Healthcare Service Use, Costs, and Treatment Patterns within a Cohort of Experienced and New Users of Preventive Migraine Medications

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Abstract

Background: Migraine is a debilitating disease associated with increased use of healthcare services. Pharmacological interventions include acute medications to reduce symptoms and restore patient functioning, and preventive migraine medications (PMM), to reduce frequency, duration, and intensity of migraine symptoms . This study examined treatment and associated healthcare service use and costs between PMM naïve and experienced patients.

Methods: Migraine patients initiating treatment with a PMM from January 1, 2010-June 30,2014 were identified in the IBM MarketScan Commercial and Medicare Supplemental Databases. Migraine medication use, service utilization, and costs were examined over the 12 months following PMM initiation; outcomes were compared between patients experienced with and naïve to PMM treatment.

Results: Adherence and persistence with PMMs was low, with only 24% of patients adherent to their index PMM. Rates of discontinuation were high, with 71.4% of the sample discontinuing their PMM over the 12-month follow up. Utilization of acute medications was common, as was PMM switching in experienced patients. Annual healthcare costs were $12,044 and $19,093 for the PMM naïve and experienced populations respectively. Migraine-specific service use accounted for approximately 20% of all-cause healthcare costs. The PMM experienced cohort consistently evidenced higher service use and costs than the PMM naïve cohort.

Conclusion: Utilization of PMM remains suboptimal and is accompanied by both lack of PMM adherence and high use of acute medications. Rates of PMM switching and use of acute medications suggest that patients have unmet needs regarding migraine management. Improved treatment regimens that effectively manage migraine symptoms are needed to improve patient level of functioning while reducing healthcare costs associated with migraine management.

Background

Migraine is a neurological disorder characterized by recurrent, throbbing, unilateral headaches of at least moderate intensity, frequently accompanied by nausea, phonophobia or photophobia.[1] Approximately 18% of women and 6% of men in the United States experience migraine, with individuals aged 30-39 years exhibiting the highest rates of migraine, estimated at 24.4% of women and 7.4% of men.[2]

Migraine can be classified as either episodic or chronic, the latter of which is characterized by headache occurring on a minimum of 15 headache days per month for more than three months, which, on at least eight days per month, has the features of migraine headache.[1] Approximately 90% of migraine sufferers are affected by episodic migraine.[3] However, migraine subtypes are not static, and episodic migraine may eventually transform to chronic migraine, and vice versa.[4] Studies have found physical factors such as obesity or female gender, treatment factors such as frequent use of acute migraine medications, and clinical factors such as presence of other pain disorders or a high headache frequency to be associated with transformation to chronic migraine.[4,5]

Migraine not only impact patients, but also place a substantial burden on both the healthcare system and society, with total costs of migraine estimated at $23 billion annually in the United States.[6] Direct costs were estimated to account for approximately half of the overall costs of migraine, and derive from increased utilization of primary care, specialist, diagnostic, and emergency healthcare services, as well as migraine treatments.[7] Indirect costs emanate from increased disability, presenteeism, and absenteeism due to migraine symptoms, and accounted for the remainder of migraine-related costs.[8]

Management of migraine is focused on reducing the frequency, severity, and duration of migraine to restore patients' level of functioning, improve quality of life, and reduce disability.[9] Pharmacological intervention, which includes preventive migraine medications (PMM) and acute migraine drugs, is the focus of migraine treatment; although due to their association with transformation to chronic migraine, overuse of acute medications should be avoided. Non-pharmacological approaches, including avoidance of triggers and alleviation of modifiable risk factors, are also important aspects of treatment.[4,9,10] Generically available PMMs are effective in increasing quality of life, reducing migraine frequency, and lowering healthcare resource use and costs; these medications can also help to limit overuse of acute medications.[11-16] Despite the benefit in migraine management afforded to patients by PMMs, studies have shown that there is poor adherence to these medications.[17-19] Further, PMMs have been found to be underutilized, with fewer than half of those patients eligible for PMMs receiving treatment.[2,5,16,20] Poor management of migraine symptoms is associated with increased healthcare costs. Medications that can effectively manage migraine symptoms stand to not only improve patient outcomes, but also reduce the burden of disease to both patients and society.[4,5,9]

This study used the IBM MarketScan Commercial and Medicare Supplemental claims databases to examine real world treatment approaches within a population of PMM users that are treatment naïve and a population of PMM-experienced patients initiating treatment with a new PMM. Patterns of PMM and acute medication use were examined to evaluate the effectiveness of generically available treatments. Further, healthcare service utilization and cost outcomes were examined within the population to evaluate the burden associated with treatment. An implicit goal of this analysis is to provide a backdrop for new and emerging PMMs.

Methods

Data Source

This retrospective, observational study utilized administrative claims data contained in the IBM MarketScan® Commercial and Medicare Supplemental Databases from January 1, 2008 through June 30, 2015. These databases comprise enrollment and demographic information as well as inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from employees, dependents, retirees, and members of more than 200 large self-insured U.S. employers and health plans.

