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Epidemiology and treatment utilization for Canadian patients with migraine: a literature review

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Abstract

The objective of this narrative review was to identify real-world evidence regarding the burden of migraine in Canada. We conducted a literature search in MEDLINE, Embase, and the Cochrane Database of Systematic Reviews for studies published between August 2010 and August 2020. Of the 3269 publications identified, 29 studies were included. Prevalence estimates varied widely across Canada, and mental health comorbidities were common. Individuals with migraine have a lower quality of life, detrimental impact on workforce productivity, and higher rates of health care resource utilization (HCRU), with HCRU and costs highest among those with chronic migraine. We found inconsistencies in care, including underutilization of medications such as triptans, and varied utilization of over-the-counter and prescription medications. Increased medication use was identified among those with chronic migraine, and only a small number of patients used migraine preventive medications. The burden of migraine in Canada is substantial. Reduced quality of life and workforce productivity, increased HCRU and costs, and underutilization of triptans and migraine preventive medications highlight an important need for more effective management of individuals with migraine.

Keywords

Chronic migraine, episodic migraine, unmet need, Canada, real-world evidence, treatment pattern, headache

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Introduction

Headache disorders, including migraine, are the third leading cause of disability worldwide.[1] In 2019, headache disorders appeared among the top 10 most highly ranked conditions in terms of disability-adjusted life years among male and female individuals aged 10 to 25 years, together with HIV/AIDS, ischemic heart disease, and stroke.[2] Migraine has also been found to be the leading cause of years lived with disability among those aged 15 to 49 years.[3] Migraine is a disabling neurovascular disorder characterized by symptoms such as pain, auras, and sensitivity to normal sensory inputs including light, sound, and head movement.[4] Migraine is generally categorized as chronic or episodic according to the number of headache days per month, with chronic migraine occurring on $\geq$15 days per month for >3 months and symptoms of migraine headache $\geq$8 days per month thereafter; episodic migraines are characterized as headaches occurring <15 days per month.[1]

The global prevalence of migraine in 2016 was estimated at 14.7% according to the Global Burden of Disease Survey.[5] In 2011, an estimated 2.7 million Canadians, or 8.3% of the population, were diagnosed with migraine.[6] These rates are considered to be underestimates of the true migraine prevalence because many individuals who experience migraine may not seek professional help and therefore do not have a clinical diagnosis of migraine.[7,8]

The goals of migraine treatment are typically to relieve pain, restore function, improve quality of life, and reduce migraine frequency. Treatment decisions are guided by factors including migraine clinical features, level of impairment, previous treatments, comorbidities and contraindications, and patient preferences.[9] Along with educational interventions, lifestyle modifications, and trigger management, current Canadian guidelines recommend treating patients using acute and preventive migraine therapies.[10,11] Acute medications include over-the-counter (OTC) treatments (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) and prescription medications (e.g., triptans).[9] The Canadian Headache Society Guideline recommends seven triptans, four NSAIDs, and acetaminophen for the acute treatment of episodic migraine and several prophylactic drugs for preventing episodic migraine. There are currently no Canadian guidelines regarding the prevention of chronic migraine.[10,11] Whereas triptans are effective when used early, these medications should not be used >9 days per month to avoid medication overuse headache, a highly prevalent and disabling secondary headache diagnosis.[9,12,13]

Despite the availability of preventive regimens, adherence to these treatments is suboptimal.[14] A retrospective claims analysis in the United States (US) highlighted a significant treatment gap in patients with chronic migraine, reporting that more than 80% of patients discontinued oral migraine-preventive medications at 12 months.[15] Further complicating treatment adherence, patients with migraine typically have multiple comorbidities,[16–18] such as anxiety disorders and depression, and require additional medications to treat their comorbid conditions.[19] Furthermore, low rates of treatment adherence in patients with migraine are associated with frequent health care visits,[20,21] resulting in a financial burden on the publicly funded health care system in Canada.[22] Migraine has been reported to negatively impact labor force participation and caregiving of others.[23] In the US, migraine has been shown to decrease worker productivity, with one literature review reporting an average loss of 4 workdays per year owing to migraine.[24] A Malaysian study demonstrated a marked loss of productivity at work (presenteeism), in addition to absenteeism.[25] Taken

together, it is clear that there is an unmet need for effective treatment and prevention of migraine.

New treatment options such as serotonin (5-HT)1F receptor agonists and calcitonin gene-related peptide receptor (CGPR) antagonists have been recently approved by the US Food and Drug Administration, although it is not currently known when or if these treatments will be available in Canada.[26,27] OnabotulinumtoxinA was approved by Health Canada in 2011 for the prevention of chronic migraine, representing the first major advancement in the field since triptans became available. Additionally, a novel class of medications, CGPR monoclonal antibodies, received Canadian regulatory approval in 2018 for the prevention of episodic and chronic migraine.[28]

As new therapeutics become available on the market, it is imperative to understand the burden of migraine in Canada to inform decision-making around access to these novel therapies. The aim of this narrative literature review was to identify real-world evidence (RWE) studies among Canadian populations with migraine to better understand the epidemiology, treatment landscape, and burden of disease for migraine in Canada.

