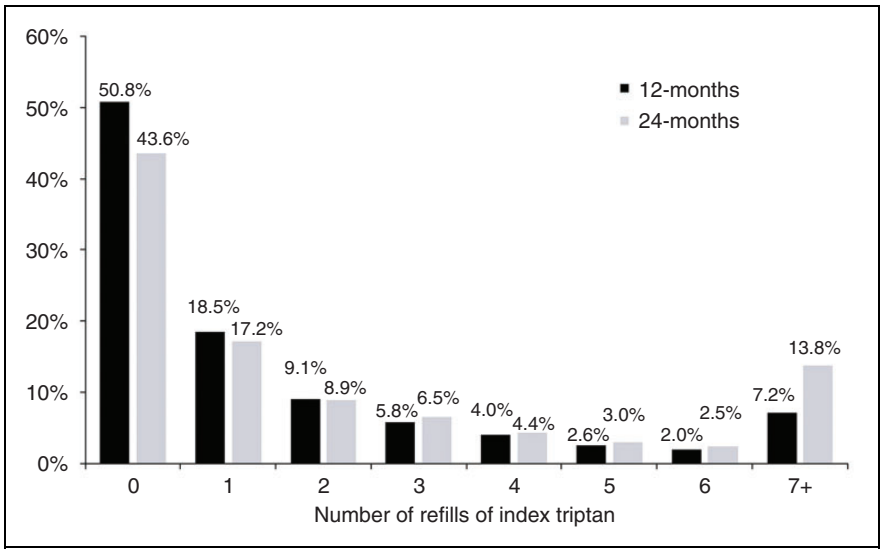

Figure 3. Proportion of patients by number of index triptan refills 12 and 24 months post-index.

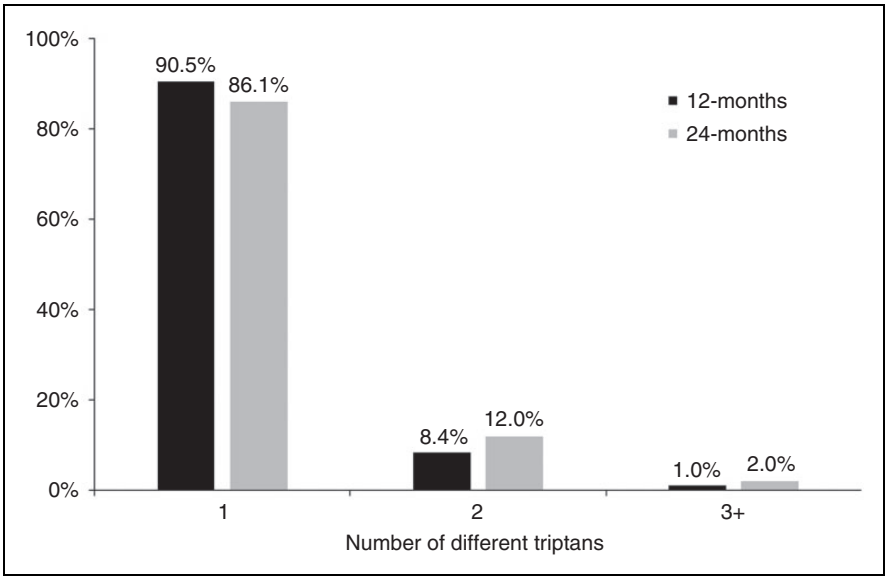

Figure 4. Number of different triptans used over 12 and 24 months post-index.

was 9.3% and 13.2% over 12 months and 24 months, respectively (data not shown).

Among patients with no refill of their index triptan, opioids (39%) and NSAIDs (22%) were the most commonly used acute medications both in the 12-month post-index period and the 24-month post-index period (any opioid: 53%; NSAID: 33%) (Figure 5). For patients who did not refill their index triptan and used an opioid (38.8% of those with no refills of index), 43% had no use of any opioid in the 12 months pre-index. For patients who did not refill their index triptan and had a migraine-related opioid prescription (14%), 60% had no migraine-related opioid prescriptions in the 12 months pre-index (data not shown). Even among patients who had $\geq$1 refill of their index triptan, use of other medications for acute treatment of migraine, such as NSAIDs (22% and 33%) and opioids (42% and 56%), was high in the 12-month and 24-month post-index periods, respectively (Figure 5).