Study Design

The study sample included patients initiating a new course of treatment with an oral PMM. Patients were required to meet the following criteria:

- ≥1 pharmacy claim for an oral PMM between 1/1/2010 and 6/30/2014
    - The date of earliest oral PMM served as the index date; the medication class prescribed on the index date was flagged as the index PMM class
- Age ≥18 on the index date
- ≥24 months of continuous enrollment in medical and pharmacy coverage before the index date (*baseline period*)
- No pharmacy claims for medications in the index PMM class during the 24-month baseline period
- ≥12 months of continuous enrollment in medical and pharmacy coverage after the index date (*follow-up period*)
- Evidence of a migraine on the index date or during the prior 30 days, as indicated by meeting ≥1 of the following criteria:
    - ≥1 inpatient (IP) claim with a diagnosis of migraine (ICD-9-CM diagnosis 346.xx) in any position (in the 30 days before or on the index date)
    - ≥2 emergency room (ER) claims with a diagnosis of migraine in any position (≥1 claim must have occurred on the index date or during the prior 30 days, the second claim may have occurred at any time in the 12-month period prior to the index date)
    - ≥2 outpatient (OP) claims with a diagnosis of migraine in any position (≥1 claim must have occurred on the index date or during the 30 days prior to index, the second claim had to have occurred between 7-180 days before that claim)
    - ≥1 OP claim with a diagnosis of migraine in any position and ≥1 pharmacy claim for a triptan or ergotamine or topiramate (≥1 of these claims in the 30 days before or on the index date and the 2nd 7-180 days before that claim)
    - ≥2 pharmacy claims for a triptan or ergotamine (≥1 claim must have occurred on index or during the 30 days prior to index, the second claim must have occurred between 7-180 days before that claim)
- No evidence of HIV or malignancy during the baseline or follow-up periods
- No evidence of onabotulinumtoxinA administration during the baseline or follow up periods

Eligible patients were further classified as either PMM experienced, defined as having evidence of prior PMM use during the baseline period, or PMM naïve, defined as having no claims for a PMM during the baseline period. PMM experienced patients were additionally required to have a diagnosis for migraine within the 90 days prior to their first PMM claim in the baseline period to ensure the medication was prescribed for migraine and not for other indicated conditions. The PMM experienced cohort was further stratified into a subgroup that used only one class of PMM during the baseline period and a subgroup that used two or more PMM classes during the baseline period.

Outcomes

Patient demographics and comorbidity burden were examined at study index, and over the last 12 months of the baseline period, respectively. All-cause and migraine-specific healthcare service utilization, including treatment with PMMs or acute migraine medications, and associated costs were assessed over the 12-month follow up period. Migraine related service utilization and costs were classified as inpatient claims with a diagnosis for migraine in the primary position and outpatient claims with a diagnosis for migraine in any position. Migraine related pharmacy use was classified as claims for PMMs or acute migraine medications. PMMs included: angiotensin-converting enzyme inhibitors (ACE-I), alpha-agonists, angiotensin II receptor blockers (ARB), anticonvulsants, antihistamines, beta blockers, calcium channel blockers (CCB), serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, and tricyclic antidepressants, while acute migraine medications included: barbiturates, ergots, muscle relaxants, neuroleptics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, other analgesics, and triptans.

Adherence and persistence with PMM therapy was examined over the 12-month follow up period. Adherence was calculated as the proportion of days covered (PDC) defined as the number of days with a PMM on hand divided by the 12-month follow up (365 days); PDC was expressed as a percentage between 0 and 100%. Patients with a PDC value of 80% or greater were classified as being adherent to PMMs. Persistence was calculated as the number of days from study index to PMM discontinuation, with discontinuation defined as a gap in therapy ≥ 60 days or the end of follow up. PMM utilization after discontinuation was examined over the remainder of the follow up period. Use of acute migraine medications during the follow up period was also assessed; specifically, utilization of acute medications over the 30 days prior to and 90 days following PMM discontinuation.

Analyses

For sample characteristics and outcomes, categorical variables were reported as frequency and percent, while continuous variables were reported as mean, median, and standard deviation. Differences between the PMM naïve and PMM experienced cohorts were examined using chi-square tests on categorical measures and t-tests on continuous measures. P-values <0.05 were a priori considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC).

Results

Patient Sample

A total of 74,533 patients met the study eligibility criteria. Of these patients, 29,919 had no evidence of PMM use in the baseline period and were classified as PMM naïve. The remaining 44,614 patients were classified as PMM experienced, as they had PMM prescription claims and a migraine diagnosis within 90 days of the first fill in the baseline period. Among the PMM experienced patients, 26,279 (58.9%) used only one class of PMM during the baseline period, and 18,335 (41.1%) used two or more PMM classes.

The sample was primarily composed of females of middle age with commercial insurance. PMM experienced patients were slightly older and more likely to be female compared to PMM naïve patients ($p < 0.001$; Table 1). Patients in the PMM experienced cohort also had a higher comorbidity burden than PMM naïve patients as (evidenced by a higher mean Deyo Charlson Comorbidity Index (DCI)); a significantly increased proportion of PMM experienced patients exhibited diagnoses for multiple comorbidities including anxiety and depression compared to the PMM naïve cohort (Table 1). Further, the PMM experienced cohort was significantly more likely than the PMM naïve cohort to evidence a migraine or chronic migraine diagnosis during the baseline period ($p < 0.001$, Table 1). Among PMM experienced patients, those with two PMM classes during baseline were slightly older ($p < 0.001$) and had a significantly higher comorbid burden than those with one PMM class.

Treatment Patterns

PMM Utilization

During the baseline period, among PMM experienced patients, 58.9% used only one PMM class, 30.0% used two PMM classes, and 11.1% used three or more classes of PMM (Table 2). Anticonvulsants were the most commonly used class of PMM at index in both the naïve and experienced cohorts; other commonly used classes included beta-blockers, tricyclics, and SNRIs. The same pattern of results was observed whether experienced patients used one or more than one PMM class during the baseline period. A significantly larger proportion of the PMM experienced cohort used each of the PMM medication classes at index compared to the PMM naïve cohort, except for anticonvulsants, which were utilized by a significantly larger proportion of the PMM naïve cohort ($p < 0.001$, Table 2). PMM experienced patients were also more likely to exhibit use of multiple PMMs at index (poly-therapy) compared to PMM naïve patients (12% v. 2%).

