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Original Article

Burden of Episodic Migraine, Chronic Migraine, and Medication Overuse Headache in Alberta

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ABSTRACT: ***Objective:*** To describe demographic and clinical characteristics, healthcare resource use, costs, and treatment patterns in three migraine cohorts. ***Methods:*** This retrospective observational study using administrative data examined patients with episodic migraine (EM), chronic migraine (CM) (without medication overuse headache [MOH]), and medication overuse headache in Alberta, Canada. Migraine patients were identified between 2012 and 2018 based on ≥ 1 diagnostic codes or triptan prescription. Patients with CM were defined using parameter estimates of a logistic regression model, and MOH was defined as patients with an average of ≥ 15 supply days covered of acute medications. EM was defined as patients without CM or MOH. Study outcomes were summarized using descriptive statistics. ***Results:*** Patients with EM (n = 144,574), CM (n = 27,283), and MOH (n = 11,485) were included. Higher rates of healthcare use and costs were observed for CM (mean [SD] all-cause cost: ($12,693 [40,664]) and MOH ($16,611.5 [$38,748]) versus episodic migraine ($4,251 [$40,637]). Across all cohorts, opioids were the most dispensed acute medication (range across cohorts: 31.7%–89.8%), while antidepressants and anticonvulsants were the most dispensed preventive medication. Preventative medication classes were used by a minority of patients in each cohort, except anticonvulsants, where 50% of medication overuse patients had a dispensation. ***Conclusions:*** Patients with CM and MOH have a greater burden of illness compared to patients with EM. The overutilization of acute medication, particularly opioids, and the underutilization of preventive medications highlight an unmet need to more effectively manage migraine.

RÉSUMÉ : Fardeau représenté par la migraine épisodique, la migraine chronique et les céphalées attribuables à la surconsommation de médicaments en Alberta. ***Objectif :*** Décrire les caractéristiques démographiques et cliniques de même que l'utilisation des ressources de santé, les coûts et les modes de traitement en lien avec trois cohortes de patients souffrant de migraine. ***Méthodes :*** Cette étude observationnelle rétrospective s'appuyant sur des données administratives a examiné des patients de l'Alberta (Canada) souffrant de migraine épisodique, de migraine chronique (sans céphalées liées à la surconsommation de médicaments) et de céphalées attribuables à la surconsommation de médicaments. Les patients migraineux ont été identifiés entre 2012 et 2018 sur la base de codes de diagnostic ≥1 ou d'une ordonnance de triptans. Les patients atteints de migraine chronique ont été définis en faisant appel aux estimations des paramètres d'un modèle de régression logistique tandis que ceux atteints de céphalées liées à la surconsommation de médicaments ont été définis comme des patients ayant une moyenne de ≥ 15 jours d'approvisionnement en médicaments destinés à des soins aigus. La migraine épisodique a été par ailleurs définie comme l'affection de patients sans migraine chronique ni céphalées liées à la surconsommation de médicaments. Les résultats de cette étude ont été résumés à l'aide de statistiques descriptives. ***Résultats :*** Des patients souffrant de migraine épisodique (*n* = 144 574), de migraine chronique (*n* = 27 283) et de céphalées attribuables à une surconsommation de médicaments (*n* = 11 485) ont été inclus dans cette étude. Des taux plus élevés d'utilisation des soins de santé et des coûts plus élevés ont été observés dans le cas de la migraine chronique (coût moyen [écart-type] toutes causes confondues : 12 693 $ [40 664 $]) et des céphalées attribuables à la surconsommation de médicaments (coût moyen [écart-type] toutes causes confondues : 16 611,50 $ [38 748 $]) en comparaison avec la migraine épisodique (coût moyen [écart-type] toutes causes confondues : 4 251 $ [40 637 $]). Dans toutes les cohortes, les opioïdes ont été les médicaments les plus prescrits en cas de migraine aiguë (fourchette de 31,7 à 89,8 %) alors que les antidépresseurs et les anticonvulsivants ont été les médicaments de nature préventive les plus prescrits. Les médicaments de nature préventive ont été utilisés par une minorité de patients dans chaque cohorte, et ce, à l'exception des anticonvulsivants, médicaments pour lesquels 50 % des patients souffrant de céphalées attribuables à la surconsommation de médicaments ont reçu une ordonnance. ***Conclusions :*** Les patients souffrant de migraine chronique et de céphalées attribuables à la surconsommation de médicaments ont une charge de morbidité plus importante que les patients souffrant de migraine épisodique. La surconsommation de

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médicaments aigus, en particulier des opioïdes, ainsi que la sous-utilisation de médicaments de nature préventive mettent en évidence un besoin non satisfait de prise en charge plus efficace de la migraine.

Keywords: Episodic migraine; chronic migraine; medication overuse; headache disorders; treatment patterns; healthcare costs

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Introduction

Migraine is a common, disabling neurological disorder[1] and the top cause of years lived with disability among people aged 15–49 years.[2] In the absence of early and effective treatment, episodic migraine (EM) may progress to chronic migraine (CM)[3] and subsequently to medication overuse headache (MOH), a severe secondary headache disorder.[4,5] Both CM and MOH tend to occur more frequently in women than in men,[6,7] and comorbidities are more common among individuals with CM.[7–9]

Previous studies have shown that healthcare resource use (HRU) among CM patients may be higher than among those with EM.[10–12] A recent Canadian study estimated the annual per-patient cost of CM to be $25,668.89 versus $15,651.34 Canadian dollar (CAD) for low-frequency (defined as an average of 4–7 migraine days per month) EM.[10] The higher costs of CM have been seen in other jurisdictions. For example, a study in the USA estimated the average annual healthcare-related cost of CM to be four times higher than EM.[12] The economic burden is also high in patients with MOH compared to EM in terms of direct and indirect costs.[13] A study examining the costs of MOH in Europe found the mean per-person annual costs of MOH to be three times higher compared to migraine.[13] Additionally, a reduction in the number of headache and migraine days experienced by a patient has been shown to reduce HRU.[14]

In the current study, we aimed to describe the burden of illness in three cohorts: patients who had CM and MOH (referred to as the MOH cohort), CM but no MOH (referred to as the CM-no-MOH cohort), and no CM and no MOH (referred to as the EM cohort). Previous comparable studies have described migraine subcohorts using older data[3,15,16] or have not focused on CM or MOH populations specifically.[3,7,10,15] There is a need for updated data to help determine gaps in knowledge and care. Specifically, there is an opportunity to improve the management of migraine by targeting newly diagnosed or recurrent patients with migraine to identify opportunities to improve treatment approaches as early as possible to improve patient outcomes. The objectives of our study were to understand the demographic and clinical characteristics, HRU and costs, and treatment patterns for newly diagnosed or recurrent migraine patients, specifically among patients with CM-no-MOH and MOH relative to patients with EM in Alberta, Canada.