Methods

Search strategy

We conducted a search (Tables S1–S3) of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews in August 2020. The search strategy was developed to identify RWE (observational) studies of migraine among adult patients (aged $\geq$18 years) in Canada without intervention or comparison that reported the incidence, prevalence, burden of illness, or treatment information, and limited to studies published in the past 10 years. Additionally, the bibliographies of included papers were manually searched for additional publications.

Selection criteria

A single reviewer screened the search results to identify relevant publications using predefined selection criteria (Table S4). The screening was conducted in two phases: 1) titles and abstracts were screened for relevance; 2) the full text of studies meeting the selection criteria were reviewed to ensure the population and outcomes were relevant. All screening was conducted using the DistillerSR platform (Evidence Partners Incorporated, Ottawa, ON, Canada).

A single reviewer extracted relevant information from the included studies. No quality appraisal was completed in this review. The publications included and excluded at each stage of the review process is presented in Figure 1.

Ethics statement

Ethical approval and patient consent were not applicable to this literature review.

Results

Of the 3269 publications identified in the search, 29 met the inclusion criteria for this review (Table 1).[6,8,20–23,29–51] All studies were observational, with half adopting a survey-based cross-sectional design. The remaining studies used a variety of methodologies, including a retrospective database analysis, physician survey, case-crossover design, and retrospective chart review. The provincial distribution of the included studies is shown in Figure 2.

Incidence and prevalence of migraine in Canada

Only one study reported the incidence of migraine in Canada. Modgill et al. used data from the Canadian National

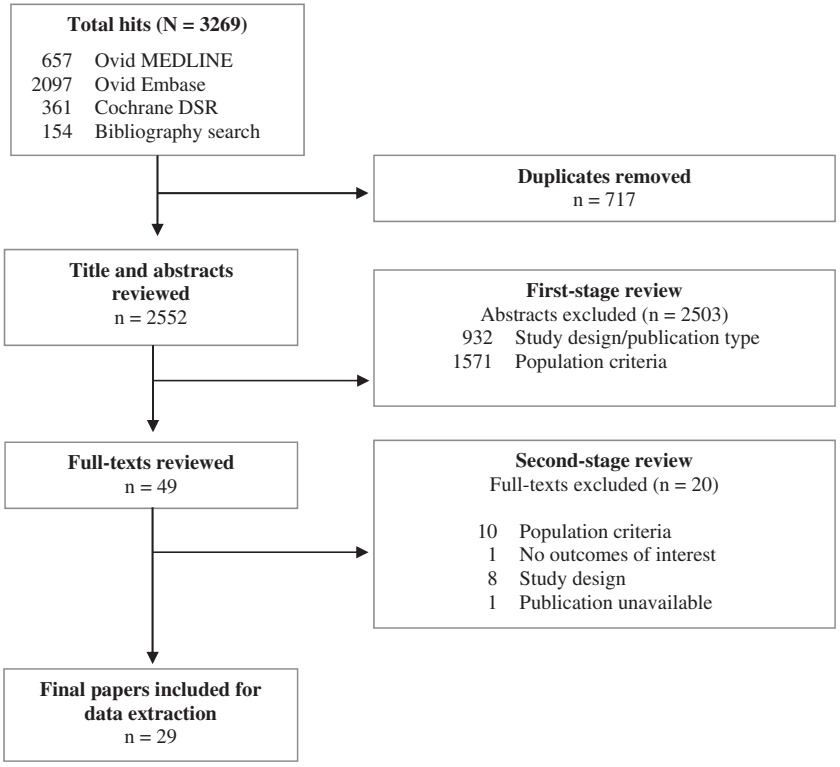

Figure 1. Study inclusion diagram.
Cochrane DSR, Cochrane Database of Systematic Reviews.