Overall adherence to index PMMs was low, with a mean ± SD PDC of 0.43 ± 0.34; further, only 24% of the population was adherent (PDC ≥80%) to the index PMM over the 12-month follow up period (data not shown in Table). Consistent with the low rates of adherence, rates of discontinuation were high. The majority (71.4%) of the sample discontinued their PMM; mean ± SD time to discontinuation was 162.0 ± 142.2 days (Table 2). Discontinuation occurred rapidly, with approximately 40% of the sample discontinuing their PMM by one month post-index; a subsequent steady decline in persistence was also observed over the remainder of the follow up period (Figure 1). Rates of adherence and discontinuation were similar between the PMM experienced and naïve cohorts. Adherence and persistence rates were also similar among experienced patients with one or more than one PMM class during the baseline period.

Patterns of PMM use over the post-period were examined in the populations of experienced and naïve patients. The majority (74.4%) of the PMM naïve population used a single PMM, the index medication, during follow up (Figure 2a). Most of these naïve patients would go on to discontinue the index PMM before the end of the 12-month post period. A small proportion of patients who discontinued later re-initiated the index PMM during the follow up period (Figure 2a). Treatment patterns among patients using a single PMM over follow up were similar between the PMM naïve and experienced samples. Conversely,

PMM experienced patients were significantly more likely than PMM naïve patients to use multiple PMMs over the follow up period (76.0% vs. 25.6%; Figure 2a). The majority of experienced patients who utilized multiple PMMs over follow up discontinued their index PMM and switched to a new PMM; discontinuation rates did not differ by the number of PMMs used during the baseline period. A small proportion of patients who discontinued their index PMM re-initiated treatment later in the follow up period. Approximately 30% of PMM experienced patients augmented therapy with a second PMM (poly-therapy) while continuing to take their index PMM (Figure 2). Additionally, experienced patients with two or more PMMs during the baseline period were more likely than those with only one PMM during baseline to add a new PMM class after the index date (86.4% vs. 68.8%). Rates of poly-therapy use were significantly lower in the PMM naïve subgroup who used more than one PMM, with only about 20% of naïve patients switching to a poly-therapy regimen. The remaining 80% of patients switched to a new PMM during the follow up period (Figure 2a).

Among the PMM experienced patients, the majority added at least one additional PMM during the follow-up period, and a significantly higher proportion of those already using two or more PMMs versus those using only one PMM during baseline added another PMM during follow-up (86.4% vs. 68.8%, $p<0.001$; Figure 2b). Regardless of the addition of a new PMM post-index, approximately 70% of PMM experienced patients discontinued the index PMM, and discontinuation rates were similar among those with one baseline PMM and those with two or more baseline PMMs. Rates of re-initiation of the index PMM were low (under 25%) and were similar among those with one versus two or more baseline PMMs.

Acute Migraine Medication Use

Utilization of acute migraine medications was common over the follow up period (Table 2). Triptans were the most commonly used acute agents within both the experienced (66.7%) and naïve (71.0%) cohorts, although among experienced patients with two or more PMMs during the baseline period, opioids were the most commonly used acute medication (66.9%). Overall, other commonly used agents included opioids (naïve: 45.6%, experienced: 59.8%), NSAIDs (naïve: 27.3%, experienced: 33.0%), and muscle relaxants (naïve: 22.8%, experienced: 34.5%). A significantly larger proportion of PMM experienced patients used all classes of acute migraine medications, with the exception of triptans, which were used by a significantly larger proportion of the PMM naïve population; the same pattern of results was observed when comparing experienced patients with more than two PMMs to those with only one PMM during baseline (Table 2). Acute migraine medication use temporarily decreased over the 30 days following index PMM discontinuation for all acute medication classes in both the experienced and naïve cohorts. The greatest declines were observed in triptans, barbiturates, opioids, and other analgesic medications. Rates of acute migraine medication use returned to baseline levels in the 90 days following index PMM discontinuation, potentially indicating a non-abatement or resurgence in migraine symptoms following PMM discontinuation.

Healthcare Costs and Service Utilization

Trends observed for all-cause and migraine-specific service use were similar (Table 3a, 3b). The PMM experienced cohort had a greater proportion of patients with inpatient (12.7% versus 7.5%) or emergency room visits (36.6% versus 29.2%) compared to the PMM naïve cohort, and among PMM experienced patients, those with two or more PMMs during baseline had a higher rate of hospitalization (16.3%) than did those with only one PMM (10.2%) during baseline (Table 3a, 3b). A similar pattern of results was observed for emergency room visits. Although the proportions of the PMM naïve and experienced cohorts with a physician office visit were similar, the PMM experienced patients had a greater number of mean physician office visits (11.8 versus 8.9), indicating increased utilization. The PMM experienced patients were also more likely to see a neurologist compared to PMM naïve patients (47.2% versus 35.9%). Utilization of brain imaging procedures was similar between the cohorts (experienced: 20.5%, naïve: 17.9%) (Table 3a, 3b).

Patients in the PMM experienced cohort had higher all-cause and migraine-specific healthcare costs and service utilization during the follow up period compared to PMM naïve patients; costs were higher for patients with two or more PMMs during the baseline period as compared to those with one PMM during baseline (Table 3a, 3b). Total all-cause healthcare costs were approximately 1.5-fold higher for the PMM experienced cohort ($19,093 versus $12,044). Within the PMM experienced cohort, costs were also 1.5 times higher for those with 2 or more PMMs ($23,702) versus those with only one PMM ($15,877) during baseline. Despite PMM experienced patients evidencing increased healthcare costs, proportional trends in costs were similar between experienced and naïve patients. Pharmacy costs accounted for approximately one-quarter of total healthcare costs, while medical costs accounted for the remaining three-quarters of total healthcare costs. Outpatient services had the greatest contribution to all-cause medical costs, accounting for more than one-half of all medical costs. Emergency room costs had the smallest contribution to medical costs.

