Persistence and switching patterns of migraine prophylactic medications in Canada: A retrospective claims analysis comparing adherence and evaluating the economic burden of illness

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ABSTRACT--Purpose: To describe patient characteristics, treatment patterns, and the burden of illness among adult migraine patients in Canada prescribed migraine prophylactics. Little is known about the relative persistence of treatments in the real-world setting and the impact of migraine prophylactic therapy on patients. As a result, migraine care in Canada continues to inadequately serve patients suffering from frequent headache days, reflecting a large unmet need. **Methods:** This retrospective study used Reformulary Group's longitudinal prescription claims database. Private payer data were analyzed to identify 2007 migraine prophylactic naïve patients, with a prior history of acute therapy, for tracking over 24 months to determine treatment patterns and costs. Patient flow is summarized in a Sankey diagram visualizing persistence and switching across different timepoints. **Results:** Patient persistence to migraine prophylactic medications was low at 24.9% (n=500); Switching from index medications to another prophylactic medication was common (27%), however 50% of patients discontinued without switching. It was observed that acute treatment and opioid use were much lower when patients established and maintained therapy on migraine prophylactics. Overall, angiotensin receptor blockers and CGRP antagonists had high persistence but were underutilized therapies while the inverse was true for antidepressants and anticonvulsants. **Conclusion:** In a real-word setting, recognizing that many patients may discontinue preventative treatment completely after their first therapy, there is a need to employ migraine-specific prophylactics and/or tolerable medications early. Treatment guidelines aligned to costs savings and/or requiring step therapy may be inadvertently failing patients. Further, the impact of migraine on the day-to-day lives of patients and high societal costs such as its impact on productivity should be weighed in considering migraine's burden of illness and the benefits of treatment.

INTRODUCTION

Migraines are headaches that create severe pulsing sensations on one side of the head and are often accompanied by nausea, vomiting and extreme sensitivity to light and sound. They can last anywhere from a few hours to days and the pain can be so severe that it interferes with daily activities (1). Based on the frequency of headache attacks, migraine can be classified as either episodic or chronic. Fewer than 15 headache days per month is characterized as episodic migraine (EM) and greater than 15 headache days per month with at least 8 days being migraine days is characterized as chronic migraine (CM) (2). High-frequency episodic migraine (HFEM) falls in between these ranges with individuals experiencing 8-14 migraine days (2). HFEM and CM are the focus of the treatment landscape where migraine prophylactics are often applicable (3, 4).

Abbreviations: Chronic migraine (CM); High-frequency episodic migraine (HFEM); Episodic migraine (EM); Burden of illness (BOI); Calcitonin gene-related peptide (CGRP); Monoclonal antibodies (mAbs); Morphine equivalent dosage (M.E.D); Healthcare professional (HCP); Confidence intervals (CIs); Standard deviations (SD); Real-world evidence (RWE); Quality of Life (QoL)

The objective of the study is to assess patient characteristics, treatment patterns, and the burden of illness among adult migraine patients in Canada prescribed migraine prophylactics. It is important to recognize that, migraine prophylactic treatments are one part of comprehensive migraine management (5).

This debilitating neurological disorder has a prevalence of around 8.3% in the Canadian population (2). In Canada, about 90% of migraine sufferers report moderate to severe pain, with 75% reporting impaired function and 33% requiring bed rest during an attack (5). The total burden of illness (BOI) for migraine includes these elements of patient aliment, health system costs, and productivity impacts (6). BOI reflects the burden that a particular disease is levying on society – healthcare system impacts, morbidity, and mortality (6). Here direct medical costs are considered as part of the BOI assessment and reported with contextualization to the total burden of illness for migraine.

Our results and in line with other findings that demonstrate the significant direct economic impact of migraine-related disability. The total estimated direct medication cost for migraine have been reported to be on the order of 4.5-8.5k annually per patient in Canada (2). The total estimated indirect productivity costs for migraine have been reported to be on the order of 8.1-13.9k annually per patient in Canada (2). Overall, the total estimated annual cost of CM and EM migraine have been estimated to be on the order of 15.6-25.6k annually per patient in Canada (2). As such, a large portion of this cost is attributed to missed work and unemployment (7), which aren't captured here in our investigation.

To the best our knowledge, no studies to date have used private payer information in Canada for the comparative assessment of migraine prophylactics and migraine disease burden. Around 70% of Canadians receive prescription drug coverage through an employer-sponsored private plan (8). This study follows the patient journey of migraine suffers to determine the burden of illness in Canada via the patterns of migraine prophylactic use and cost. Few studies have evaluated the persistence among prophylactic treatment in general (9-13). Fewer yet, explore differences in patient outcomes or include emerging therapy classes such as CGRPs (4, 14, 15).

In this study, we uncover opportunities for a shift in the treatment paradigm by reviewing adult migraine patients' patterns of migraine prophylactics and acute therapy use. Using Reformulary's claims database, it was possible to assess relative rate of uses, persistence rate, switching rate, and concomitant acute therapy use rates by drug class. Optimizing treatment patterns could decrease patient suffering and health care service utilization, ultimately enabling a higher quality of life (QoL) and unencumbered productivity.

METHODS

Study design and data sources

This study is a real-world evidence (RWE) based, retrospective claims database investigation of migraine prophylactic use, treatment effectiveness, and migraine burden of illness in Canada. The patient population for the longitudinal claims-based study was comprised of individuals that have submitted claims to privately sponsored drug plans in Canada (Reformulary Group, Canada). This was a subset of the Reformulary database containing prescription drugs covering roughly 5 million Canadians. The claims data analyzed are representative of the Canadian population covering 25% of all private drug plan claims in Canada. Overall, the Reformulary database contains over 1.3 billion claims submitted on behalf of almost 13.5 million unique claimants since July 1, 2013. While anonymous, the aggregated data is longitudinal capturing patient treatment use, switching, and discontinuation over time. Approximately 1.75 million claimants have a full longitudinal history. Reversals and rejected claims have been excluded from consideration. In cases where individuals have had more coverage in more than 1 plan within the private sector, claims data and history are consolidated.

Anonymous and aggregated claims data have been utilized and thus no ethics approval or patient informed consent was required.