Discussion

Understanding current patterns of real-world prescribing can help identify gaps in migraine management, define potential roles for emerging acute treatment,

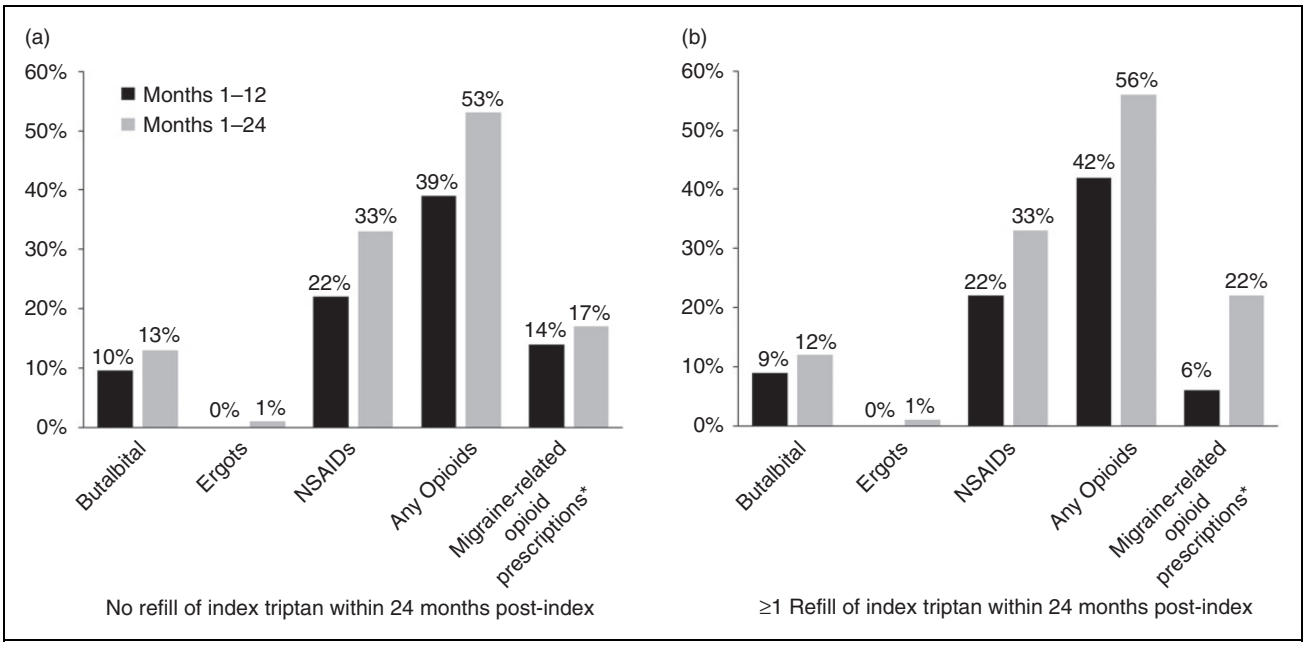

Figure 5. Use of non-triptan acute medications 12 and 24 months post-index in (a) patients with no refill of index triptan and (b) patients with ≥1 refill of index triptan over 24 months post-index.
Note: No users of acetaminophen were found, likely due to over-the-counter availability. Categories listed below are not mutually exclusive. Includes guideline and non-guideline listed opioids.
*Prescription filled within 15 days of a claim with a migraine diagnosis.
NSAIDs: non-steroidal anti-inflammatory drugs.

and inform future research. Triptans have been the leading prescription option for the acute treatment of migraine since their emergence in the early 1990s. Hence, the goal of this study was to evaluate triptan fill patterns and use of non-triptan acute treatments among a subset of migraine patients identified as new initiators of triptans using recent data from a large national insurer in the United States. Our study has three noteworthy findings with potentially important implications for clinical practice and guidelines.