There was also an approximate 1.6-fold difference in migraine-specific healthcare costs between the PMM experienced and naïve cohorts, with the PMM experienced patients having higher costs over the follow up period. Among the experienced cohort, migraine-specific costs were 2.3 times higher in patients with two or more PMMs ($3,992) compared to those of patients with only one PMM ($2,766) during the baseline period (Table 3b). Again, proportional trends costs were largely similar between the naïve and experienced cohorts for migraine specific costs. Outpatient services again accounted for the majority of migraine-specific medical costs. Inpatient costs had the smallest contribution to migraine specific medical costs, although, PMM experienced members had increased inpatient costs compared to PMM naïve members.

Average costs for individual healthcare encounters were also described in the full sample of both experienced and naïve patients. Although the mean ± SD costs associated with an inpatient admission ($12,050 ± $10,133) or emergency room visit ($1,003 ± $1,028) far exceeded that of office ($124 ± $68) and neurologist visits ($135 ± $76), these latter services were more often utilized, leading to them accounting for a larger proportion of all-cause and migraine-specific healthcare costs.

Discussion

This retrospective study utilized administrative healthcare claims to examine treatment patterns, service utilization, and healthcare costs associated with migraine management within a population of patients newly initiating or switching PMM treatment. Consistent with previous studies on migraine and PMM utilization, our population was found to consist primarily of middle-aged females.[2] Chronic migraine were also relatively rare within the sample, with only 3.1% of the PMM naïve sample and 7.2% of the PMM experienced sample having a specific diagnosis code indicating chronic migraine. These proportions largely replicate those found previously; the lower proportion of chronic migraine within the PMM naïve sample may be due to reduced diagnosis of chronic migraine or utilization of chronic migraine codes within newly treated migraine patients.[4,21] The reduced rate of chronic migraine in the PMM naïve sample may also point to transformation from episodic to chronic migraine over the course of disease within the sample.[4, 21] Finally, it may be that chronic migraine patients have “given up” in terms of seeking effective preventive medications.

Migraine specific and all-cause healthcare costs were increased within the PMM experienced cohort, and within the experienced cohort, were higher for those who used two or more PMMs during baseline compared to those who used only one PMM. Although the increased comorbidity burden within the PMM experienced patients could account for a portion of this increase, the similar increase in migraine-specific costs suggests that comorbidities alone do not account for the increased cost of care observed within the PMM experienced cohort. It is likely that at least a portion of these costs emanate from the increased duration or severity of disease.[21]

From a treatment perspective, the results of this study confirm findings from other analyses that adherence and persistence with PMMs is poor.[17-19] Low rates of both adherence and persistence were observed in both PMM experienced and naïve patients suggesting that lack of patient education or migraine experience within the PMM naïve cohort is not the only reason for poor adherence and discontinuation. Treatment patterns also indicate that currently available PMMs may leave patients with unmet needs regarding migraine management. In this study, high rates of PMM discontinuation followed by PMM switching, poly-therapy, or reliance on acute migraine medications were observed. These patterns of treatment suggest that currently available PMMs may not be fully effective or may be associated with side effects, causing patients to switch to different PMMs or supplement their treatment regimen with either acute medications or poly-therapy regimens. Additionally, cyclical patterns of PMM treatment indicated by rates of discontinuation, switching, and PMM re-initiation, especially within the PMM experienced sample, indicate that many patients are unable to manage their migraine symptoms, even with revisions to their treatment regimen. Acute medications intended to treat symptoms after onset, as opposed to preventing symptoms, were found to account for well over half of all migraine-specific pharmacy costs. This finding indicates that most patients are not relying on preventive medications to manage their disease, but instead are treating breakthrough pain in a reactive fashion.

The overall picture of the PMM experienced cohort was one of multiple medication switches, increased use of acute medications, thus increasing risk of transformation to chronic migraine, and increased costs compared with PMM naïve patients. Optimization of migraine treatment regimens to take a more proactive approach to symptom management is needed not only to help patients manage their migraine symptoms, but also to help reduce the cost of care associated with migraine management.

Limitations of this study include those that pertain to any administrative claims-based study, as these data are collected for the purpose of facilitating payment for medical services and lack clinical specificity found in medical records and physician notes. Further, this study sample was comprised of patients covered by commercial insurance; therefore, findings may not be generalizable to populations with other forms of insurance or to the uninsured. PMMs examined as part of this analysis are not migraine-specific therapies, although patients were required to have a diagnosis for migraine. Despite the requirement for a migraine diagnosis in close proximity to the initiation of PMM therapy, the possibility that PMMs may have been prescribed for conditions other than migraine prevention cannot be ruled out. Finally, patients were required to maintain 24 months of enrollment in the database prior to study index and an additional twelve months of enrollment following the index date, therefore study outcomes were not captured for those who discontinued enrollment during follow-up.

Overall this study found that despite the utilization of PMMs and other acute agents, many patients are unable to adequately manage symptoms of migraine and evidenced by ongoing use of acute migraine medications and migraine healthcare utilization. The more experienced the patients in terms of PMMs, the greater the acute medication use and the greater the cost. Since adherence was poor, the strategy of multiple sequential switches with current medications seems counterproductive. The results suggest that new treatments with greater efficacy or increased tolerability are needed in order to improve management of migraine symptoms and disease and overall disease progression. In conclusion, the low rates of adherence and persistence observed within this sample almost certainly contribute to poor migraine management; they likely also contribute to escalated healthcare costs, some of which are associated with inefficient or ineffective management of migraine symptoms. Further study to elucidate the underlying factors that contribute to poor adherence and persistence are certainly warranted.