Methods

Study Design and Data Sources

This retrospective observational study examined three cohorts of newly diagnosed or recurrent patients with migraine using administrative data, in Alberta, Canada, a province with 4.6 million residents as of October 1, 2022.[17] Healthcare in Alberta is administered through a provincial healthcare authority in the context of Canada's universal publicly funded healthcare system. Population-based administrative data were acquired from Alberta Health (Government of Alberta Ministry of Health) and included data from the provincial Alberta Blue Cross Pharmacy Claims, National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD), Pharmaceutical Information Network (PIN), Population Registry, Practitioner Claims, and vital statistics (deaths) datasets.[18]

Study Population

The EM, CM-no-MOH, and MOH cohorts were derived from a total migraine (TM) cohort. The case definition for the TM cohort was based on an algorithm from Muzina et al.[19] In short, the TM cohort included patients 18 years or older at the index date (defined below) who had: 1) ≥ 1 International Classification of Diseases (ICD) code(s) for migraine in the DAD, NACRS, or Practitioner Claims datasets (Supplementary Material 1); or 2) ≥ 1 prescription dispense (PIN dataset) for migraine-specific medication for acute treatment (i.e., triptan) from April 1, 2012, to March 31, 2018 (case ascertainment period). The index date was defined as the first (earliest) ICD-9-CM/ICD-10-CA code for migraine appearing in any position in the DAD, NACRS, or Practitioner Claims datasets, or the first pharmacy claim for a triptan appearing in the PIN dataset, within the case ascertainment period. Newly diagnosed or recurrent cases were patients without an ICD-9-CM/ICD-10-CA code for migraine and without a triptan dispense in the 2 years preceding their index date (an initial data extraction period from April 1, 2010 was applied to allow for a 2-year pre-index period). Patients were excluded if they had no record of health insurance coverage eligibility in the Alberta provincial registry or were aged < 18 years at the index date. The absence of a healthcare record for an event of interest (e.g., hospitalization) was taken to mean the event did not occur. From the TM cohort, patients were identified as CM-no-MOH, MOH, or EM within their first year of index.

Patients with CM were identified from parameter estimates of a logistic regression model described by Pavlovic et al. (2019).[20] The fitted model was used to generate predicted probabilities for each patient based on the following four predictors assessed in the 1-year period post-index date: (1) number of healthcare visits of any type (i.e., hospitalizations, physician visits, ambulatory visits, and ED visits (< 24, ≥ 24); (2) number of pharmacy prescriptions for acute migraine medications, including opioids (< 15, ≥ 15); (3) number of pharmacy prescriptions for unique migraine preventive drug classes equal to (0, 1, ≥2) and; 4) sex. Patients with a predicted probability ≥ 0.55 were categorized as having CM.

Patients were categorized as having MOH if they had≥15 days of coverage per month of simple analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) for 3 months as well as patients with ≥10 days of coverage per month of triptans, opioids, or mixed analgesics for 3 months within a 1-year look-forward period (i.e., 1-year post-index date in the TM cohort).[21]

From the two algorithms used to define CM and MOH, patients were classified into four categories: CM and MOH (MOH cohort), CM no MOH (CM-no-MOH cohort), MOH no CM (not analyzed for the purpose of this study), and no CM and no MOH (EM cohort).

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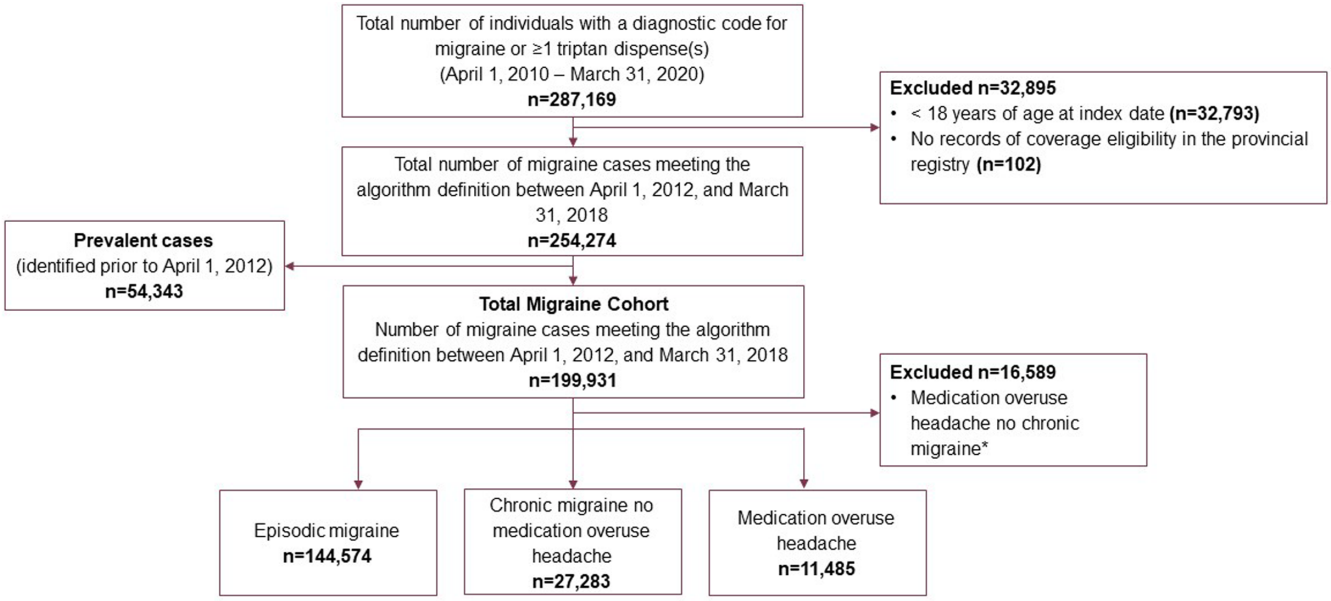

Figure 1: Derivation of episodic migraine, chronic migraine no medication overuse headache, and medication overuse headache cohorts in Alberta, Canada, 2012–2018. The total migraine cohort was defined using a migraine algorithm adapted from Muzina et al.[19] The index date was defined as the first (earliest) ICD-9-CM/ICD-10-CA code for migraine appearing in any position in the DAD, NACRS, or practitioner claims datasets, or the first pharmacy claim for a triptan appearing in the PIN dataset, from April 1, 2012, to March 31, 2018. Only newly diagnosed or recurrent cases were included (i.e., patients who did not have an ICD-9-CM/ICD-10-CA code for migraine or a triptan dispense in the 2 years preceding their index date).*Patients in the medication overuse headache no chronic migraine cohort were likely misclassified by the algorithms as medication overuse headache without chronic migraine is very rare clinically.

Variables

Demographic and clinical characteristics of interest included age at index date, sex, and the Charlson Comorbidity Index (CCI).[22] Age and sex were drawn from the Population Registry.[18] The CCI was derived using methods from Quan et al.[23] based on information in the DAD, NACRS, and Practitioner Claims 2 years prior to and including the index date.

The HRU variables included hospitalizations, ambulatory visits (including ED), ED visits, and physician encounters. Physician encounters were stratified by specialty (general practitioner [GP]/family physician [FP], SP). HRU and costs associated with physician claims, hospitalizations, and ED visits are reported separately for all-cause and migraine-related visits. Migraine-related visits were defined as the presence of a migraine code in any diagnosis position. Total healthcare costs were calculated for each patient as the sum of all medication (migraine-related only), hospitalization, physician, diagnostic imaging (i.e., magnetic resonance imaging and computed tomography), and ambulatory care costs (including ED visits). Statistics Canada's all-items Consumer Price Index was used to normalize costs to 2020 constant CAD.[24]

Acute medications were categorized into NSAIDs, triptans, antiemetics, and opioids. Preventive medications were categorized into antihypertensives (beta-blockers, calcium channel blockers, and angiotensin II receptor blockers), anticonvulsants, antidepressants (tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors), neurotoxins, monoclonal antibodies, and antamines such as pizotifen.