To assess persistence and treatment dynamics by drug class, the study evaluated

prophylactic-naïve patients to eliminate the impact and variability in previous treatment use.

Study time periods

A 24-month index period from October 2017-September 2019 was used in our analysis as the data window analyzed for a patient's first use of a migraine prophylactic. The first date of migraine prophylactic use for a patient is defined as their index date. A 12-month look-back period prior to their index period was used to confirm no previous history of migraine prophylactic use. Triptan use (>= 1 Triptan claim or a 90-day supply) and having used a migraine prophylactic drug were employed as gated criteria to ensure that study participants were migraine patients.

A post-index period spans from a patient's index date to 24 months later, representing their treatment journey with migraine prophylactics. This time period was used to identify treatment patterns, determine the share of a class of migraine prophylactic and observe persistency and switching rates. Finally, a 3-month post-analysis period was applied to ensure that the patients selected in the analysis period were still active and that there were no endpoint switches. Figure 1 shows a schematic representation of the study.

Inclusion criteria. Patients were included in the analysis if they met the following criteria: Aged ≥ 18 years old; at least 1 claim or 90-day supply of a triptan in the pre-index period; claims covering at least 3 months for a migraine prophylactic in the post-index period

Exclusion Criteria. Patients were excluded from the analysis if they did not meet the inclusion criteria or were, more than 1 migraine prophylactic claim on the index date; did not have continuous insurance plan during the 3 months post-analysis period; a beta-blocker claim with other congestive heart failure (CHF) medications; concomitant claims for other tricyclic anti-depressants (not including amitriptyline and nortriptyline); concomitant claims for other anticonvulsant medications (not including gabapentin, topiramate, and divalproex).

Data analysis

The following definitions and rules applied in the analysis of data and patient segmentation:

Persistence. Persistence to migraine prophylactics encompasses patients who have maintained prophylactic therapy throughout the study. No more than 90 days have lapsed between successive Rx fills throughout the study period, irrespective to switches to different migraine prophylactics. Persistence to the index migraine prophylactic encompasses patients who have maintained prophylactic therapy with the index treatment throughout the study. No more than 90 days lapsed between successive Rx fills throughout the study period, continues therapy on the index migraine prophylactic, and does not switch to other migraine prophylactics.

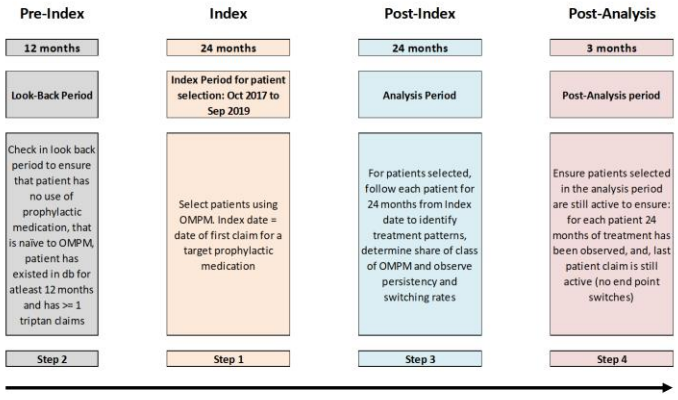


Figure 1 – Schematic representation of study design and patients' selection

Switching. When a patient discontinues a migraine prophylactic and, within 30 days prior to or 90 days after the discontinuation date (grace period) of that migraine prophylactic, started another migraine prophylactic (excluding the previously discontinued migraine prophylactic).

Grace period. A 90-day time period is allowed between successive Rx fills to allow for baseline non-compliance, i.e., if a patient discontinues therapy for any reason and resumes therapy on the same drug/class within 90-day period, the patient will be considered to have persisted on the drug/class.

Opioid use. The average daily morphine equivalent dosage (M.E.D). This represents opioid dosage, standardized to equivalents of morphine based on their respective conversion factors (16).

Line of therapy. The order in which different therapies were given to patients due to outcomes such as not being adequately treated by their current treatment, experiencing intolerable side effects, or their disease progressing requiring a different therapeutic approach. LoT in this study is defined in terms of drug class Start/Add-on/Switch and any change in class of drugs or combination of classes of drugs ("Therapy") leads to progression in LoT provided it is a Start/Add-on/Switch on or to a 'new class'.

A Start/Add-on/Switch on or to a 'new class' requires being naive to the class, i.e the patient has never used that class of prophylactics previously. Where a patient is taking 2 or more classes of drugs ("Combination therapy") in a given line, discontinuation of one class does not progress LoT. Similarly, if a patient on Combination therapy lapses and restarts taking a class they had previously taken, it does not progress their LoT.

Final line of therapyresults show the number of patients taking a specific class of drug, at their most current LoT, at the end of the study.

Intersection of Persistence and LoT. Given a patient continues taking the index class (irrespective of whether they add other drug class or not, they are deemed to be persistent to their index class. Adding or switching to another therapy progresses a patient to a subsequent LoT.

Average Opioid Days. The sum total of days' supply of opioid drugs divided by the number of patients in the group.

Average Therapy Days in LOT. The sum total of days between the date of start of therapy, in a given LoT, and the last date before the start of next therapy divided by the number of patients in the group.

30-Day Costs. Total eligible cost for a medication (medication cost and dispensing fees), normalized to 30-days based the costs for migraine prophylactic persistent patients

Cost Analysis

Costs were evaluated as follows and reported in Canadian ($) dollars: costs include eligible drug and dispensing costs from the perspective of the private payer data available to Reformulary Group and inferred healthcare system costs for drug switches. Costs are presented on an annualized and per patient basis. Treating each drug switch as a healthcare interaction, likely mediated by a Neurologist/headache specialist, a cost of $180 per switch has been added to drug costs. Additional healthcare professional (HCP) interactions are expected such as follow-ups and assessments, however are not captured in the Reformulary dataset. It is worth noting, Canadian provincial governments are responsible for providing healthcare services but do not comprehensively cover prescription drugs, they are instead covered through a patchwork of public and private coverage (17).