Declarations

Ethics approval and consent to participate

This study used anonymized, de-identified retrospective claims data from the MarketScan databases, and no patient identifiable data were used. Data were analyzed and reported on a group level, and Institutional Review Board approval was not required.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from IBM, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of IBM.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

M.B., S.S. and P.D. were involved in the conception of this study. M.B. and K.C were involved in the analysis of the data. All authors were involved in the design of the study, the interpretation of the data, and the drafting or revision of the manuscript. All authors have read and approved the final version of this submitted manuscript, and all authors agree to be accountable for all aspects of the work.

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Abbreviations

ACE-I	Angiotensin-Converting Enzyme Inhibitors
ARB	Angiotensin II Receptor Blockers
CCB	Calcium Channel Blockers
DCI	Deyo-Charlson Comorbidity Index
ER	Emergency Room
HIV	Human Immunodeficiency Virus
IP	Inpatient
IRB	Institutional Review Board
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OP	Outpatient
PDC	Proportion of Days Covered
PMM	Preventative Migraine Medications
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor

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Tables

Table 1. Demographics

	PMM Naïve	PMM Experienced			
		All PMM Experienced	1 Baseline PMM	2+ Baseline PMMs	
	N=29,919	N=44,614	N=26,279	N=18,335	p-value[11]
Age, mean (SD)	43.0 (12.3)	45.0 (12.3)	44.0 (12.3)	46.3 (12.1)	<0.001
Female, %	83.3%	85.1%	85.2%	84.9%	<0.001
Geographic Region, %					<0.001
Northeast	15.6%	13.6%	14.3%	12.5%	
North Central	22.8%	24.0%	23.6%	24.6%	
South	38.8%	42.8%	42.0%	44.0%	
West	22.3%	19.0%	19.5%	18.3%	
Unknown	0.6%	0.7%	0.7%	0.7%	
Payer, %					<0.001
Commercial	96.9%	95.4%	96.2%	94.4%	
Medicare	3.1%	4.6%	3.8%	5.6%	
DCI, mean (SD)	0.25 (0.59)	0.38 (0.79)	0.30 (0.68)	0.49 (0.92)	<0.001
Comorbidities, %					
Anxiety	13.1%	18.2%	15.9%	21.7%	<0.001
Asthma	8.1%	9.9%	8.8%	11.4%	<0.001
Cardiac arrhythmias	4.1%	6.5%	5.0%	8.6%	<0.001
Chronic pain	23.7%	34.6%	30.2%	40.9%	<0.001
Low back pain	16.6%	23.3%	20.5%	27.3%	<0.001
Depression	14.1%	25.1%	20.6%	31.4%	<0.001

Diabetes	3.4%	7.7%	5.6%	10.7%	<0.001
Endometriosis	1.1%	1.5%	1.3%	1.7%	<0.001
Epilepsy	1.5%	2.9%	2.4%	3.7%	<0.001
Hypertension	15.1%	30.8%	23.7%	41.0%	<0.001
Inflammatory bowel disease	9.4%	13.7%	11.6%	16.6%	<0.001
Irritable bowel syndrome	2.8%	4.1%	3.4%	5.2%	<0.001
Menopause/menopause-related symptoms	6.1%	7.5%	6.9%	8.4%	<0.001
Menorrhagia	4.2%	4.1%	4.2%	4.0%	0.724
Migraine	73.9%	83.6%	81.8%	86.2%	<0.001
Chronic migraine	3.1%	7.2%	5.9%	9.1%	<0.001
Myocardial infarction	0.6%	0.6%	0.4%	0.8%	0.708
Osteoarthritis	10.4%	17.0%	14.1%	21.3%	<0.001
Osteoporosis	4.8%	6.4%	5.9%	7.0%	<0.001
Stroke	3.3%	3.7%	3.0%	4.7%	0.002

DCI: Deyo Charlson Comorbidity Index; PMM: preventive migraine medication; SD: standard deviation

[1]PMM Naïve vs. PMM Experienced

[2]Measured on the index date

[3]Measured during the 12 months prior to the index date

Table 2. Treatment Characteristics

	PMM Naïve	PMM Experienced			
		All PMM Experienced	1 Baseline PMM	2+ Baseline PMMs	
	N=29,919	N=44,614	N=26,279	N=18,335	p-value[1][1]
Index PMM Class[2], %					
ACEI	6.0%	7.7%	6.6%	9.2%	<0.001
Alpha-agonists	0.7%	2.4%	1.4%	3.8%	<0.001
ARB	0.1%	0.2%	0.1%	0.4%	<0.001
Anticonvulsants	43.5%	30.7%	33.9%	26.2%	<0.001
Antihistamines	0.5%	1.2%	0.8%	1.8%	<0.001
Beta Blockers	20.3%	22.3%	22.0%	22.6%	<0.001
CCB	4.1%	7.8%	6.2%	10.2%	<0.001
SNRI Antidepressants	7.6%	15.0%	13.6%	17.0%	<0.001
Tricyclic Antidepressants	19.0%	24.3%	24.2%	24.4%	<0.001
Adherence to Index PMM Class					
PDC, mean (SD)	0.40 (0.33)	0.44 (0.34)	0.44 (0.34)	0.45 (0.34)	<0.001
PDC, median	0.25	0.33	0.33	0.34	
PDC ≥80%, %	21.7%	25.3%	25.1%	26.3%	<0.001
Discontinuation of Index PMM Class					
Discontinued, %	73.5%	69.5%	70.1%	68.9%	<0.001
Days to discontinuation, mean (SD)	153.9 (140.7)	169.3 (143.4)	167.1 (142.8)	171.2 (143.8)	<0.001
Days to discontinuation, median	89.0	105.0			<0.001
PMM Use During Follow Up[3]					