Population Health Survey (NPHS), a nationally representative longitudinal study, and reported a cumulative incidence of migraine during the follow-up period (1994/1995–2006/2007) of 12.4% (confidence interval [CI]: 11.5–13.5).[42] In contrast, several studies reported prevalence estimates for migraine in Canada (Table 2);[6,33,36] these ranged from 8.3%[6] to 10.2%,[33] with data from several national surveys. Prevalence varied at the provincial level, with estimates ranging from 6.8% in Quebec[6] to 10.7% in Ontario.[36]

Data from various iterations of the Canadian Community Health Survey (CCHS) were used in several studies;[31,37,43,47] estimates ranged from a weighted prevalence of migraine of 8.4%[40] to a weighted point prevalence of 10.2% for migraine.[33] Other studies were limited to specific geographic regions (9.7% among adults residing in British Columbia[38] and 10.7% in Ontario).[46] Four studies examined the migraine prevalence among specific populations (e.g., individuals with mood disorders, generalized anxiety disorder, or those who had experienced childhood abuse) using the CCHS.[31,37,43,47] Using data from the 2002 CCHS, Nguyen et al. reported that 9.3% of individuals without mood episodes had migraines (compared with 28.5% among individuals with manic and depressive episodes, 19.5% among those with manic episodes alone, and 18.7% among those with depressive episodes alone).[43] In a study using the 2005 CCHS regional sample from Manitoba and Saskatchewan, Fuller-Thomson et al.

Table 1. Characteristics of included studies.

First author	Canadian province(s)	Study design	Sample size	Study data source and study length
Amadio 2015[29]	7 provinces (Alberta, Manitoba, New Brunswick, Nova Scotia, Ontario, Saskatchewan, and Prince Edward Island)	Cross-sectional	14,085 users of triptans	Drug prescribing databases; 12 months (1 January 2012 to 31 December 2012)
Altura 2019[30]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	949 patients with migraine	2011–2012 Survey of Living with Neurological Conditions in Canada
Bhimji 2020[51]	Saskatchewan	Retrospective chart audit	36	Chart audit, 1 year
Brennenstuhl 2015[31]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	Men: 10,358, women: 12,638	2012 Canadian Community Health Survey – Mental Health
Colman 2016[32]	Ontario	Cross-sectional	101,114	Canadian Community Health Survey; 3 years (2003, 2005, 2007)
Cooke and Becker 2010[8]	National	Cross-sectional	1210 women	Canadian Women and Migraine Survey; data collection from 6 to 24 July 2005
Dooley 2016[33]	9 provinces and territories (Alberta, Saskatchewan, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Nunavut, Northwest Territories)	Cross-sectional	48,645 eligible survey respondents, 4614 reporting migraine	2013 Canadian Community Health Survey, as well as 2009 and 2005 datasets

(continued)

Table 1. Continued.

First author	Canadian province(s)	Study design	Sample size	Study data source and study length
Fuller-Thomson and Hodgins 2020[34]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	21,744 respondents, 2223 with migraine	2012 Canadian Community Health Survey – Mental Health
Fuller-Thomson 2017[35]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	19,270 without migraine, 2232 with migraine	2012 Canadian Community Health Survey – Mental Health
Fuller-Thomson 2013[36]	6 provinces (Prince Edward Island, Nova Scotia, Quebec, Saskatchewan, Ontario, Alberta)	Cross-sectional	6577	2005 Canadian Community Health Survey
Fuller-Thomson 2010[37]	Manitoba and Saskatchewan	Cross-sectional	13,089	Regional sample of 2005 Canadian Community Health Survey
Hammond 2020[38]	British Columbia	Cross-sectional	11,910	Regional sample of 2011–2012 Canadian Community Health Survey – Annual Component
Hammond Stinchcombe 2019[39]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland, and Labrador)	Cross-sectional	Men: 21,549, Women: 22,176	Canadian Longitudinal Study on Aging; 4 years (2011–2015)

(continued)

Table 1. Continued.

First author	Canadian province(s)	Study design	Sample size	Study data source and study length
Hinnell 2010[40]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland, and Labrador)	Cross-sectional	400,055 individuals (39,797 with migraine)	2001–2005 Canadian Community Health Survey
Metcalfe 2010[41]	13 provinces and territories (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Nunavut, Northwest Territories, Yukon)	Cross-sectional (2001, 2003, and 2005 Canadian Community Health Survey)	39,797	2001, 2003 and 2005 Canadian Community Health Survey
Modgill 2012[42]	Nationally representative community sample	Retrospective cohort	15,254	Canadian National Population Health Survey; 12 years (1994/1995 to 2006/2007)
Nguyen 2013[43]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	36,984	2002 Canadian Community Health Survey
Nijjar 2011[44]	Ontario	Prospective survey	311 completed surveys	Surveys distributed to emergency physicians
Nijjar 2010[45]	Ontario	Retrospective review	100	Retrospective review; June 2006 to July 2007

(continued)

Table 1. Continued.