Productivity loss is a significant manifestation of debilitating migraine disability (7). However, these are best assessed through

direct patient market research that has not been collected as part of this study. Instead, findings from a recent Canadian study are referenced (2). Additional costs beyond the scope our investigation include medical devices, surgical interventions.

Statistical Analysis Plan

Descriptive analyses were performed using SAS (SAS Institute, Cary, North Carolina). Subgroups for persistence to migraine prophylactics and persistence to the index migraine prophylactic to generate analysis for different patient journeys. Descriptive statistics were used to evaluate patient characteristics, abortive and propylitic therapy usage, persistence, and switches. Means and standard deviations (SD) were reported for most measures to reflect spread.

In evaluating the discontinuation and switching patterns of prophylactic therapies, Sankey visualization treatment progression was generated using R, version 4.2.0 (The R Foundation for Statistical Computing, Vienna).

Kaplan-Meier survival analysis was used to model the retention of patients on each drug class over 365 days. The Kaplan-Meier analysis was also performed using R. Statistical testing and confidence intervals for patient retention figures were 2-tailed and generated at a level of p=0.05 to qualitatively compare trends across drug classes. Additional statistics are reported in the supplementary data (Figure S1 & Table T1).

RESULTS

Baseline characteristics

Demographics for the 2007 study patients included in the analyses are detailed in Table 1. The 83% of patients were female and overall the mean age was 48.8 (12) years. Patients from all regions of the Canada were represented, with the largest proportion being from Ontario (59.5%). While the data was obtained from a national sample of the private payers, it does have higher proportional coverage in Ontario despite the prevalence of migraine being consistent across Canada.

Figure 2 depicts the patient selection and flow for the study. A total of 2007 patients met the inclusion/ exclusion criteria and were included in the analyses. Most exclusions were made to ensure that patients were migraine prophylactic naïve and had taken a triptan for migraine management as a confirmation of headache management need.

Table 1. Demographic and baseline characteristics of study patient population at index date

Characteristic		
Total Sample	2007	
Mean Age (SD)	48.79 years (11.96)	
Age distribution, years	n	Percent
18-24	28	1.40%
25-34	207	10.31%
35-44	488	24.31%
45-54	660	32.88%
55-64	423	21.08%
65+	201	10.01%
Female, (%)	1663	82.86%
Geographic region	n	Percent
Alberta	273	13.60%
British Columbia	265	13.20%
Manitoba	55	2.74%
New Brunswick	36	1.79%
Newfoundland	9	0.45%
Nova Scotia	2	1.10%
Ontario	1194	59.49%
Prince Edward Island	5	0.25%
Quebec	119	5.93%
Saskatchewan	28	1.40%
Territories	1	0.05%

Treatment Patterns

Table 2 depicts the impact of migraine prophylaxis on acute/opioid drug use. Overall,

opioid and acute medication use decreased significantly with adherence to migraine prophylactics. The utilization of acute medication dropped from 100% pre-index to 24% among those persistent to prophylactics as a class of therapy and 71.1% for those who were not persistent prophylactics as a class of therapy. The utilization of acute medication dropped from 29.9% pre-index to 10% among those persistent to prophylactics as a class of therapy but remained high at 31.5% for those who were not persistent to prophylactics as a class of therapy. The specific impact of each treatment class on abortive treatment will be presented subsequently.

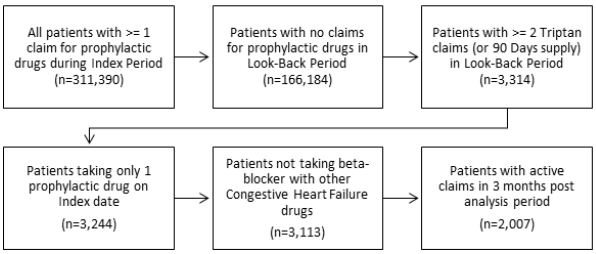


Figure 2 – Patient Selection and Flow

Table 2. Impact of migraine prophylaxis on acute/opioid drug use in the total 2007 cases

Pre-index Acute Use	Pre-index Opioid Use	Post-index Acute Use	Post-index Opioid Use
		Persistent to Prophylactics	
		24%	10%
100%	29.9%	Not Persistent to Prophylactics	
		71%	31%

Table 3 describes the persistence among patients to their index migraine prophylactic. The total number of patients initiating each therapy is given followed by summaries of discontinuation and the number of patients that were persistent at various timepoints throughout the study. Overall, a high proportion of patients that initiated migraine prophylactics discontinued without switching to another therapy (50%). This indicates the importance of matching patients with appropriate therapy early on in their journey to minimize attrition.

Error! Reference source not found. and Figure . The analysis follows 2007 patients initially administered a migraine prophylactic. Within 4 months, 50% had discontinued their initial treatment. After 12 months of observation, 68% had discontinued their initial treatment. However, it is important to note that CGRPs and angiotensin receptor blockers were adhered to at much higher rates than other migraine prophylactics. CGRPs had a persistence of 73.7% and 52.6% at 4 months and 12 months, respectively. Angiotensin receptor blockers had a persistence of 79.9% and 64.7% at 4 months and 12 months, respectively.

Figure shows the class share of migraine prophylactics at index and the conclusion of the study for patients that remained persistent to preventative therapy. It can be seen that CGRPs and angiotensin receptor blockers use was much more prevalent by the end of the study as a result of switching. Conversely, antidepressant and anticonvulsant use decreased significantly by proportion but remain key players in migraine prophylactic treatment.