Statistical Analysis

Baseline characteristics were summarized as means and standard deviations (SDs) for continuous variables and as counts and proportions for categorical variables. HRU end points were summarized as the number and proportion of patients in the cohort, the number and proportion of patients with at least one event, and the mean (SD) number of events per person per year. Total costs per patient per year were summarized as means and SDs. Treatment patterns were summarized as the total number of acute and preventive medications dispensed, the rate of medication dispenses per person per year, the number and proportion of patients with at least one medication dispense, and the rate of medication dispenses per person per year among patients with at least one dispense. The annualized number of days covered was estimated as the total number of days medication was available (adjusted for overlap in prescriptions) divided by the number of days of follow-up multiplied by 365. Statistical significance between groups was examined using nonparametric Kruskal–Wallis test for numerical variables, chi-square test for categorical variables, and exact chi-square test for categorical variables when there are cells with expected values less than 5. SAS 9.4 was used to complete all analyses (SAS Institute, Cary, North Carolina).

Ethics

The study received ethics approval from the Health Research Ethics Board of Alberta – Community Health Committee.

Reporting

The study followed the reporting standards set by the A STrengthening the Reporting of Observational studies in Epidemiology statement.[25]

Results

There were 144,574, 27,283, and 11,485 patients in the EM, CM-no-MOH, and MOH cohorts, respectively (Fig. 1). The median follow-up was 2.9 years. All three cohorts were mutually exclusive.

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Table 1: Patient characteristics at index across three migraine cohorts in Alberta, Canada, 2012–2018

Characteristic	EM (n = 144,574)	CM-no-MOH (n = 27,283)	MOH (n = 11,485)
Age (years), mean (SD)[a]	38.6 (14.2)	42.3 (16.9)	46.4 (14.9)
Sex, n (%)[a]			
Female	97,174 (67.2)	27,278 (100.0)	11,045 (96.2)
Male	47,400 (32.8)	<10	440 (3.8)
Charlson Comorbidity Index score, n (%)[b]			
0	118949 (82.3)	18,207 (66.7)	6479 (56.4)
1 to 2	22,097 (15.3)	7203 (26.4)	3776 (32.9)
3+	2863 (2.0)	1754 (6.4)	1167 (10.2)
No healthcare visits within the defined baseline window	108 (0.1)	<10	15 (0.1)
N/A[c]	557 (0.4)	117 (0.4)	48 (0.4)
Comorbidities, n (%)			
Depression	21,770 (15.1)	8318 (30.6)	5029 (44.0)
Anxiety	19,164 (13.3)	6892 (25.4)	3766 (32.9)
Allergy	4339 (3.0)	1534 (5.6)	663 (5.8)
Cardiovascular disease (including hypertension, high cholesterol, and stroke)	22,559 (15.7)	7394 (27.2)	3729 (32.6)
Respiratory disorders (including COPD, emphysema, and asthma)	14,103 (9.8)	4682 (17.2)	2699 (23.6)
Arthritis	703 (0.5)	327 (1.2)	322 (2.8)
Chronic pain disorder	2126 (1.5)	1300 (4.8)	1401 (12.3)
Stroke	1727 (1.2)	733 (2.7)	246 (2.2)
Fibromyalgia	151 (0.1)	248 (0.9)	385 (3.4)
Obesity	8498 (5.9)	3241 (11.9)	1728 (15.1)

CM-no-MOH = chronic migraine no medication overuse headache; COPD = chronic obstructive pulmonary disease; EM = episodic migraine; MOH = medication overuse headache; SD = standard deviation, N/A = not applicable.
The differences across the three cohorts were statistically significant ($p < 0.001$) for age, sex, and the CCI.
[a]Refers to age at index date. Age and sex were derived from the Population Registry.
[b]The Charlson Comorbidity Index Score was derived from the Discharge Abstract Database, National Ambulatory Care Reporting System, and Practitioner Claims, 2 years prior to or including the index date.
[c]Individual was out of province at some point in the 2 years pre-index period.

Demographics and Clinical Characteristics

The mean age of the EM, CM-no-MOH, and MOH cohorts was 38.6, 42.3, and 46.4 years, respectively. Patients in the CM-no-MOH and MOH cohorts had higher CCI scores (% CCI ≥ 1: 32.8% and 43.1%, respectively) than the EM cohort (% CCI ≥ 1: 17.3%; Table 1). Nearly all patients in the CM-no-MOH (>99.9%) and the MOH (96.2%) cohorts were female compared to the EM (67.2%) cohort.

Healthcare Resource Utilization and Costs

The mean [SD] annual rate per patient per year of all-cause hospitalization was 0.1 [3.5] visits per patient per year for the EM cohort, 0.4 [2.7] for the CM-no-MOH cohort, and the highest for the MOH cohort (0.5 [2.0]) (Fig. 2). The mean [SD] annual rate of all-cause ED visits was more than twice as high in the CM-no-MOH and MOH cohorts (2.4 [9.4] and 3.1 [9.1] visits per patient per year, respectively) as in the EM cohort (1.1 [7.3]). Similar trends were observed with visits to a GP/FP or specialists, where patients in the CM-no-MOH and MOH cohorts had higher mean rates of all-cause visits per patient/year (Fig. 2).

The mean [SD] annual cost (CAD) of all-cause hospitalization was higher for the CM-no-MOH cohorts ($5,123 [$30,816]) and MOH ($6,577 [$26,900] per patient per year) than for the EM cohort ($1,508 [$31,640]). A similar pattern was observed for ED visits, ambulatory care, and physician visits (Fig. 3). Migraine-related costs (hospital, physician, and ambulatory visits) accounted for 8.0%, 4.0%, and 3.9% of all-cause costs, for the CM-no-MOH, MOH, and EM cohorts, respectively. The total all-cause mean (SD) cost per patient per year for all HRU end points was highest for the MOH cohort ($16,611.5 [$38,748]), followed by the CM-no-MOH cohort ($12,693 [40,664]) which were both more than two times higher than the EM cohort ($4,251 [$40,637]).

Treatment Patterns

Opioids were most frequently dispensed across all cohorts; 89.8% MOH cohort, 50.4% of the CM-no-MOH cohort, and 31.7% of the EM cohort received opioids (Table 2). Of the patients who received at least one opioid prescription dispense, the mean [SD] rate of opioid medications dispensed per patient per year was over 13 times higher for the MOH (17.5 [37.8]) cohort than for the EM cohort (1.3 [6.2]). Among all patients, the mean [SD] rate of opioid prescription dispenses per patient per year for the MOH cohort (15.7 [36.2]) was over 15 times higher than CM-no-MOH cohort (0.9 [4.4]) and over 30 times higher than for the EM cohort (0.4 [3.5]; Table 2).

NSAIDs were prescribed to 58.0% of the MOH, 32.3% of the EM, and 42.6% of the CM-no-MOH cohorts (Table 2). Among all patients, the annual mean [SD] dispense rate of NSAIDS for the MOH cohort (1.5 [6.3]) was three times as high for the CM-no-MOH (0.5 [2.7]) and five times as high for the EM cohort (0.3 [2.7]).

Nearly half of patients in the MOH cohort (46.5%), 27.9% in the CM-no-MOH, and 30.1% in the EM cohorts received triptans. Among all patients, the annual mean dispense rate [SD] for triptans in the MOH cohort (1.9 [6.9]) was more than three times compared to both the CM-no-MOH (0.5 [4.5]) and EM (0.6 [5.0]]) cohorts. Overall, relative to other cohorts, the MOH cohort had the highest annual mean number of acute medications dispenses across all acute medication classes.