Our first key finding is that about half (50.8%) of the patients who initiated a new triptan prescription did not refill their initial prescription over 12 months of follow-up. The lack of refills has many potential causes which are difficult to distinguish based on claims data. Some patients might not refill because they have such a low headache frequency that a single prescription meets their needs for a year. However, several lines of evidence from our analysis suggest that this scenario is unlikely. First, even when we extended follow-up to 24 months, we still found that 44% of the patients did not refill their initial triptan. Second, when we allowed a fill for the initial triptan or a different triptan agent to count towards the number of triptan fills, we still found similarly high proportions of patients without a second fill for any triptan agent over 12 months and 24 months of follow-up. Third, the number of pills for the initial triptan prescription was four or less in about 60% over 12 months, 45% had no refills over 12 months, and 38% had no refills over 24 months. While it is still likely that some of the patients without triptan refills may have low migraine frequency or milder attacks that respond to treatment with over-the-counter agents, the data support the importance of other reasons for triptan discontinuation. Our results are also in line with earlier studies, which report lack of triptan refills ranging from 38–66% based on claims data (8,10,13–16,20). Surveys of patients and physicians also report discontinuation rates in this range (35–41%) (21,22) and mirrors previous work demonstrating adherence challenges in migraine (23). While our study data source did not permit evaluation of the reasons for discontinuation, previous studies highlight lack of efficacy and adverse events as primary reasons for triptan discontinuation (23–25). Specifically, undesirable side effects such as dizziness, nausea, and fatigue have been reported as contributing to triptan discontinuation (24,25).

Our second finding is that triptan switching is an uncommon treatment pattern in real-world clinical practice. Among people who initiated a first triptan, 9.5% received a second triptan over 12 months and 13.9% received a second triptan over 24 months. Among those who did not refill their initial triptan,

only 9.3% received a second triptan over 12 months and 13.2% over 24 months. Such low rates of switching among triptans have also been reported in prior studies (4–15%) (10,13–16). Our findings suggest that in current clinical practice a second triptan is rarely prescribed after a patient fails their first triptan. Reasons for low levels of prescribing a second triptan are uncertain. Perhaps some prescribers are familiar and comfortable prescribing only a single triptan. Another factor may be a reluctance to try a second triptan on the part of patients or prescribers after poor results based on efficacy or tolerability with the first. Though the recent AHS Consensus Statement recommends a trial of at least two oral triptans for the acute treatment of migraine prior to switching to a different medication class, evidence for this recommendation is limited. Prior observational research has shown that switching from one triptan to another is not associated with reductions in headache-related disability one year later (24). In our overall sample of commercially insured patients from a large national insurer in the United States, trial of a second triptan was rare. Hence, clinical guideline recommendations and/or payer policies requiring a trial of at least two triptans may pose an undue burden on many patients with existing unmet needs for optimally managing their migraine attacks.

Our third key finding is that after discontinuing a triptan, more than half of migraine patients identified as new triptan users (53%) who did not refill their initial triptan had filled at least one opioid prescription over 24 months of follow-up. Other frequently filled non-triptan medication options over the 24-month follow-up included NSAIDs (33%) and butalbital combinations (13%). Relatively high rates of comorbidities such as pain conditions, present in 26% of the sample, likely contribute to the high rates of all-cause opioid prescriptions. Of the patients who received an opioid prescription, one-third of these patients had a medical claim with a migraine diagnosis in the 15 days prior to the prescription, suggesting that the opioid prescriptions were migraine-related. Reasons for the frequent use of opioids are uncertain and contrary to guidelines. One possibility is that if a triptan fails, prescribers are uncertain about alternative treatments to offer. Another possibility is that some of the migraine-related opioid use is related to acute treatment of migraine in an emergency department setting, where higher rates of opioid use have been documented (27). The high rate of opioid use is highly concerning given the fact that organizations such as the AHS, AAN, and the Institute for Clinical and Economic Review (ICER) do not recommend the use of opioids for migraine (4,28,29). Even more concerning is the fact that even among patients with one or more refills of their initial triptan, any opioid use (56%) and migraine-related opioid use (22%) was high over 24 months of follow-up, possibly suggesting unmet need (i.e. insufficient treatment response) even among those who do not have tolerability issues with triptans. Our findings point to the clear need for new effective treatments with fewer side effects for optimal management of migraine.