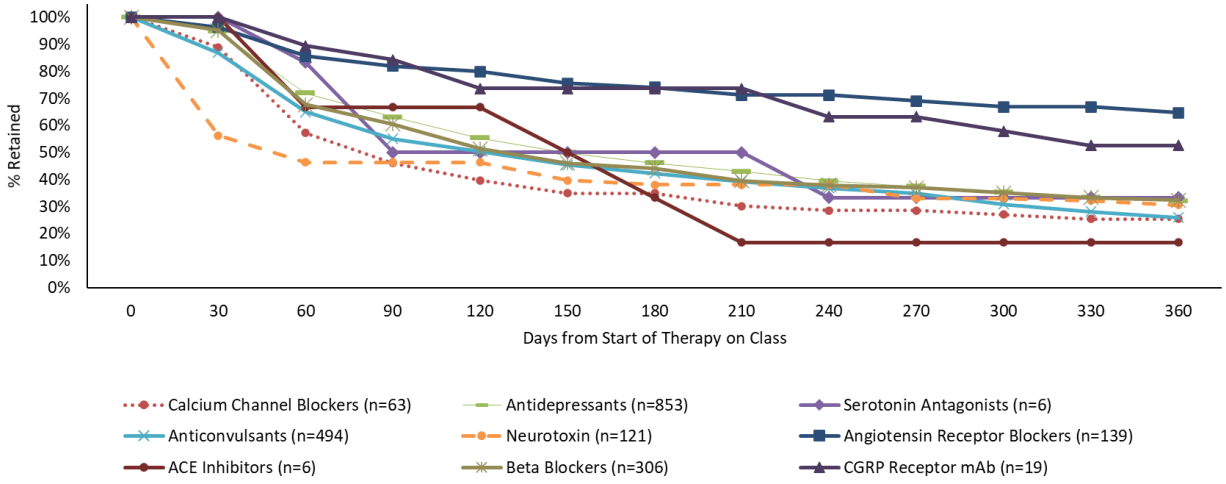
Figure 6 provides an overview of treatment journeys as a Sankey diagram with nodes as treatments and the curves between two nodes showing the flow between treatment drug classes or towards discontinuation.

Healthcare Utilization and Costs

The costs for migraine medications over the 24 months of the study are summarized in Table 2. Migraine prophylactics were the most significant aspect of patient medication costs. Looking at the treatment patterns among patients in our study, the annualized cost of migraine treatment sought within their 24 months analysis period was $1295.60 per patient. Medications costs include eligible drug and dispensing costs from

Table 3. Overall treatment discontinuation rate and persistence status to initial index migraine prophylactic

	Antidepressants	Anticonvulsants	Beta Blockers	Angiotensin Receptor Blockers	Neurotoxin	Calcium Channel Blockers	CGRP Receptor mAb	Serotonin Antagonists	ACE Inhibitors
Number (%) Total = 2007	853 (42.50%)	494 (24.61%)	306 (15.25%)	139 (6.93%)	121 (6.03%)	63 (3.14%)	19 (0.95%)	6 (0.30%)	6 (0.30%)
Number discontinued without switching (%) Total = 1004	440 (43.82%)	256 (25.50%)	147 (14.6%)	46 (4.58%)	72 (7.17%)	33 (3.29%)	3 (0.30)	4 (0.40%)	3 (0.30)
Number persistent after 180 days (%) Total = 927	393 (42.39%)	209 (22.55%)	135 (14.56%)	103 (11.11%)	46 (4.96%)	22 (2.37%)	14 (1.51%)	3 (0.32%)	2 (0.22)
Number persistent after 360 days (%) Total = 656	273 (41.62%)	128 (19.51%)	99 (15.09%)	90 (13.72%)	37 (5.64%)	16 (2.44%)	10 (1.52%)	2 (0.30%)	1 (0.15%)
Number persistent at end of study (%) Total = 408	169 (41.42%)	70 (17.16%)	65 (15.93%)	69 (16.91%)	12 (2.94%)	11 (2.70%)	10 (2.45%)	1 (0.25%)	1 (0.25%)



–**Figure 3.** Retention curves by Drug Class

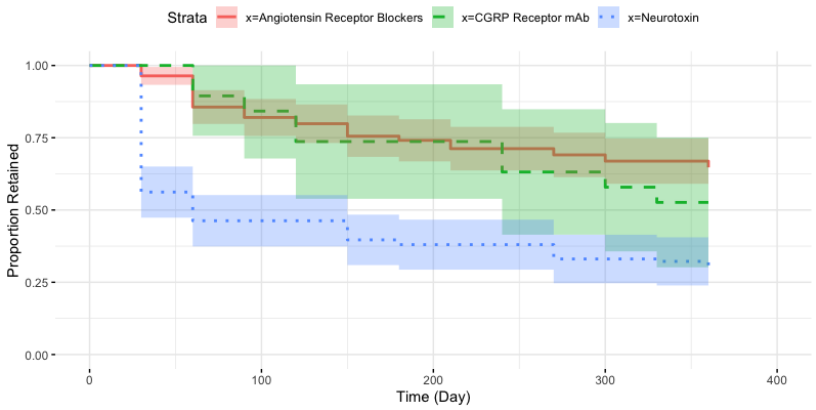


Figure 4. Statistical significance of variance in patient retention (CI=0.95). Angiotensin Receptor Blockers and CGRPs exhibited statistically significantly higher patient retention than most other drug classes but were equivalent at 360 days.

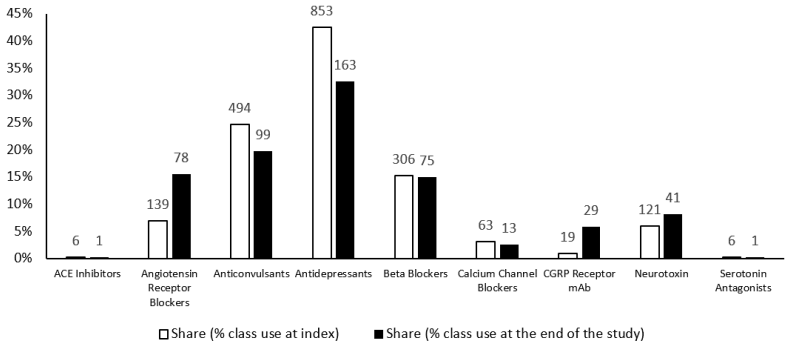


Figure 5. Class share among patients persistent to migraine prophylactics (Data labels = n-size).