Patients with any ACEI, %	8.0%	16.1%	11.8%	22.3%	<0.001
ACEI prescriptions, mean (SD)	4.9 (3.8)	5.2 (3.7)	5.2 (3.7)	5.3 (3.7)	<0.001
Patients with any alpha-agonist, %	1.2%	4.2%	2.4%	6.9%	<0.001
Alpha-agonist prescriptions, mean (SD)	2.6 (2.7)	3.7 (3.5)	3.4 (3.5)	3.8 (3.6)	<0.001
Patients with any ARB*, %	0.1%	0.6%	0.3%	0.9%	<0.001
ARB prescriptions, mean (SD)	2.8 (2.7)	4.9 (3.6)	5.0 (3.8)	4.9 (3.5)	<0.001
Patients with any anticonvulsant, %	52.9%	65.6%	63.0%	69.3%	<0.001
Anticonvulsant prescriptions, mean (SD)	4.4 (4.0)	5.9 (4.8)	5.7 (4.7)	6.3 (5.0)	<0.001
Patients with any antihistamine, %	0.7%	1.9%	1.3%	2.7%	<0.001
Antihistamine prescriptions, mean (SD)	2.1 (2.3)	2.9 (2.9)	2.5 (2.7)	3.1 (3.0)	<0.001
Patients with any beta blocker, %	26.3%	43.6%	38.4%	51.0%	<0.001
Beta blocker prescriptions, mean (SD)	4.5 (3.8)	5.3 (3.9)	5.1 (3.9)	5.4 (3.8)	<0.001
Patients with any CCB, %	6.1%	13.6%	10.7%	17.8%	<0.001
CCB prescriptions, mean (SD)	3.9 (3.6)	4.7 (3.8)	4.5 (3.8)	4.9 (3.8)	<0.001
Patients with any SNRI antidepressant, %	11.7%	32.3%	25.1%	42.7%	<0.001
SNRI antidepressant prescriptions, mean (SD)	5.0 (4.1)	6.1 (4.4)	5.8 (4.3)	6.3 (4.4)	<0.001
Patients with any tricyclic antidepressant, %	25.7%	39.8%	36.3%	44.7%	<0.001
Tricyclic antidepressant prescriptions, mean (SD)	3.7 (3.5)	4.7 (4.0)	4.4 (3.9)	4.9 (4.1)	<0.001
Acute Migraine Medication Use During Follow Up[3]					
Patients with any barbiturate, %	12.3%	17.0%	15.4%	19.3%	<0.001
Barbiturate prescriptions, mean (SD)	3.7 (5.6)	4.5 (5.5)	4.2 (5.2)	4.8 (5.8)	<0.001

Patients with any ergotamine, %	0.9%	2.4%	1.8%	3.2%	<0.001
Ergotamine prescriptions, mean (SD)	2.1 (2.1)	2.7 (3.1)	2.5 (3.0)	2.8 (3.1)	<0.001
Patients with any prescription NSAID, %	27.3%	33.0%	31.3%	35.4%	<0.001
NSAID prescriptions, mean (SD)	2.2 (2.1)	2.7 (2.5)	2.5 (2.4)	2.8 (2.7)	<0.001
Patients with any opioid, %	45.6%	59.8%	54.8%	66.9%	<0.001
Opioid prescriptions, mean (SD)	5.2 (6.9)	7.5 (8.6)	6.5 (7.9)	8.7 (9.2)	<0.001
Patients with any triptan, %	71.0%	66.7%	68.8%	63.6%	<0.001
Triptan prescriptions, mean (SD)	6.2 (5.4)	6.4 (5.6)	6.4 (5.4)	6.4 (6.0)	<0.001
Patients with any muscle relaxant, %	22.8%	34.5%	30.1%	40.8%	<0.001
Muscle relaxant prescriptions, mean (SD)	3.3 (3.7)	4.4 (4.3)	4.0 (4.1)	4.8 (4.5)	<0.001
Patients with any neuroleptic, %	15.6%	23.8%	20.5%	28.5%	<0.001
Neuroleptic prescriptions, mean (SD)	2.1 (3.0)	2.8 (3.5)	2.5 (3.1)	3.2 (3.9)	<0.001
Patients with any other analgesic acute medication, %	2.5%	4.3%	3.6%	5.3%	<0.001
Other analgesic acute medication prescriptions, mean (SD)	2.0 (1.9)	2.6 (2.7)	2.3 (2.4)	2.8 (3.0)	<0.001

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; NSAID: non-steroidal antinflammatory drug; PDC: percent of days covered; PMM: preventive migraine medication; SD: standard deviation; SNRI: serotonin norepinephrine reuptake inhibitor

[1]PMM Naïve vs. PMM Experienced

[2]This category represents the types of PMM observed on the index date. Patients with >1 PMM type recorded on the index date appear in >1 row