First author	Canadian province(s)	Study design	Sample size	Study data source and study length
Ramage 2014[6]	All	Cross-sectional	22,720	Neurological Conditions Prevalence File, which was derived from the 2010 and 2011 Canadian Community Health Survey – Annual Component, and the 2011 Survey of Living with Neurological Conditions in Canada
Sajobi 2019[23]	Alberta	Prospective	263	Neurological Disease and Depression Study, 2012 and January 2013
Sanderson 2013[21]	International (United States, Canada, the United Kingdom, Germany, France, and Australia)	Cross-sectional	1165 completed the main questionnaire (including 50 patients from Canada with chronic migraine, and 55 patients with episodic migraine)	International Burden of Migraine Study (IBMS-II); 3 months
Slatculescu 2018[46]	Ontario	Cross-sectional	42,553	Regional sample of 2013–2014 Canadian Community Health Survey
Sommer 2019[47]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cross-sectional	25,113	2012 Canadian Community Health Survey – Mental Health
Stokes 2011[22]	Canada	Cross-sectional	Canada (N = 681)	International Burden of Migraine Study; 3-month web-based study matched to medical records

(continued)

Table 1. Continued.

First author	Canadian province(s)	Study design	Sample size	Study data source and study length
Swanson 2013[48]	Canada	Cohort	9342	2000/2001 National Population Health Survey
Szyszkowicz 2012[49]	Ontario	Case-crossover	898 in Toronto, 4568 in Ottawa	Toronto: between 1 April 1999 and 31 March 2002. Ottawa: between 1 April 1992 and 31 December 2000
van Walraven 2016[50]	Ontario	Cross-sectional	101,114 (11,314 with migraines)	2001–2008 Canadian Community Heath Survey
Wolfson 2019[20]	10 provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador)	Cohort	51,338	Canadian Longitudinal Study on Aging; 20 years with 3-year sampling interval

reported that the prevalence of migraine was almost twice as high for individuals who reported childhood physical abuse than for those who did not (17.9% vs. 8.8%).[37] Examining the 2012 CCHS–Mental Health Supplement, Sommer et al. reported that migraines were prevalent among 10.3% (95% CI: 9.7–11.0) of individuals whereas the prevalence of migraine among those with generalized anxiety disorder was 27.5% (95% CI: 23.0–32.6).[47] Using data from the same source (2012 CCHS–Mental Health Supplement), Brennenstuhl and Fuller-Thomson explored the relationship between childhood violence and migraine.[31] Those authors reported a significant difference in the prevalence of migraine among women compared with men (14.2% vs. 6.5%, respectively; $p < 0.001$), and childhood adversity (including self-reported physical abuse, sexual abuse, and witnessing domestic violence) was significantly associated with migraine in both men (odds ratio [OR] 1.50–1.70, by type of adversity) and women (OR 1.32–1.64).[31]

Prevalence estimates were also provided in other prospective studies.[8,20,48] In a sample of 1210 women from the Canadian Women and Migraine Survey, Cooke and Becker reported a prevalence of migraine of 26.0%.[8] Using baseline data from the Canadian Longitudinal Study on Aging (2011–2015), Wolfson et al. reported a lifetime self-reported prevalence of 143.1 (95% CI: 138.1–148.6) per 1000 for migraine.[20] Using the NPHS, Swanson et al. noted that 4.1%, 9.1%, and 1.3% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively, at baseline.[48]

Burden of disease for migraine in Canada

Humanistic burden. Twenty-two studies described comorbidities among patients with migraine.[6,21–23,30–40,42,43,45–48,50]