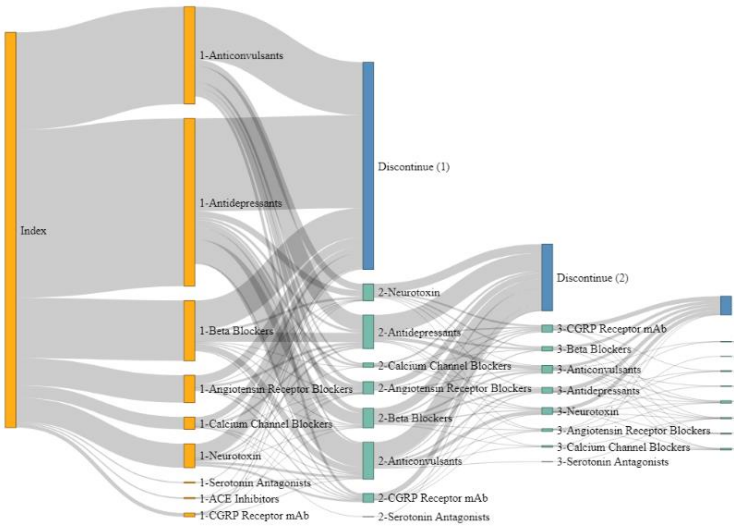


Figure 6. Sankey Chart: Treatment journey of migraine patients, notably discontinuation at each stage of therapy is high

the perspective of the private payer data available to Reformulary Group. Beyond that, cycling through treatments will have an impact on the healthcare system as well as a burden on patients. Treating each switch as a healthcare interaction, likely mediated by an neurologist/headache specialist, we have added a cost of $180 per switch to capture the disease burden of migraine (2). This led to an HCP cost of $197.89 per patient. This methodology is similar to the approach of Kikui et al (18). In their study, HCP costs were estimated by multiplying unit costs for physician visits, emergency room visits, and hospitalizations obtained by the number of visits and medication costs.

The frequency and costs associated with HCP visits over the 24 months of the study are summarized in Table 5. Half of the study population only tried their index medication before discontinuing preventative therapy (50%). Switching to other medications was common. Costs are determined by assuming interactions are mediated by a neurologist/headache specialist, the most common pathways of receiving treatment.

The 30-day cost of migraine prophylactics by drug class are summarized in table 6. Neurotoxin and CGRPs were the most expensive classes of therapy. The costs reflect the total eligible cost for a medication, normalized to 30-days based on the prescription length.

Figure 7 captures the initial prescribing patterns of HCPs for migraine prophylaxis. The majority of patients are initiated with low-cost treatment options.

Figure 8 displays the retention of patients to migraine prophylactic medications after 1 year and the associated cost for a 30-day supply. With the exception of angiotensin receptor blockers, most low-cost medications have low to moderate patient retention. While, CGRPs and neurotoxins have moderate to high patient retention. Drug retention in observational studies, such as this, can be considered as a composite measure of effectiveness, safety and tolerability (19).

Table 2. Total eligible drug claim costs (medication cost and dispensing fees): A) All patients B) Patients persistent to migraine prophylactics C) Patients non-persistent to migraine prophylactics D) Patients persistent to index migraine prophylactic

A)	**All Patients, n = 2007**	**Cost/patient/24 months**
Prophylactic (n = 2007)	$1,915,449	$954.38
Acute (n = 1908)	$2,883,053	$1,511.03
Opioids (n = 834)	$401,821	$481.80
Overall	$5,200,323	$2,591.09
B)	**Patients Persistent to Prophylactics, n = 500**	**Cost/patient/24 months**
Prophylactic (n = 500)	$878,232	$1,756.46
Acute (n = 482)	$797,999	$1,655.60
Opioids (n = 201)	$83,659	$416.21
Overall	$1,759,890	$3,519.78

Table 4 continues

C)	Patients Not Persistent to Prophylactics, n = 1507	Cost/patient/24 months
Prophylactic (n = 1507)	$1,037,216	$688.27
Acute (n = 1426)	$2,085,054	$1,462.17
Opioids (n = 633)	$318,163	$502.63
Overall	$3,440,433	$2,282.97
D)	**Patients Persistent to Index Prophylactic, n = 408**	**Cost/patient/24 months**
Prophylactic (n = 408)	$538,218	$1,319.16
Acute (n = 390)	$594,311	$1,523.88
Opioids (n = 152)	$71,279	$475.20
Overall	$1,203,809	$2,950.51

Table 3. Cost of healthcare provider visits for migraine patients over 24 months of the study

LOT	n	Cost/Rx	Total HCP Cost/ 24 month
Index Therapy	2,007	$180.00	$361,260.00
Switches	2,406	$180.00	$433,080.00
Total			$794,340.00
Annualized average HCP cost/patient, n=2007			$197.89

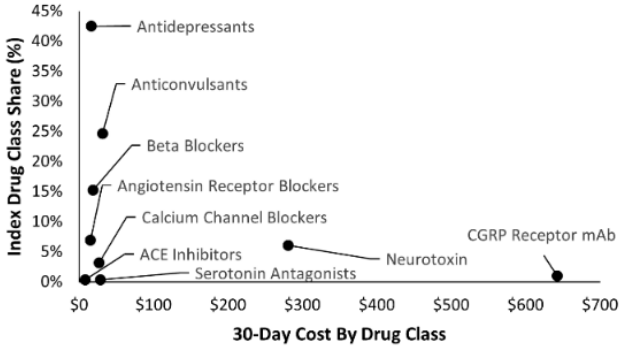


Figure 7. Index drug class percentage for all patients (N=2007) and 30-Day treatment cost by drug class.

Table 4. Monthly costs by drug class, calculated from patients persistent throughout the study

Prophylactic 30-Day Costs By Drug Class	
ACE Inhibitors	$7.89
Angiotensin Receptor Blockers	$14.87
Anticonvulsants	$31.75
Antidepressants	$16.53
Beta Blockers	$18.91
CGRP Receptor mAb	$642.21
Calcium Channel Blockers	$26.58
Neurotoxin	$280.83
Serotonin Antagonists	$28.85

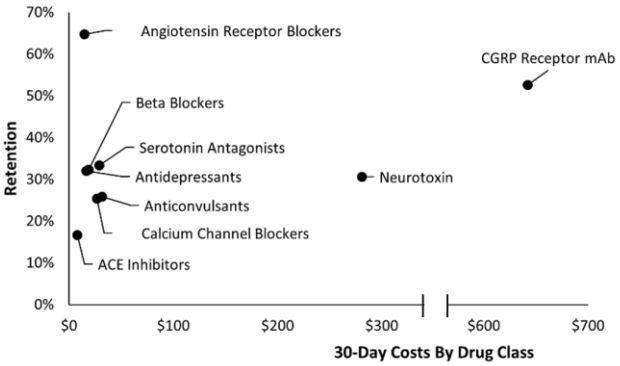


Figure 8. Retention to migraine prophylactic medications after 1 year and the associated cost for a 30-day supply

Figure 9 9 shows the degree of opioid dependence by drug class and the associated cost for a 30-day supply. Angiotensin receptor blockers, CGRPs, neurotoxin, and calcium channel blockers have the lowest days of opioid use in relation to the number of days that were maintained on these therapies. This indicates that opioids were needed less often with these migraine prophylactics.