The most dispensed medication among patients receiving at least one preventive prescription dispense was antidepressants for the EM (13.7%) and CM-no-MOH cohorts (31.2%) and anticonvulsants for the MOH cohort (50.2%; Table 3). Notably, less than 15% of the EM cohort and less than 50% of the MOH and CM-no-MOH cohorts received a preventive medication within each medication class examined (Table 3). There were no dispenses for monoclonal antibodies as calcitonin gene-related peptide monoclonal antibodies were not yet available in Alberta at the time of data collection (April 1, 2012 to March 31, 2018).

The mean number of days covered for acute and preventive medications over the study period decreased between 0 and 6 months and > 18–24 months, with the most significant decline after 6 months (Figs. 4 and 5). For opioids, the mean [SD] number of days covered remained substantially higher than all other acute medications in the periods examined for the MOH cohort (Fig. 4).

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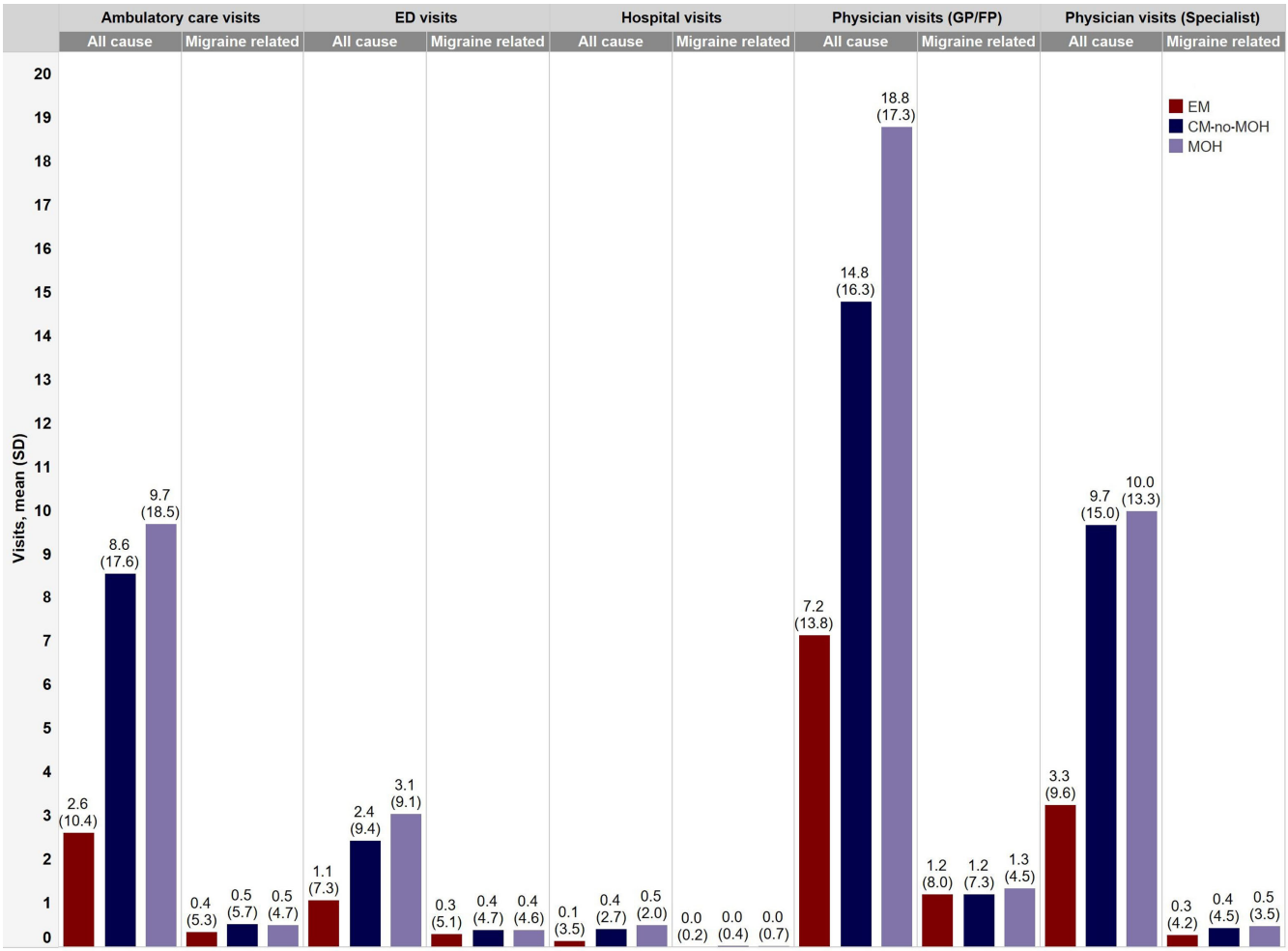

Figure 2: Healthcare resource use per patient per year in three migraine cohorts in Alberta, Canada, 2012–2018. CM-no-MOH = chronic migraine no medication overuse headache; ED = emergency department; EM = episodic migraine; FP = family physician; GP = general physician; MOH = medication overuse headache; SD = standard deviation. Ambulatory care visits include ED visits.

Discussion

This comprehensive study described the burden of illness for over 27,000 patients with CM-no-MOH and 11,000 patients with MOH in Alberta, Canada, using administrative data from 2012 to 2018. Our findings suggest, compared with the EM cohort, that adult patients with newly diagnosed or recurrent CM-no-MOH or MOH had a higher burden of illness in terms of HRU and costs. Of the three cohorts, patients in the MOH cohort had the highest overall HRU and costs. Notably, the mean total costs of all HRU were three times higher and the mean rate of opioid medication dispenses was over 13 times higher (among patients with≥1 prescription dispense) in the MOH cohort than the EM cohort. Furthermore, while the CM-no-MOH and MOH cohorts had higher proportions of patients who received ≥ 1 dispense of anticonvulsants or antidepressants for preventive use, these drug classes were dispensed to less than half of patients in the cohorts. Together, this indicates a general overuse of opioids and an underutilization of preventive medications in the management of CM-no-MOH and MOH.

The demographic and clinical characteristics of patients in Canada with CM or MOH have been described previously.[3,7,10,15] While our findings were generally consistent with those reports, the high female representation in the CM-no-MOH and MOH cohorts and another Alberta study[7] was distinct. Previous research indicates that men are also affected significantly by migraine,[15,16] and earlier studies have generally reported a lower proportion of females among CM and MOH patients, ranging from 73.0% to 89.0%.[3,10,16] However, the algorithm we applied to identify CM included a predictor variable for female sex. Additionally, all patients had to engage with the healthcare system in order to be included in our study, and women are more likely to seek medical treatment [26]

The elevated HRU and associated costs in the CM-no-MOH and MOH cohorts suggest a relatively high burden of illness in these groups. HRU is substantially higher in patients with CM compared to EM, as found in a previous study comparing CM to EM or tension-type headache.[12] As evident from our study, the economic burden was higher in patients with MOH compared to patients with CM-no-MOH and may be attributed, in part, to high medication use among these patients. As a highly preventable secondary headache disorder, studies have shown that the treatment of MOH (i.e., breaking the vicious cycle and reducing medication intake to an amount that no longer causes MOH) significantly reduced HRU and associated costs.[27,28] In a large