[3]Means were computed among patients with utilization in the category

Table 3a. All-Cause Healthcare Service Utilization and Costs

	PMM Naïve	PMM Experienced			
		All PMM Experienced	1 Baseline PMM	2+ Baseline PMMs	
	N=29,919	N=44,614	N=26,279	N=18,335	p-value[1]
Service Utilization[2]					
Inpatient admission, %	7.5%	12.7%	10.2%	16.3%	<0.001
Inpatient admissions, mean (SD)	1.3 (0.8)	1.6 (1.4)	1.4 (1.2)	1.7 (1.5)	<0.001
ER visit, %	29.2%	36.6%	33.3%	41.5%	<0.001
ER visits, mean (SD)	2.1 (3.1)	2.7 (4.4)	2.3 (3.3)	3.1 (5.4)	<0.001
Brain imaging procedure[3], %	17.9%	20.5%	18.5%	23.3%	<0.001
Brain imaging procedures, mean (SD)	1.2 (0.6)	1.3 (0.9)	1.2 (0.8)	1.4 (1.0)	<0.001
Physician office visit, %	98.4%	99.1%	99.0%	99.3%	<0.001
Physician office visits, mean (SD)	8.9 (6.7)	11.8 (8.9)	10.7 (8.0)	13.5 (9.9)	<0.001
Neurologist office visit, %	35.9%	47.2%	44.9%	50.4%	<0.001
Neurologist office visits, mean (SD)	2.7 (2.0)	3.0 (2.3)	2.9 (2.2)	3.1 (2.4)	<0.001
Other outpatient service, %	96.8%	98.2%	97.8%	98.8%	<0.001
Other outpatient services , mean (SD)	13.7 (14.8)	18.2 (18.5)	16.2 (16.8)	21.1 (20.3)	<0.001
Pharmacy claim, %	100.0%	100.0%	100.0%	100.0%	
Pharmacy claims, mean (SD)	33.0 (24.6)	51.8 (35.8)	44.7 (31.1)	61.9 (39.6)	<0.001
Healthcare Costs, mean (SD)					

Inpatient	$2,072 ($14,070)	$3,790 ($18,774)	$2,858 ($15,573)	$5,127 ($22,516)	<0.001
ER	$613 ($2,504)	$994 ($3,835)	$762 ($2,730)	$1,325 ($4,992)	<0.001
Total outpatient	$6,311 ($11,615)	$9,211 ($15,797)	$7,937 ($14,563)	$11,037 ($17,251)	<0.001
Brain imaging[3]	$196 ($642)	$231 ($727)	$205 ($663)	$267 ($808)	<0.001
Physician office visits	$1,042 ($1,006)	$1,388 ($1,418)	$1,246 ($1,323)	$1,591 ($1,521)	<0.001
Neurologist office visits	$133 ($257)	$184 ($302)	$170 ($287)	$203 ($321)	<0.001
Other outpatient services	$5,073 ($11,127)	$7,593 ($15,158)	$6,486 ($14,000)	$9,179 ($16,551)	<0.001
Pharmacy	$3,049 ($5,992)	$5,098 ($8,991)	$4,320 ($8,481)	$6,213 ($9,567)	<0.001
Total healthcare	$12,044 ($22,732)	$19,093 ($31,936)	$15,877 ($27,639)	$23,702 ($36,754)	<0.001

ER: emergency room; PMM: preventive migraine medication; SD: standard deviation

[1]PMM Naïve vs. PMM Experienced

[2]Means were computed among patients with utilization in the category

[3]Includes CT, MRI, PET, and SPECT procedures for brain

Table 3b. Migraine-Related Healthcare Service Utilization and Costs

	PMM Naïve	PMM Experienced			
		All PMM Experienced	1 Baseline PMM	2+ Baseline PMMs	
	N=29,919	N=44,614	N=26,279	N=18,335	p-value[1]
Migraine-Related Service Utilization[2]					
Inpatient admission, %	0.4%	1.1%	0.8%	1.6%	<0.001
Inpatient admissions, mean (SD)	1.1 (0.4)	1.3 (0.8)	1.2 (0.6)	1.4 (0.9)	<0.001
ER visit, %	7.1%	9.9%	8.4%	12.1%	<0.001
ER visits, mean (SD)	1.8 (2.8)	2.3 (3.6)	1.9 (2.8)	2.6 (4.3)	<0.001
Brain imaging procedure[3], %	5.4%	5.4%	5.0%	6.0%	0.919
Brain imaging procedures, mean (SD)	1.0 (0.3)	1.1 (0.5)	1.1 (0.3)	1.1 (0.6)	<0.001
Physician office visit, %	63.3%	69.8%	69.2%	70.8%	<0.001
Physician office visits, mean (SD)	2.8 (2.6)	3.3 (4.5)	3.1 (4.1)	3.6 (4.9)	<0.001
Neurologist office visit, %	27.1%	36.2%	35.0%	38.0%	<0.001
Neurologist office visits, mean (SD)	2.4 (1.6)	2.5 (1.9)	2.5 (1.8)	2.6 (2.0)	<0.001
Other outpatient service, %	31.2%	37.9%	35.8%	40.9%	<0.001
Other outpatient services , mean (SD)	2.8 (5.3)	3.3 (6.7)	3.0 (6.0)	3.7 (7.4)	<0.001
Migraine-Related Healthcare Costs, mean (SD)					
Inpatient	$46 ($960)	$161 ($2,105)	$108 ($1,691)	$238 ($2,584)	<0.001
ER	$129 ($1,106)	$210 ($1,410)	$154 ($1,068)	$291 ($1,786)	<0.001
Total outpatient	$550	$748	$668	$863	<0.001