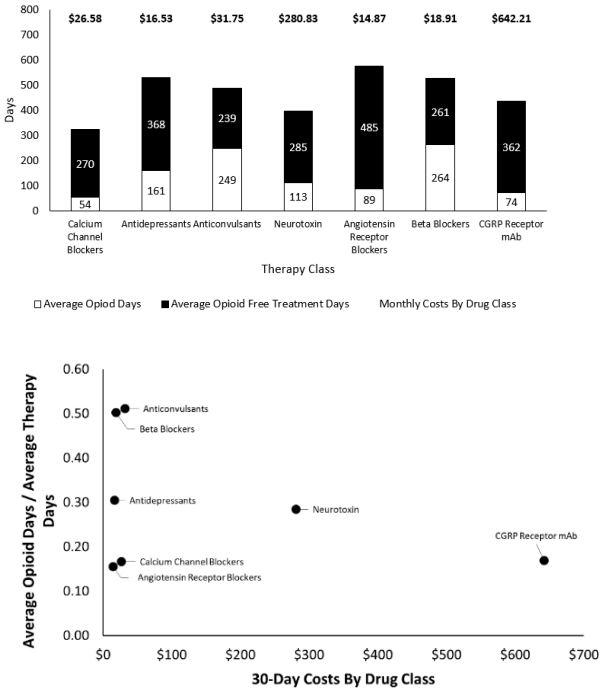


Figure 9. Top: Average days of therapy and corresponding average opioid days for patients that were persistent to migraine prophylaxis. Bottom: Degree of opioid dependence and the associated cost for a 30-day supply by drug class. Among patients persistent to migraine prophylactics (N = 500). No patients were persistent to Serotonin Antagonists or ACE Inhibitors and were therefore excluded from the figure.

DISCUSSION

To date, few studies have attempted to characterize the relative persistence of different migraine prophylactic treatments in Canada. In addition, to our knowledge, no studies to date have used private payer information in Canada for the comparative migraine prophylactics and an assessment of migraine burden. This study explored the treatment landscape in Canada, migraine burden, and implications of the neurological disorder on the health care system.

In this study, we looked at the treatment patterns of adult migraine patients with prophylactics and medication costs. Using Reformulary's claims database, the primary objectives of this study were to understand the following by drug class: rate of use for migraine prophylactic medications, persistence rate, the switching rate, and concomitant acute medication use. We also endeavored to assess the cost burden of treatment across therapy classes.

Baseline Characteristics

82.9% of patients in the sample were women and the mean age overall was 48.79 years old. Although migraine can afflict both genders and individuals of all ages, it is most common in women and younger adults (1), (20). Our study population is reflective of the prevalence of migraine being highest in people's 40s and chronic migraine being 4.7 times more common in women than men (21). Therefore, our results can inform the unmet need in typical migraine populations. However, gendered differences in the response to therapy and adverse events have not been considered fully in medical approaches to therapy and drug development which primarily have male study participants (22). RWE studies can mitigate this bias in being more aligned to patient populations or through subgroup analysis.

It is well documented that rates of prophylactic medication therapy in migraine patients are low (11) however as many as 1 in 4 migraineurs are candidates for prophylactic therapy (5). As such, many Canadians suffering from migraine may not be receiving adequate and holistic care.

Index-class share was broadly reflective of the strong preference for anti-depressant and anti-convulsant prophylactic use found in literature (13), (23) , (24). It is important to note that medication use does vary by jurisdiction and

can be influenced by local HCP prescribing preferences as well as reimbursement guidelines. Within Canada, guidelines have been developed to help physicians nationwide to assess and manage headaches in adults (5), (25).

Treatment Patterns

This study aimed to compare migraine prophylactic therapy in preventative treatment naïve patients. Persistence reporting is based on adherence to index migraine prophylactic, similarly to most studies (12), (11), (13), (26). Efficacy has been demonstrated in different ways such as patients experiencing a decrease in migraine episodes during treatment or an increase when prophylaxis was stopped (25). Acute anti-migraine medication discontinuation has also been used to show the benefit of migraine prophylactic therapy (15). Post-Index Health Care Resource Utilization have also been used to assess impact (13).

Our study showed that migraine prophylaxis has a significant impact on acute/opioid drug use. Opioid use in migraine is an indication of severe headache treated with an abortive intervention. However, migraine treatment with opioids is not a perfect panacea. Opioid use, in general, comes with its own physiological impacts and challenges, namely cognitive impairment interfering with daily functioning, driving ability, information processing, information recall, productivity, and conceptual tracking (27), (28). There are also risks of opioid dependence. Therefore, is it noteworthy that acute opioid medication use decreases when patients are persistent to migraine prophylactics. In this study, we can see that the impact of migraine prophylactics on opioid usage varies by class. Angiotensin receptor blockers, CGRP receptor mAbs, calcium channel blockers, and neurotoxins had the lowest proportion of opioid days required during treatment.