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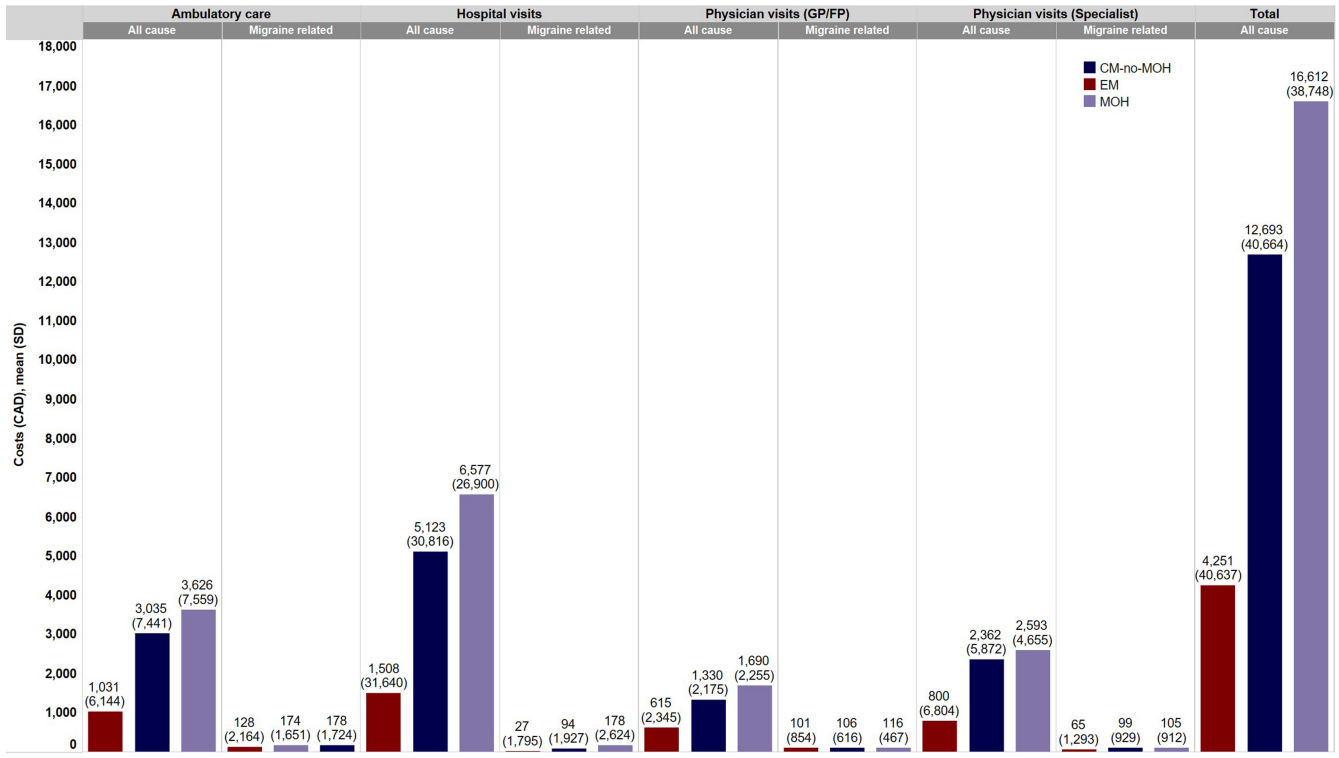

Figure 3: Healthcare costs (in 2020 CAD) per patient per year in three migraine cohorts in Alberta, Canada, 2012–2018. CAD = Canadian; CM-no-MoH = chronic migraine no medication overuse headache; ED = emergency department; EM = episodic migraine; FP = family physician; GP = general physician; MOH = medication overuse headache; SD = standard deviation. Total healthcare costs included medications (migraine-related only), hospitalizations, physician visits, diagnostic imaging (i.e., magnetic resonance imaging and computed tomography), and ambulatory care costs (including ED visits).

multinational and multicenter study, a detoxification program for patients with MOH reduced direct healthcare costs by 52% on average.[27] Comorbidities may have also contributed to the high HRU observed in the study. We observed CCI scores that were generally higher for the MOH cohort than for other cohorts, suggesting a higher risk of 1-year mortality. Earlier studies of chronic or frequent migraine have identified higher proportions of patients with comorbidities, including depression, anxiety, non-migraine headache, pain, gastric ulcers, asthma, allergies, diabetes, and cardiovascular conditions.[7,9] The high use of antidepressants may be related to the presence of comorbid anxiety and depression in the CM-no-MOH and MOH cohorts as comorbidities often inform the treatment strategies. Costs in our study may have been underestimated. A recent study from Canada estimated the mean total annual cost of CM to be $25,669 per patient among those who failed at least two prophylactic therapies for CM,[10] nearly twice the estimate for the CM cohort in our study ($12,693). Besides different inclusion criteria, the previous study assessed both direct and indirect costs including out-of-pocket expenses,[10] which we did not assess.

The higher use of acute medication in the MOH cohort, and possibly the higher age of this group, may reflect the nature of progression from EM to CM to MOH over time. The overuse of medications is a modifiable risk factor for progression from EM to CM,[4] and patients who experience CM are at risk for MOH through excessive use of acute treatment medications.[4,29] For patients, the experience of MOH is a vicious cycle of increasing headache frequency despite increasing acute medication use. For clinicians, the overuse of acute medication – defined as the use of triptans, ergots, combination analgesics, or opioid-containing medications for ≥ 10 days per month, or the use of acetaminophen or NSAIDs ≥ 15 days per month[21] – is an indicator for a poorly controlled headache.[4]

Acute medication utilization in the MOH cohort generally exceeded the Canadian guideline recommendations, which include patient education, abrupt withdrawal (or gradual for opioids and opioid-containing analgesics), use of preventive medications, effective acute medications to treat severe attacks with limitations on frequency of use, and patient follow-up and support.[21,30,31] Opioids are generally not recommended for routine treatment of migraine as their prolonged use can lead to addiction, a higher risk of MOH compared to other acute therapies, and other adverse side effects, and they are often not as effective as triptans and NSAIDs.[30] Yet the majority of patients in our MOH cohort (89.8%) had at least one dispense for opioids and the number of days covered was high in the > 18–24 months time period. In contrast, 31.7% of the EM cohort had at least one dispense for opioids, more closely resembling opioid use in studies of emergency settings (17.6% opioid use in Italy[32] and 35.9% in the USA).[33] Of note, our results excluded opioid use in hospital (e.g., during surgery), since the treatments captured in this study did not include hospital-administered medications. The literature supports our finding that MOH populations have higher proportions of overuse for more potent drugs such as opioids.[34] The misalignment between recommendations and treatment suggests an unmet need among individuals at risk for or with MOH, with one reason being possibly related to contraindications or challenges with other therapies, such as

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Table 2: Acute medication dispenses for three migraine cohorts in Alberta, Canada, 2012–2018