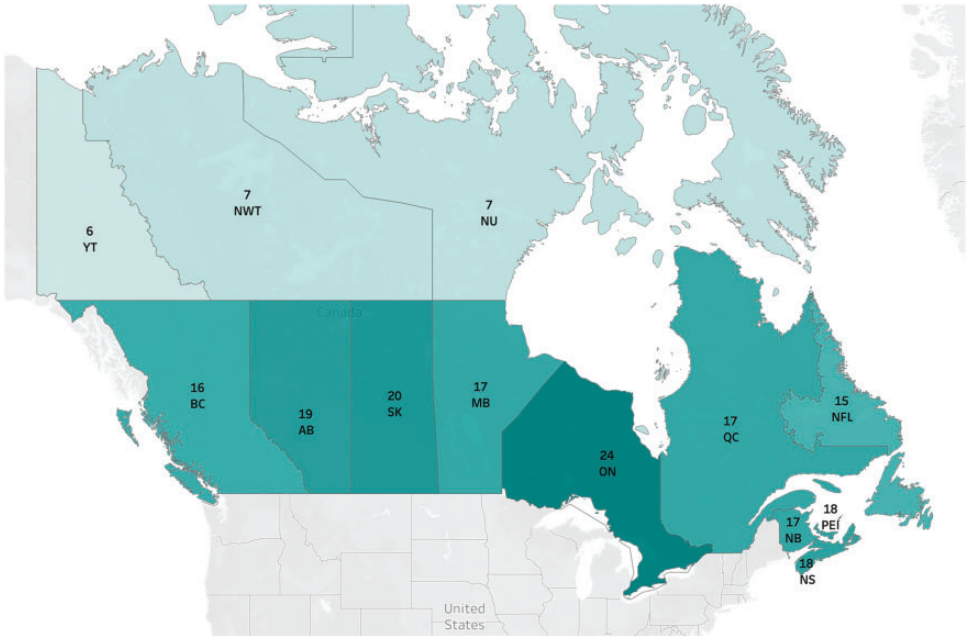

Figure 2. Geographic visualization of included studies.
Note: Several studies include more than one province.
AB, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NFL, Newfoundland and Labrador; NS, Nova Scotia; NU, Nunavut; NWT, Northwest Territories; ON, Ontario; PEI, Prince Edward Island; QC, Quebec; SK, Saskatchewan; YT, Yukon.

Comorbidities were common among patients with migraine, especially those with chronic migraine.[23] Sanderson et al. reported that among survey respondents with episodic migraine, 45% reported having more than two comorbidities whereas among those with chronic migraine, 74% reported having more than two comorbidities.[21]

Mental health comorbidities (e.g., anxiety, depression, suicidal ideation) were reported across several studies in patients with chronic and episodic migraine (Figure 3).[32,34–36,43] Stokes et al. reported comorbid psychiatric disorders in 38.2% and 27.3% of those with chronic and episodic migraines, respectively.[22] Four studies suggested that suicidal ideation is relatively common among patients with migraine, potentially indicating the disease burden in this population.[32,34,43,47] Colman et al. reported that serious suicidal thoughts in the previous year and during the lifetime were markedly higher among patients with migraine in Ontario.[32] Similarly, Sommer et al. reported that comorbid generalized anxiety disorder and migraine were associated with increased odds of suicidal ideation.[47] Nguyen et al. reported that among patients with migraine but without mood disorders, 14.6% reported lifetime suicidal ideation.[43] Fuller-Thomson and Hodgins reported that the prevalence of suicide attempts was significantly higher among those with than in those without migraine (8.7% vs. 2.3%).[34]

Seven studies were identified that reported health-related quality of life

Table 2. Prevalence of migraine reported in the included studies.

Study	Data source and year	Reported prevalence
Brennenstuhl and Fuller-Thomson (2015)[31]	CCHS (2012–Mental Health Supplement)	Authors reported a significant difference in the prevalence of migraine among women compared with men (14.2% vs. 6.5%; $p < 0.001$) and noted that for both men and women, childhood adversities (including self-reported physical abuse, sexual abuse, and witnessing domestic violence) were significantly associated with migraine
Cooke and Becker (2010)[8]	Canadian Women and Migraine Study (2005)	Prevalence of migraine headaches 26%
Dooley et al. (2016)[33]	CCHS (2013)	Weighted point prevalence of 10.2% for migraine
Fuller-Thomson et al. (2010)[37]	CCHS (2005); regional sample of 13,089 men and women from Manitoba and Saskatchewan	Prevalence of migraine was nearly twice as high for participants who reported childhood physical abuse in comparison with those who did not (17.9% vs. 8.8%)
Hammond et al. (2020)[38]	CCHS (2011–2012 Annual Component); Adults ($\geq$18 years of age) residing in British Columbia	Weighted prevalence of migraine was 9.7% (95% CI: 9.1–10.2)
Hinnell et al. (2010)[40]	CCHS (2001–2005)	Weighted prevalence of migraine 8.4%
Nguyen et al. (2013)[43]	CCHS (2002)	Of participants without mood episodes, 9.3% had migraines, compared with 28.5% of those with manic and depressive episodes, 19.5% of those with manic episodes alone, and 18.7% of those with depressive episodes alone
Slatculescu et al. (2018)[46]	CCHS (2013–2014): Ontario	Prevalence of migraine 10.7%
Sommer et al. (2019)[47]	CCHS (2012–Mental Health Supplement)	Migraines were prevalent among 10.3% (95% CI: 9.7–11.0) of individuals; the prevalence of migraine among those with generalized anxiety disorder was 27.5% (95% CI: 23.0–32.6)
Swanson et al. (2013)[48]	NPHS (Cycle 4 2000/2001)	At baseline, 4.13%, 9.13%, and 1.33% of the sample reported current depression only, migraine only, and comorbid depression and migraine, respectively
Wolfson et al. (2018)[20]	Canadian Longitudinal Study on Aging (2011–2015)	Lifetime self-reported prevalence of 143.1 (95% CI: 138.1–148.6) per 1000 for migraine Examined by province, the prevalence (per 1000) of migraine was 147.7 (95% CI: 138.4–158.5) in Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick), 123.8 (95% CI: 115.1–133.0) in Quebec, 156.0 (95% CI: 145.9–167.4) in Ontario, 127.0 (95% CI: 119.2–136.0) in the Prairie Provinces (Manitoba, Saskatchewan, and Alberta), and 157.3 (95% CI: 147.9–168.4) in British Columbia[20]

CCHS, Canadian Community Health Survey; CI, confidence interval; NPHS, National Population Health Survey.