	($1,795)	($2,325)	($2,097)	($2,612)	
Brain imaging[3]	$54 ($310)	$54 ($325)	$50 ($297)	$60 ($361)	0.847
Physician office visits	$217 ($330)	$281 ($462)	$262 ($411)	$308 ($524)	<0.001
Neurologist office visits	$86 ($192)	$117 ($222)	$110 ($209)	$127 ($238)	<0.001
Other outpatient services	$279 ($1,633)	$414 ($2,095)	$357 ($1,894)	$495 ($2,351)	<0.001
Pharmacy	$1,201 ($2,182)	$2,150 ($3,979)	$1,837 ($4,006)	$2,600 ($3,897)	<0.001
PMMs	$257 ($573)	$816 ($1,292)	$617 ($1,081)	$1,101 ($1,500)	<0.001
Acute migraine medications	$943 ($2,060)	$1,334 ($3,602)	$1,220 ($3,719)	$1,499 ($3,423)	<0.001
Total healthcare	$1,925 ($3,424)	$3,270 ($5,774)	$2,766 ($5,290)	$3,992 ($6,335)	<0.001

ER: emergency room; PMM: preventive migraine medication; SD: standard deviation

[1]PMM Naïve vs. PMM Experienced

[2]Means were computed among patients with utilization in the category

[3]Includes CT, MRI, PET, and SPECT procedures for brain

Figures

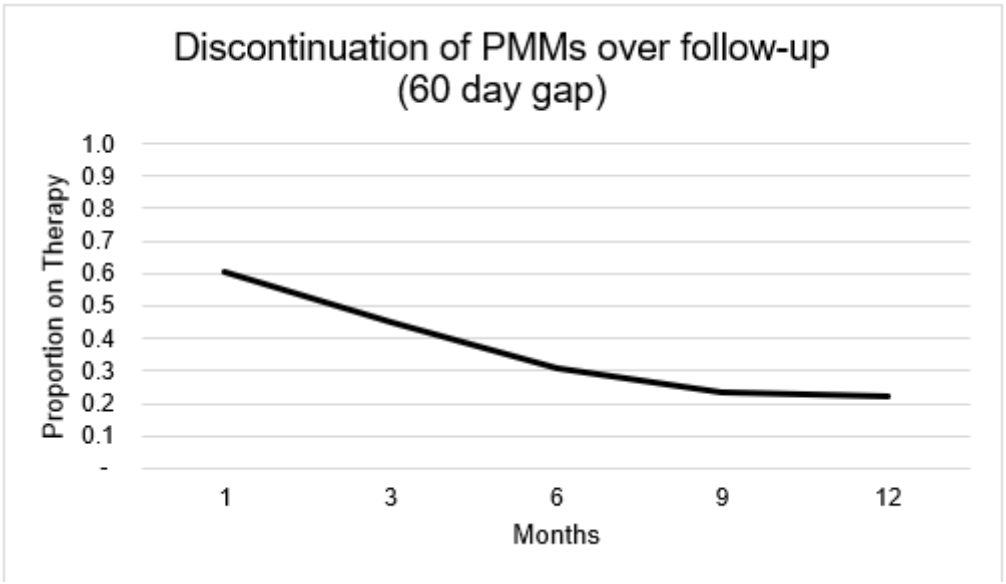

Figure 2

PMM Persistence

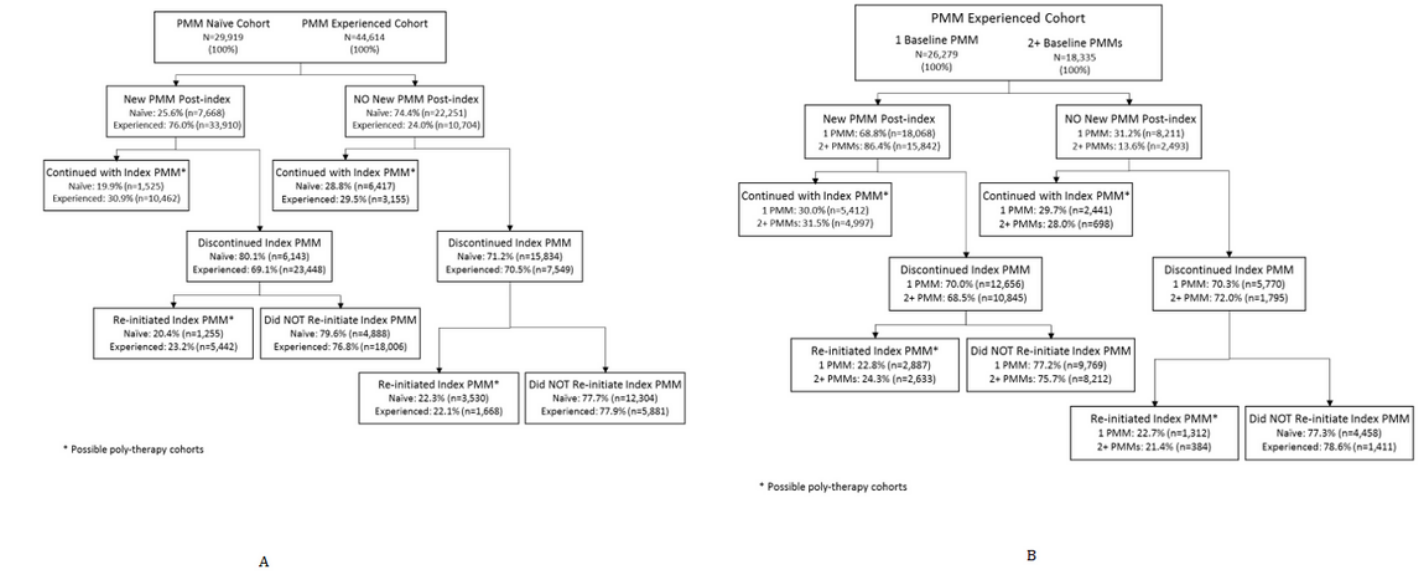

Figure 4

PMM Use During Follow Up, PMM Naïve vs. PMM Experienced Cohorts. PMM Use During Follow Up, PMM Experienced Cohort, 1 Baseline PMM vs. 2+ Baseline PMMs.