This study has several limitations. Our study is limited to commercially insured adults with a medical diagnosis of migraine and a prescription for a triptan, which represents a subset of the overall migraine population due to significant rates of underdiagnosis and undertreatment, which have been documented in previous studies (30). Our sample is further restricted to patients newly initiating a triptan, defined as no fills for a triptan in the 12 months prior to index date (41% of all triptan users in our study), and may have included some non-new triptan users who filled a prescription for a triptan less than once per year. Hence, our results are generalizable to the subset of those patients diagnosed with migraine who newly initiated a triptan after at least one year of no evidence of use of triptans. A medical diagnosis of migraine was captured as any medical claim with an associated ICD-9 code of 346.XX and, as with any analysis using administrative claims data, coding and entry errors may exist.

While this study represents a more recent dataset than prior published analyses of treatment patterns in migraine, the index year used for these analyses was 2013 with a 24-month follow-up period. Thus, is it possible that treatment patterns may have changed in more recent years. However, the first triptan was introduced more than 20 years ago and the first generic approximately 5 years before our study identification period. Therefore, substantial differences in triptan treatment patterns due to changes in triptan approval and availability are unlikely. However, with the emergent opioid crisis, opioid use may be higher or lower than observed in this sample due to awareness and changes in prescribing patterns.

As is common with administrative claims datasets, information on the reasons why people do not refill their index triptan is not available (e.g. effectiveness, tolerability issues, cost, etc.). Given that claims data do not capture information on the severity and frequency of migraine headaches, we are unable to determine if those who discontinue triptans continue to have migraine attacks that require acute treatment. However, the finding that many people who do not refill the index triptan use other migraine-related acute treatments suggests that many of these people do experience migraine headaches that require acute treatment. It should also be noted that the guideline

listed medications under the acetaminophen and NSAID classes (e.g. aspirin, ibuprofen, naproxen) are also available over the counter and are unlikely to be captured completely in the prescription claims data; hence, our results may underestimate the use of these classes. In fact, no users of acetaminophen were identified in our analysis. Finally, prescription claims do not have information on the indication for which the medication was prescribed. Hence, an opioid prescription may have been used for reasons other than migraine. To mitigate this effect, we required the fill of opioids and opioid combinations to occur within 15 days of a visit with a migraine diagnosis to be considered a migraine-related opioid prescription.

Conclusion

This study of a geographically diverse commercially insured population of a large national insurer in the United States found that a substantial proportion of the patients with migraine who newly started a triptan did not refill their initial triptan or switch to a second (different) triptan over 12 months and 24 months of follow-up. These findings, combined with the high rates of opioid use among these patients, potentially suggest insufficient response or tolerability issues with the current standard of care. Future research should examine the health resource utilization and costs associated with these suboptimal treatment patterns.

Article highlights

- This study of a commercially insured population in the United States found that 50.8% of patients with migraine newly starting a triptan do not refill their initial triptan over 12 months of follow-up and 43.6% do not refill over 24 months of follow-up.
- Switching between triptans was uncommon, with only 9.5% of patients receiving a second triptan over 12 months and 13.9% receiving a second triptan over 24 months. Among those who did not refill their initial triptan, only 9.3% received a second triptan over 12 months and 13.2% over 24 months.
- Use of other medications for acute treatment of migraine, such as opioids and NSAIDS, was high in the 12-month and 24-month post-index periods among patients with and without a refill of their index triptan.
- The low rate of switching between triptans and high rates of opioid use in real-world practice potentially suggest insufficient response or tolerability issues with the current standard of care.

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