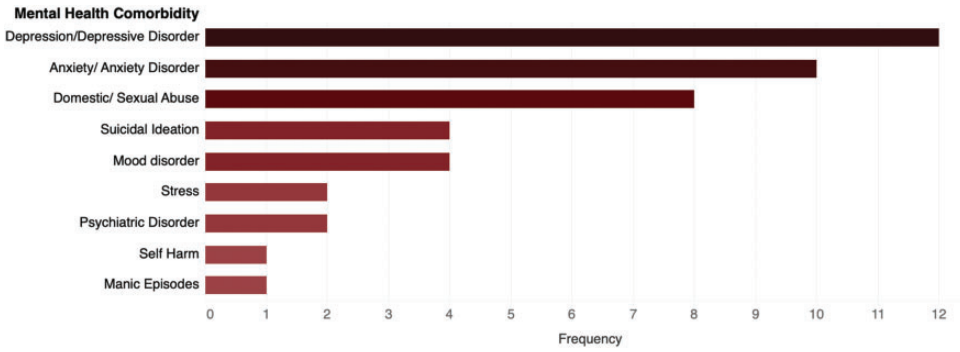

Figure 3. Frequency of mental health comorbidities reported in the included studies (n = 22).
Note: This figure presents a broad look at the number of studies in this review reporting mental health comorbidities across a broad spectrum of general and specific populations. Whereas it is difficult to draw conclusions from this given the heterogeneous nature of the included studies, the figure does provide a high-level picture of the relative co-occurrence of migraine and different mental health comorbidities in the Canadian literature involving real-world evidence.

(HRQoL) among patients with migraine in Canada.[8,21–23,30,33,40] The Migraine Disability Assessment Test was used to assess migraine severity and disability in three of the included studies;[21–23] the percentage of Canadians with chronic migraine who qualified as having severe or very severe disability ranged from 70.0% to 90.0% whereas the range of individuals with episodic migraine who reported severe or very severe disability was 21.0% to 46.6% (Figure 4).

One study reported that patients with migraine had an average utility score of 0.80 (95% CI: 0.80–0.80).[30] The utility score is a value typically between 0 and 1 that reflects a patient's HRQoL as a proportion of perfect health (a score of 1 indicating perfect health). Interestingly, that study found lower utility scores for men (OR 0.67, 95% CI: 0.59–0.75) than women with migraine (OR 0.82, 95% CI: 0.79–0.86). Notably, men in that study also had more neurological comorbidities, with approximately three times the odds of having another neurological condition.[30]

Labor force productivity. In this review, we identified seven studies reporting labor force outcomes for people with migraine in Canada.[6,8,22,23,30,43,48] Results from these studies suggest that migraine symptoms negatively impact labor force participation. Cooke and Becker found that among Canadian women surveyed, those with frequent migraines had lost an average of 18.3 workdays in the previous 6 months owing to either reduced function or total incapacitation.[8]

The included studies reported that individuals with chronic migraine had poorer labor force outcomes than those with episodic migraine. Overall, reported employment rates were lower in patients with chronic migraine (32.7% to 50.0% for full-time positions) in comparison with patients who had episodic migraine (46.0% to 71.8%).[22,23] One additional study examined labor force outcomes in people with migraine and comorbid mental health and/or psychiatric conditions, noting that these types of comorbid conditions were a further detriment to employment outcomes in people with migraine.[43]

Health care resource use and costs. Ten studies were identified that reported health care

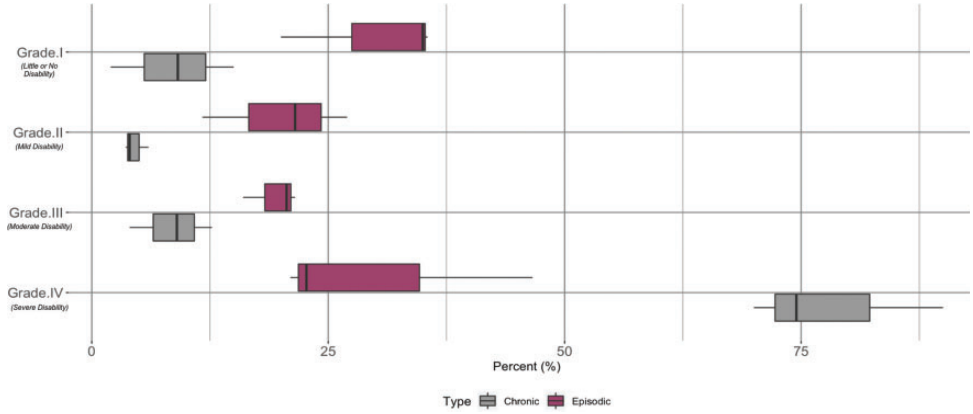

Figure 4. Percentage of patients in each disability category according to MIDAS scores reported in the included studies (n = 3) for patients with chronic or episodic migraine.
Note: All three studies reported results for both chronic and episodic migraine.
MIDAS, migraine disability assessment.