	EM (n = 144,574)	CM-no-MOH (n = 27,283)	MOH (n = 11,485)
Antiemetics			
All patients			
Total prescription dispenses, Sum	35,029	26,413	36,894
Number of dispenses per year, Mean (SD)	0.1 (1.8)	0.4 (2.2)	1.2 (7.1)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	16,689 (11.5)	7449 (27.3)	4135 (36.0)
Number of prescription dispenses per year, Mean (SD)	1.1 (5.2)	1.5 (4.0)	3.3 (11.5)
NSAIDs			
All patients			
Total prescription dispenses, Sum	96,014	31,264	46,394
Number of dispenses per year, Mean (SD)	0.3 (2.7)	0.5 (2.7)	1.5 (6.3)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	46,683 (32.3)	11,619 (42.6)	6659 (58.0)
Number of prescription dispenses per year, Mean (SD)	1.0 (4.7)	1.1 (4.1)	2.7 (8.1)
Opioids			
All patients			
Total prescription dispenses, Sum	192998	81,891	509760
Number of dispenses per year, Mean (SD)	0.4 (3.5)	0.9 (4.4)	15.7 (36.2)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	45,760 (31.7)	13,752 (50.4)	10,309 (89.8)
Number of prescription dispenses per year, Mean (SD)	1.3 (6.2)	1.8 (6.1)	17.5 (37.8)
Triptans			
All patients			
Total prescription dispenses, Sum	132576	24,448	50,029
Number of dispenses per year, Mean (SD)	0.6 (5.0)	0.5 (4.5)	1.9 (6.9)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	43,452 (30.1)	7621 (27.9)	5335 (46.5)
Number of prescription dispenses per year, Mean (SD)	2.0 (9.1)	2.0 (8.3)	4.0 (9.7)

CM-no-MOH = chronic migraine no medication overuse headache; EM = episodic migraine; MOH = medication overuse headache; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.
The differences across the three cohorts were statistically significant ($p < 0.001$) for all variables.

Table 3: Preventive medication dispenses for three migraine cohorts in Alberta, Canada, 2012–2018

	EM (n = 144,574)	CM-no-MOH (n = 27,283)	MOH (n = 11,485)
Antamines			
All patients			
Total prescription dispenses, Sum	139	245	156
Number of dispenses per year, Mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	50 (0.0)	35 (0.1)	24 (0.2)
Number of prescription dispenses per year, Mean (SD)	1.5 (3.7)	1.6 (2.6)	2.7 (3.6)
Anticonvulsant			
All patients			
Total prescription dispenses, Sum	100125	92,641	161594
Number of dispenses per year, Mean (SD)	0.2 (2.7)	1.1 (7.7)	4.9 (22.4)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	10,954 (7.6)	6359 (23.3)	5765 (50.2)
Number of prescription dispenses per year, Mean (SD)	3.1 (9.2)	4.7 (15.4)	9.8 (30.8)
Antidepressants			
All patients			
Total prescription dispenses, Sum	135404	97,331	109159
Number of dispenses per year, Mean (SD)	0.4 (3.3)	1.3 (7.9)	3.3 (15.4)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	19,861 (13.7)	8513 (31.2)	5492 (47.8)
Number of prescription dispenses per year, Mean (SD)	2.7 (8.5)	4.1 (13.8)	7.0 (21.7)
Antihypertensives			
All patients			
Total prescription dispenses, Sum	71,226	47,845	38,633
Number of dispenses per year, Mean (SD)	0.2 (2.6)	0.7 (3.4)	1.2 (7.0)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	8861 (6.1)	4393 (16.1)	2489 (21.7)
Number of prescription dispenses per year, Mean (SD)	2.9 (10.1)	4.1 (7.7)	5.4 (14.3)
Neurotoxin			
All patients			
Total prescription dispenses, Sum	12,741	9113	7577
Number of dispenses per year, Mean (SD)	0.0 (0.6)	0.1 (0.7)	0.3 (1.2)

(*Continued*)

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Table 3: (*Continued*)

	EM (n = 144,574)	CM-no-MOH (n = 27,283)	MOH (n = 11,485)
Patients with 1+ dispenses			
Patients with 1+ prescriptions, n(%)	3005 (2.1)	1815 (6.7)	1385 (12.1)
Number of prescription dispenses per year, Mean (SD)	1.7 (3.8)	1.9 (1.7)	2.1 (2.9)

CM-no-MOH = chronic migraine no medication overuse headache; EM = episodic migraine; MOH = medication overuse headache; SD = standard deviation.
The differences across the three cohorts were statistically significant ($p < 0.001$) for all variables.

triptans.[16] Relative to opioids, a smaller proportion of patients in the MOH cohort received triptans (46.5%); this proportion is attributable, in part, to the fact that triptans were not covered on the public formulary at the time of data collection.

The goals of preventive therapy include reducing the frequency, severity, and duration of migraine attacks as well as disability from migraine.[35] In the context of CM, a robust response can prevent progression to MOH. This study showed increased use of anticonvulsant and antidepressant dispenses in the CM-no-MOH and MOH cohorts compared to the EM cohort, which is aligned with treatment goals. However, with less than 50% of patients receiving anticonvulsants and antidepressants in the CM-no-MOH and MOH cohorts, there may have been patients who could have benefitted from the use of such medications to reduce the need for increasing acute medications, notably opioids. Evidence suggests that preventive medications are effective in reducing the need for and use of acute medications without deliberate withdrawal.[4,35] Further, the use of early oral preventive medicine for EM may help prevent the transformation of EM to CM, otherwise known as chronification.[31,35,36]

The large size and scope of our study is a methodological strength, providing a comprehensive evaluation of the burden of illness from CM-no-MOH and MOH by including the HRU, costs,