Persistence to migraine therapy is critically important for patients to experience the benefits of preventative migraine care. The rapid decline in adherence among most classes suggests inadequate relief and/or intolerable side effects. CGRPs are known to be very successful migraine prophylactics and have exhibited some of the lowest failure rates among difficult patients with a record of at least two migraine prophylactics in a recent Canadian study that reviewed patient medical charts (2). CGRPs are migraine-specific and known to have few side effects (29). ARBs have not been studied as extensively as other classes, but have minimal side effects (30). Their efficacy, minimal side effect profile, and low cost make them an attractive option (30). While neurotoxins such as Botox have been reported to be remarkably "clean" treatments for the prevention and suppression of headache, minor side effects can occur such as neck and pain and stiffness (31). Serotonin Antagonists are also reported to have mild or moderate side effects in most cases (32). Correspondingly, these medications with more tolerable side effect profiles had the highest rates of patient persistence. Recognizing that many patients will discontinue their index therapy and not give preventative therapy another shot, there is a need to employ migraine-specific prophylactics and/or medications with favorable side effect profiles. Specific barriers to the uptake of new medicines and the adoption of new treatment paradigms could be their recent demonstrations of clinical effectiveness and an incomplete understanding of side effects by HCPs. A pervasive lack of head-to-head clinical trial data in industry makes it difficult for HCPs to make informed clinical decisions without comparative effectiveness and risk data (33).

Treatment guidelines over emphasizing cost and/or requiring step therapy may also inadvertently be failing patients. Specifically, branded innovator products such as CGRPs might only be recommended coverage for patients with chronic migraine who had ≥2 therapies failures (34). Formally described as step therapy, this form of prior authorization requires HCPs to prescribe a less expensive, step-one drug before escalating to a costlier drug (35). These factors may be contributing to antidepressants and anticonvulsant, which are well-known treatment options that fit the low-cost requirement for initial use, having prevalent use in Canada where step therapy guidelines are

extensively used to contain drug costs (36). Treatment guidelines aligned to costs savings cannot replace clinical judgment and physicians must leverage their expertise to advocate for treatment(s) that they deemed medically necessary over formulary and cost-saving based prescribing (37). RWE studies such as ours can contribute to the body of knowledge used to inform treatment and reimbursement decisions.

Healthcare Utilization and Costs

Although often unseen and underappreciated, migraine disability has a profound impact on patient well-being and the healthcare system. Amoozegar et.al. offer a Canadian perspective on migraine related HCRU through a retrospective medical chart review (2). However, an eligibility criteria of failure on at least two prophylactic migraine treatments does not allow for a comparative assessment of migraine prophylactics.

In our study, annualized direct medical costs related to migraine treatment were $1493.44 per patient on average for medication and HCP costs. Annualized drug costs ranged from $94.64 with ACE Inhibitors to $7,706.49 for CGRPs among patients persistent to their index migraine prophylactic. The majority of patients were treated with low-cost medicines, reflecting current treatment guidelines and the pervasive use of step therapy. It is well documented that productivity and additional costs outside of medication for the majority of the migraine BOI, eclipsing medication costs (2). The costs that make up the total disease burden for migraine include: medications, HCP consultations, laboratory tests, devices, caregiver of family assistance, transportation for medical appointments, and lost productivity. As such, overall patient impact should be prioritized in the selection of treatments. While more expensive therapies lead to more direct drug costs, treatment effectiveness increases may lead to reduced healthcare resource utilization costs. For example, CGRPs like Erenumab have been shown or can be inferred to reduce acute medication use and significantly decrease HCRU here and in literature (38). Neurotoxins and angiotensin receptor blockers were two additional classes of mediations exhibiting strong patient retention and decreases in acute medication use, reflecting their effectiveness.

Limitations

There were a few incidents of Botox claims with 7 days or 30 days supply instead of the 12 weeks (84 days) per the recommended dosing regimen its product monograph. However, the 90-day grace period used in the analysis minimized the impact of this on calculations of retention and persistency. Therefore, Botox retention and persistency figures did not have as much buffer for baseline non-compliance as in other drug classes.

Validation of migraine disorder by medical diagnosis is a current limitation of the study. However, the use of migraine prophylactics among the patient cohort is a reflection of treatment aligned to CM and HFEM. We acknowledge that concomitant drug use for comorbidities, often present with migraine, cannot be fully isolated but were controlled with our inclusion/exclusion criteria.

Another limitation of the study is that dose escalation/de-escalation could not be able to be captured and therefore consider drug switches. However, the 5 patients having within class switches (3 = beta blockers, 2 = CGRPs) tried other therapies. Additional data limitations are that the subset of drugs captured for each therapeutic classes (Supplementary Information – Table T2) and those included in drug coverage plans are not fully comprehensive of all possible therapies. Migraineurs treated with non-reimbursable medications or medications obtained through a PSP program may not have been identified.

Additional follow-up on the reasons for treatment discontinuation is necessary to better assess adherence to the different classes of treatment and a limitation in this study. Factors such as safety, efficacy, cost, or tolerability cannot currently be isolated. However, the overall acceptance of the treatment can be assessed through persistence as an aggregate parameter.

It is well known that there are gendered and demographic differences in the response to therapy and adverse events that a patient may experience. Seldom are these considered in the clinical trials that lead to approval and availability of new therapies. RWE, however, has the potential to investigate these differences to optimize therapy at for different patient subgroups.

Finally, the impact of migraine on productivity, QoL, and other non-drug medical and non-medical costs were not captured. Nevertheless, this study provides a current assessment of the impact of treatment selection on patient persistence, comparative outcomes in the real word setting, and the unmet need for effective migraine therapy. These limitations are common in real-world data studies and should be considered when interpreting results.

CONCLUSIONS

This study assesses migraine care and the burden of illness in Canada via the patterns of medication use and cost. The retrospective claims analysis leveraged real-world evidence to further our understanding of outcomes by treatment class for migraine prophylactic naïve patients and the burden of illness through cost. This study closes an evidence gap to support best care practices for migraine in Canada. Among migraine prophylactic naïve adult migraine patients, treatment persistence was poor, with most patients discontinuing their index therapy within 6 months of treatment initiation. CGRPs and angiotensin receptor blockers appeared to be an effective but underutilized therapy. Concomitant opioid use decreased drastically with these therapies and neurotoxins. Further, high persistence to these drug classes may also indicate favorable efficacy tolerability, and/or safety profiles. This study highlights the impact of treatment selection on patient persistence and outcomes in a real-world setting, migraine-specific therapies and existing therapies with favorable tolerability profiles ought to be the standard of care. Treatment guidelines over emphasizing cost and/or requiring step therapy are inadvertently failing patients. It is important for payers and providers to consider the overall patient experience, particularly productivity and externalities that increase the burden of migraine well beyond drug costs. Clinical research into the reasons for discontinuation and migraine impact on QoL could further our understanding of migraine in support of optimal disease management. Additional research is required to elucidate the full burden of migraine and medication non-persistence considering additional costs and patient reported outcomes such as productivity and QoL.