resource utilization (HCRU) among patients with migraine in Canada.[8,20–22,32,38,41,44,49,50] Among studies that compared the HCRU of people with and without migraine, migraine was associated with increased resource utilization, including an increased number of physician visits to both a general practitioner (GP) and to a specialist.[8,20,50] Wolfson et al. found that migraine was associated with a significantly increased risk of an emergency department (ED) visits over a 12-month period, relative to people without migraine (relative risk [RR] = 1.14, 95% CI: 1.08–1.21), as well as an increase in GP visits (RR = 1.02, 95% CI: 1.01–1.03) and specialist visits (RR = 1.05, 95%: 1.02–1.08) over a 12-month period relative to people without migraine.[20] van Walraven et al. reported a median of 24 (interquartile range [IQR]: 11–47) GP visits over a 2-year period among people with migraine.[50] Cooke and Becker reported that 83% of women with headache reported a physician visit for their condition and 15% reported a neurologist visit in their lifetime.[8]

Of studies that reported outcomes for patients with episodic and chronic migraine, the latter tended to be associated with greater HCRU across the health care system, with rates of system use in the prior 3 months ranging from 22.0% to 52.0% in patients with chronic migraine compared with 16.0% to 35.0% in those with episodic migraine.[21,22] Sanderson et al. found that patients with chronic migraine reported having higher HCRU in the previous 3 months than patients who had episodic migraine, including ED visits (chronic: 52.0%, episodic: 35.0%), hospitalizations (chronic: 22.0%, episodic: 16.0%), and health care provider visits (chronic: 46.0%, episodic: 29.0%).[21] Similarly, Stokes et al. found that more patients with chronic migraine reported visiting a GP over a 3-month period (chronic: 48%, episodic: 12%) or having a neurologist visit (chronic: 9%, episodic: 3%).[22]

Two of the included studies examined costs associated with migraine in Canada.[22,30] One study reported the percentage of patients with migraine who indicated out-of-pocket health care expenditures,[30] and the other study reported costs to health care payers associated with resources used to treat headache.[22] Altura et al. found

that among people with migraine, 2.6% (95% CI: 1.3–3.8) reported out-of-pocket expenditures for an assistive device, 16.2% (95% CI: 11.3–21.1) for rehabilitation therapy, 1.2% (95% CI: 0.5–1.8) for homecare devices, and 55.5% (95% CI: 49.0–62.0) for medications.[30]

Among both patients with chronic and episodic migraine, the largest contributors to total cost were medications at CAD 772 and CAD 258 annually per person (2010 Canadian dollars), respectively.[22] Additionally, total annual direct medical costs per patient were substantially higher for patients with chronic migraine compared with those who had episodic migraine at CAD 1883 and CAD 687, respectively.[22] Other annual costs included medical procedures (chronic: CAD 292, episodic: CAD 124), health care provider reimbursements (chronic: CAD 507, episodic: CAD 113), and hospitalizations or ED visits (chronic: CAD 313, episodic: CAD 192).[22]

Treatment landscape in Canada. Nine studies examined the treatment landscape of migraine in Canada.[6,8,21,22,29,41,44,45,51] The variability in study designs, data sources, and regional representation all necessitate caution when interpreting these findings (Supplementary Material).

Acute medication

Medication use, including OTC and prescription medications, was examined broadly in the literature.[6,8] In a Canada-wide survey, Ramage-Morin and Gilmour found that 42% of those with migraine reported taking a prescription medication for migraine in the past 3 months; the authors noted that this was owing to OTC prescriptions not being included in the survey.[6] Using data from the Canadian Women and Migraine Survey, Cooke and Becker reported that 10% of respondents were not using any medications.[8] Those taking medication reported taking OTC therapies as their primary treatment (e.g., ibuprofen: 38%, acetaminophen: 8%) whereas others used prescription medications, including codeine-containing analgesics (23%) and triptans (8.0%).[8]