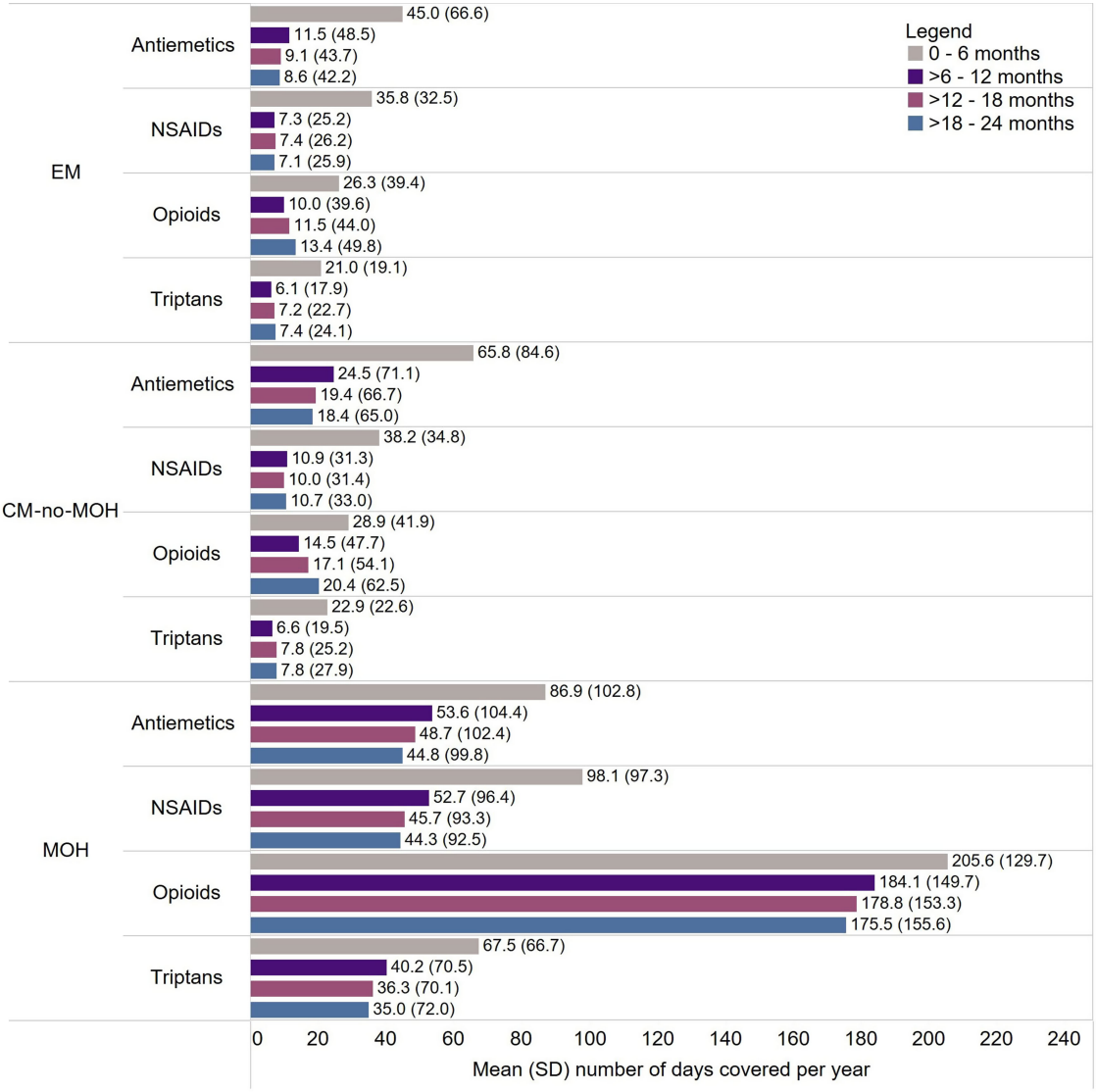

Figure 4: The number of days covered for acute migraine-related prescription dispenses per year for patients in three migraine cohorts in Alberta, Canada, 2012 = 2018. CM-no-MOH = chronic migraine no medication overuse headache; EM = episodic migraine; MOH = medication overuse headache; SD = standard deviation.

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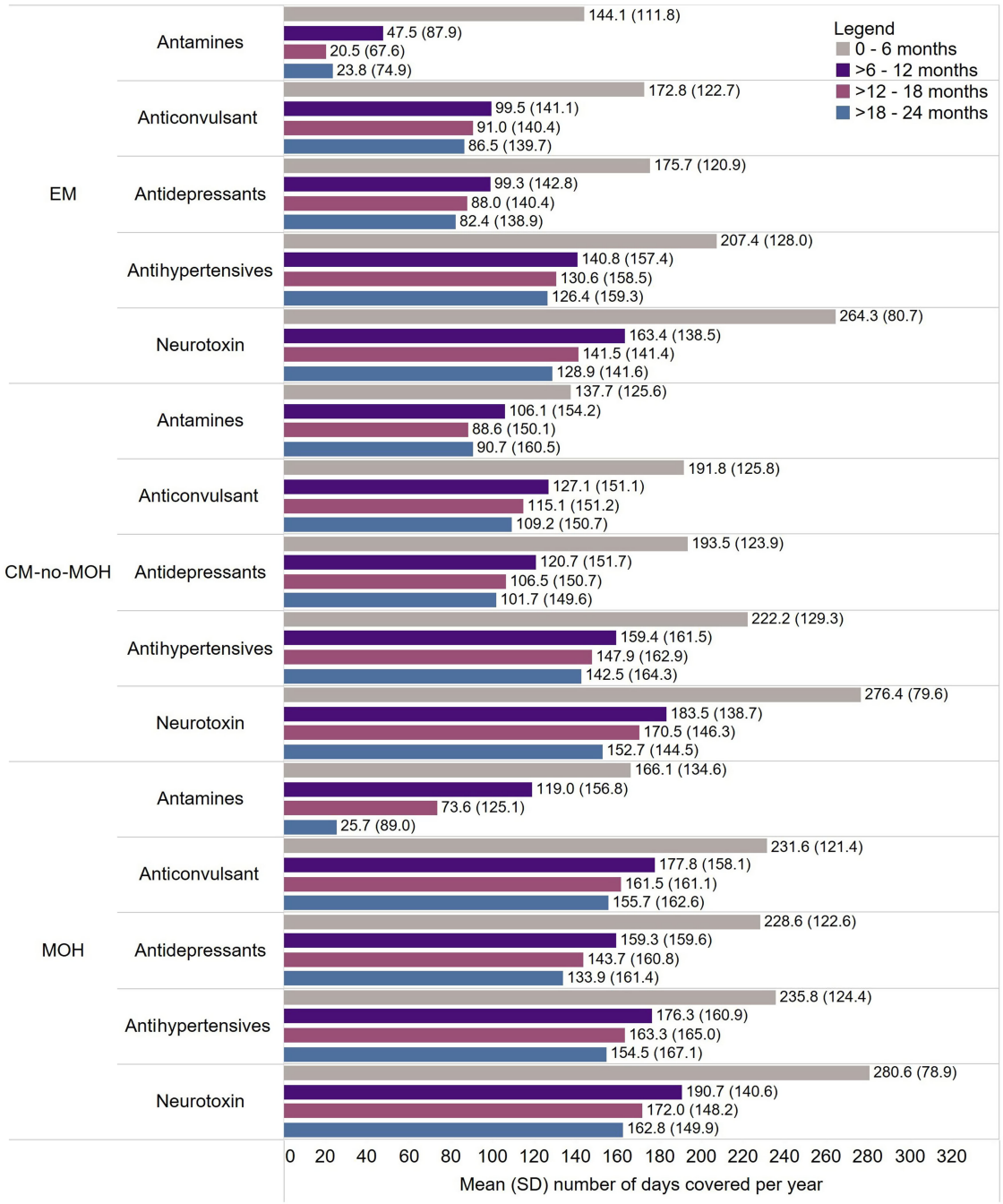

Figure 5: The number of days covered for preventive migraine-related prescription dispenses per year for patients in three migraine cohorts in Alberta, Canada, 2012–2018. CM-no-MOH = chronic migraine no medication overuse headache; EM = episodic migraine; MOH = medication overuse headache; SD = standard deviation.

and treatment burden that would not typically be covered in a single study. Our CM-no-MOH and MOH cohort sample size exceeded those in many previous epidemiologic studies.[3,12,15,16] In addition, the PIN database captured all pharmacy dispenses, both private and public, which allowed for comprehensive analyses of prescription treatment patterns. Prior studies in Canada had also been performed several years ago. Thus, this updated data is useful to help determine contemporary gaps in patient care.

As with any observational study, we acknowledge the possibility of unmeasured risk factors, such as lifestyle and family history. The outcomes in our study were unadjusted for baseline covariates, such as other comorbidities, making it difficult to attribute the observed patterns of patient characteristics, HRU, and costs to migraine specifically (versus a preexisting or co-occurring medical condition or other patient characteristics). Given that all patients required a medical encounter for cohort entry, it is possible that patients with unmet needs or more severe migraine were disproportionately included, while people who managed their symptoms using over-the-counter medications or chose not to seek care were excluded. Furthermore, there may have been possible misclassification bias as triptans can be used to treat other conditions such as cluster headaches. As the study focused on

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newly diagnosed or recurrent cases of migraine, patients who had a migraine diagnostic code or dispensation between 2010 and 2012, but not after, were omitted. Further, patients were classified into cohort within a year of index; therefore, misclassification bias may be present and disease status can evolve over follow-up. Additionally, we excluded patients that the algorithms classified as MOH without CM (8.3% of the TM cohort), which is clinically a misclassification as it is very rare to have MOH without CM and may potentially reduce the generalizability of our findings.