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Conflict of interest. The authors declare that they have no competing interests

Authors' contributions. NK and AO analyzed and interpreted the patient data regarding migraine treatment. SZ, DZ, NB, and RB contributed to the design of the study and writing the manuscript. All authors read and approved the final manuscript**.**

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SUPPLEMENTS

OJO, A., ZHANG, S., BLEIBDREY , N., ZIMSKIND , D., KESHVANI , N., & CHALMERS , R. Persistence and switching patterns of migraine prophylactic medications in Canada: a retrospective claims analysis comparing adherence and evaluating the economic burden of illness . J PHARM PHAR SCI. 2022, *25*, 402–417. HTTPS://DOI.ORG/10.18433/JPPS33158

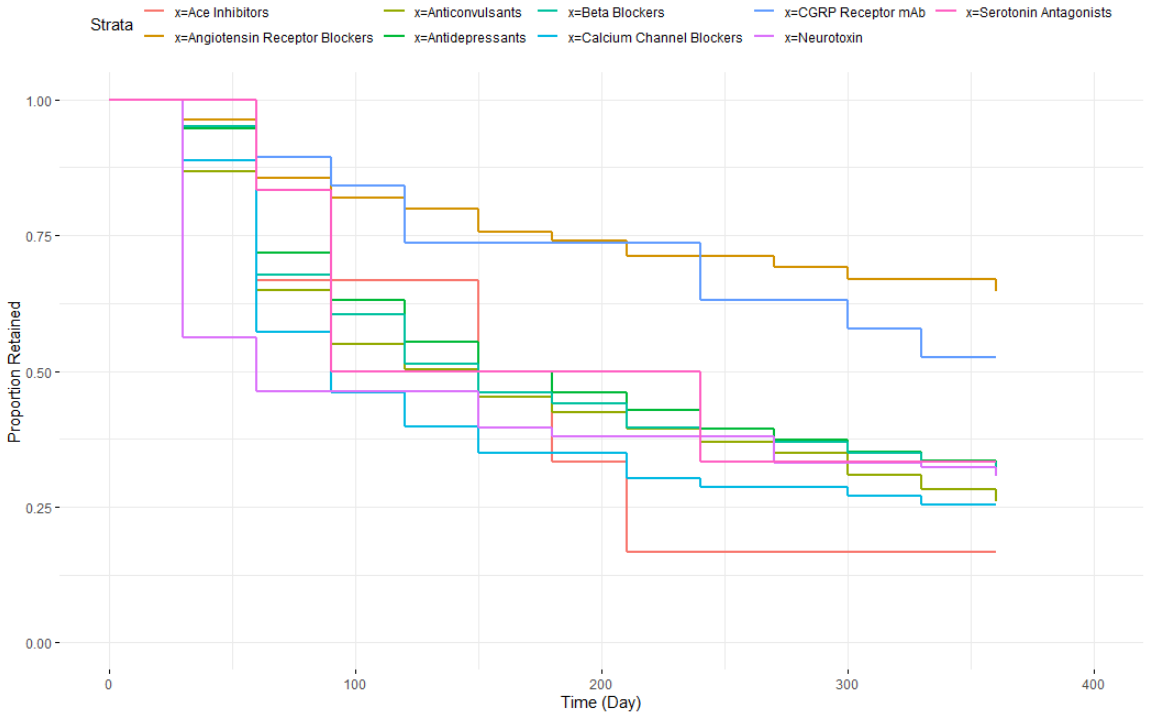

Figure S1 – Kaplan-Meier survival analysis of patient retention on each drug class over 365 days

Table T1 – 1 year patient retention and confidence intervals from Kaplan-Meier survival analysis

Drug Class	1 year retention	90% CI
Angiotensin Receptor Blockers	0.647	(0.581 – 0.714)
CGRP Receptor mAb	0.526	(0.338 – 0.715)
Serotonin Antagonists	0.333	(0.0168 – 0.650)
Beta Blockers	0.324	(0.280 – 0.368)
Antidepressants	0.320	(0.0294 -0.346)
Neurotoxin	0.306	(0.237 – 0.375)
Anticonvulsants	0.259	(0.227 – 0.292)
Calcium Channel Blockers	0.254	(0.164 – 0.344)
ACE Inhibitors	0.167	(0.000 - 0.417)

Table T2 – Medication Definitions

Drug Categories	Compounds
Triptan	Almotriptan (Axert)
	Eletriptan (Relpax)
	Frovatriptan (Frova)
	Lasmiditan (Reyvow)
	Naratriptan (Amerge)
	Rizatriptan (Maxalt)
	Sumatriptan (Imitrex, Onzetra Xsail, Sumavel DosePro, Zembrace)
	Zolmitriptan (Zomig)
Migraine prophylactic	Propranolol
	Metoprolol
	Nadolol
	Amitriptyline
	Nortiptyline
	Topiramate
	Candesartan
	Gabapentin
	Divalproex
	Pizotifen
	onabotulinumtoxinA
	Flunarizine
	Venlafaxine
CGRP inhibitors	Eptinezumab,
	Galcanezumab,
	Fremanezumab
	Erenumab
Opioid (Generic Name)	Acetaminophen and Codeine
	Butorphanol Tartrate
	Codeine
	Cyclobenzaprine
	Fentanyl
	Hydrocodone bitartrate and acetaminophen
	Hydrocodone Bitartrate and Ibuprofen
	Hydromorphone
	Hydromorphone Hydrochloride
	Meperidine
	Meperidine - promethazine
	Meperidine-promethazine
	Morphine
	Nalbuphine
	Oxycodone and Acetaminophen
	Oxycodone and Aspirin
	Oxycodone Hydrochloride
	Oxycodone Hydrochloride and Acetaminophen
	Tramadol
	Tramadol HCL
	Tramadol Hydrochloride
	Tramadol Hydrochloride and Acetaminophen