There were limitations to using administrative data to estimate the burden of illness. The full economic societal burden of migraine includes medication costs due to comorbidities and productivity losses which were not captured in our data. Over-the-counter medications and medications dispensed in-hospital are not included in the PIN database.[18] Furthermore, as the PIN database captures dispensations of prescription medication rather than usage, this may overestimate the amount patients actually take. It is also possible that the true number of CM and MOH cases is underestimated since the Practitioner Claims data is a dataset collected for the purpose of paying medical doctors and other allied practitioners for fee-for-service and shadow-billed claims; it may not be specific enough to identify all migraine diagnoses. As well, some individuals may have been misclassified as CM given our use of a logistic regression model as opposed to a diagnosis to identify CM. Additionally, the model parameters were obtained for a small sample of only 108 patients, and the study populations may not be comparable given the exclusions used in the Pavlovic et al. (2019) study.[20] We acknowledge that ICD codes are not a confirmed diagnosis of disease; while we increased the sensitivity of the study inclusion criteria by requiring more than one criterion – either a diagnosis or a triptan dispense – this may have impacted the specificity.

Conclusion

The effects of CM and MOH can be substantial for patients and the healthcare system. We found that patients in Alberta who have CM-no-MOH or MOH have a significantly greater burden of illness in terms of higher HRU and associated costs than patients with EM. The overutilization of opioids in these groups, especially the MOH cohort, and the underutilization of preventive therapies, represent a misalignment with treatment guidelines and indicate an unmet need in migraine management. Additional research is needed to understand these patterns to develop new approaches to manage CM early and prevent progression to MOH. These new approaches may need to account for comorbidities among patients living with CM and MOH as our study observed high comorbidity scores, HRU, and costs in these cohorts. Additionally, examining newer treatments for migraine such as calcitonin gene-related peptide monoclonal antibodies and its association with HRU is an avenue for future research. The high variability in dispense rates for both acute and preventive medications suggests a need among healthcare professionals for greater awareness and continuing medical education on treatment guidelines and the current state of care and its impacts, to effectively manage CM and MOH and improve the outcomes for these patients.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.289.

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References

1. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018;19:17.
2. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390:1211–59.
3. Stokes M, Becker WJ, Lipton RB, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the international burden of migraine study (IBMS). Headache. 2011;51:1058–77.
4. Sun-Edelstein C, Rapoport AM, Rattanawong W, Srikiatkhachorn A. The evolution of medication overuse headache: history, pathophysiology and clinical update. CNS Drugs. 2021;35:545–65.
5. Headache Classification Subcommittee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38:1–211.
6. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol. 2004;3:475–83.
7. Richer L, Wong KO, Martins KJB, et al. Characteristics of adults with migraine in Alberta, Canada: a population-based study. Can J Neurol Sci. 2022;49:239–48.
8. Blumenfeld AM, Varon SF, Wilcox TK, et al. HRQoL and resource use among chronic and episodic migraineurs: results from the international burden of migraine study (IBMS). Cephalalgia. 2011;31:301–15.
9. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. J Headache Pain. 2020;21:23.
10. Amoozegar F, Khan Z, Oviedo-Ovando M, Sauriol S, Rochdi D. The burden of illness of migraine in Canada: new insights on humanistic and economic cost. Can J Neurol Sci. 2022;49:249–62.
11. Becker WJ, Boudreau G, Finkelstein I, et al. OnabotulinumtoxinA reduces health resource utilization in chronic migraine: PREDICT study. Can J Neurol Sci. 2022;50:1–10.
12. Shao Q, Rascati KL, Barner JC, Lawson KA, Sonawane KB, Rousseau JF. Healthcare utilization and costs among patients with chronic migraine, episodic migraine, and tension-type headache enrolled in commercial insurance plans. Headache. 2022;62:141–58.
13. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the eurolight project. Eur J Neurol. 2012;19:703–11.

14. Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. Springerplus. 2015;4:826.
15. Altura KC, Patten SB, Williams JVA, Fiest KM, Jetté N. Living with migraine in Canada - a national community-based study. Can J Neurol Sci. 2019;46:216–23.
16. Deighton AM, Harris LA, Johnston K, et al. The burden of medication overuse headache and patterns of switching and discontinuation among triptan users: a systematic literature review. BMC Neurol. 2021;21:425.
17. Government of Alberta. Population Statistics, 2023. https://www.alberta.ca/population-statistics.aspx#:~:text=Highlights%3A%202022%2D46%20medium%20(reference)%20scenario&text=reach%20over%206.4%20million%20people,from%2038.9%20years%20in%202021
18. Alberta Health Analytics and Performance Reporting Branch. Overview of Administrative Health Datasets. Edmonton: Government of Alberta; 2017. https://open.alberta.ca/dataset/657ed26d-eb2c-4432-b9cb-0ca2158f165d/resource/38f47433-b33d-4d1e-b959-df312e9d9855/download/research-health-datasets.pdf
19. Muzina DJ, Chen W, Bowlin SJ. A large pharmacy claims-based descriptive analysis of patients with migraine and associated pharmacologic treatment patterns. Neuropsych Dis Treat. 2011;7:663.
20. Pavlovic JM, Yu JS, Silberstein SD, et al. Development of a claims-based algorithm to identify potentially undiagnosed chronic migraine patients. Cephalalgia. 2019;39:465–76.
21. Becker WJ, Findlay T, Moga C, Scott NA, Harstall C, Taenzer P. Guideline for primary care management of headache in adults. Can Fam Physician. 2015;61:670–9.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
23. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676–82.
24. Statistics Canada. Table 18-10-0256-01 Consumer Price Index (CPI) statistics, measures of core inflation and other related statistics - Bank of Canada definitions. Ottawa: Statistics Canada; 2022. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810025601
25. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Epidemiology. 2007;18:805–35.
26. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurol Sci. 2020;41:429–36.
27. Jellestad PL, Carlsen LN, Westergaard ML, et al. Economic benefits of treating medication-overuse headache - results from the multicenter COMOESTAS project. Cephalalgia. 2019;39:274–85.
28. Shah AM, Bendtsen L, Zeeberg P, Jensen RH. Reduction of medication costs after detoxification for medication-overuse headache. Headache. 2013;53:665–72.
29. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache. 2019;59:306–38.
30. Worthington I, Pringsheim T, Gawel MJ, et al. Canadian headache society guideline: acute drug therapy for migraine headache. Can J Neurol Sci. 2013;40:S1–s80.
31. Pringsheim T, Davenport W, Mackie G, et al. Canadian headache society guideline for migraine prophylaxis. Can J Neurol Sci. 2012;39:S1–59.
32. Negro A, Spuntarelli V, Sciattella P, Martelletti P. Rapid referral for headache management from emergency department to headache centre: four years data. J Headache Pain. 2020;21:25.
33. Shao Q, Rascati KL, Lawson KA, Wilson JP, Shah S, Garrett JS. Impact of emergency department opioid use on future health resource utilization among patients with migraine. Headache. 2021;61:287–99.
34. Kristoffersen ES, Lundqvist C. Medication-overuse headache: a review. J Pain Res. 2014;7:367–78.
35. American Headache Society. The American headache society position statement on integrating new migraine treatments into clinical practice. Headache. 2019;59:1–18.
36. Manzoni GC, Camarda C, Torelli P. Chronification of migraine: what clinical strategies to combat it? Neurol Sci. 2013;34:S57–60.

https://doi.org/10.1017/cjn.2023.289