Further details on triptan use among patients with migraine in real-world settings were also reported.[29,44] Comparing provincial differences in triptan use, Amadio et al. analyzed publicly funded triptan dispenses in Alberta, Manitoba, New Brunswick, Nova Scotia, Ontario, Saskatchewan, and Prince Edward Island.[29] That study highlighted differences in the prevalence of triptan use among provinces, ranging from 0.04% in Ontario ($N = 1090$) to 1% in Manitoba ($N = 6555$). The authors suggested that this may be owing to differences in coverage eligibility among provinces.[29] Nijjar et al. surveyed emergency physicians in Ontario.[44] The authors reported that approximately 66% of respondents did not prescribe triptans for the treatment of migraine during ED visits. Reasons for this approach included that triptans were unavailable owing to current protocols/formularies (45%) and uncertainty about the evidence and/or the availability of alternatives (20%). Among departments with headache protocols, fewer than 1% included triptans (approximately 16% reported the inclusion of antiemetics, 11% included NSAIDs, 9% included ergotamines, and 2% included opiates).[44]

Additionally, two studies reported findings for patients with chronic and episodic migraine.[21,22] In a global cross-sectional survey study that included a Canadian subpopulation, Sanderson et al. reported that 82% of patients with chronic migraine had tried >3 acute medications whereas only 69% of those with episodic migraine had tried >3 acute agents.[21] Using data from the International Burden of Migraine Study among participants residing in Canada, Stokes at al. found that 70% of

patients with chronic migraine reported using acute medications in the previous 4 weeks.[22] Specifically, 61% had used simple analgesics alone or in combination with opiates or barbiturates, 13% used combination analgesics without opiates or barbiturates, 30% used NSAIDS, and 20% used triptans. In contrast, 80% of patients with episodic migraine in that study reported using acute medications in the previous 4 weeks, with 61% having used simple analgesics alone or in combination with opiates or barbiturates; 10% used combination analgesics without opiates or barbiturates, 41% used NSAIDS, and 9% used triptans (Figure 5).[22]

Finally, utilization of opioids was reported by Nijjar et al. who examined patients referred to an urban tertiary pain clinic. The authors found that opiate use among these participants was more prevalent than triptan use, with 72% having used an opiate and 27% using multiple opiates, in comparison with 48% having tried at least one triptan in the past and 31% actively using triptans.[45] Another study examined opioid utilization among patients with chronic pain, using a retrospective chart audit of patients attending the Medication Assessment Centre in Saskatchewan.[51] Of the assessed patients, 11% were reported to be taking opioids for migraine management. It is important to note that these two studies examined patients at specialized, single centers focusing on pain management; thus, the findings are not necessarily generalizable.

Preventive medication

Sanderson et al. and Stokes et al. also reported preventive medication use for patients with chronic and episodic migraine.[21,22] Sanderson et al. reported that 50% of patients with chronic migraine surveyed had never tried preventive medications whereas 67% of those with episodic migraine had never tried preventive agents.[21] Data from the International Burden of Migraine Study found that 22% of patients with chronic migraine reported using preventive medications in the previous 4 weeks (antidepressants: 15%, antiepileptics: 4%, cardiovascular drugs: 7%, other medications: 14.8%).[22] In contrast, 9% of patients with episodic migraine in that study reported using preventive

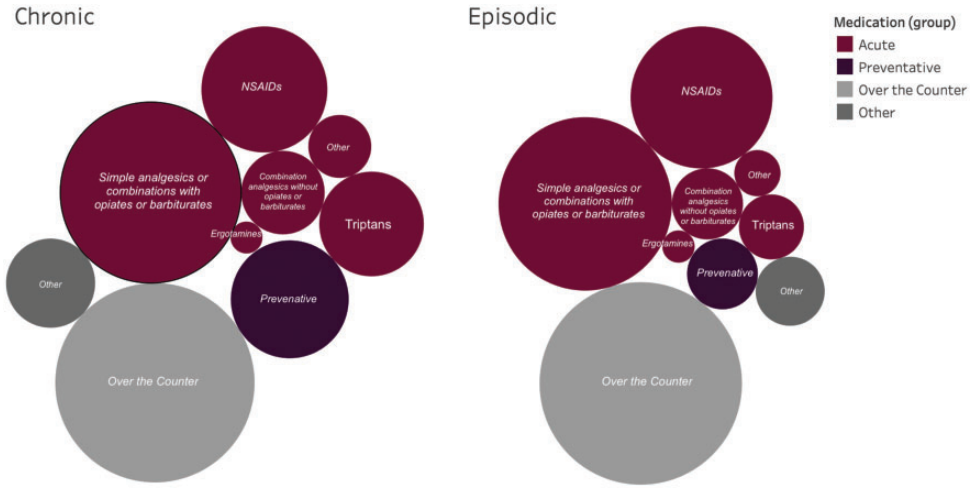

Figure 5. Medication use reported in Stoke et al. 2019.

medications in the previous 4 weeks (antidepressants: 4%, antiepileptics: 2%, cardiovascular drugs: 4%, other medications: 10%).[22] When compared with the acute medication use described in these two studies, it is clear that preventive medication is less frequently utilized among patients with both chronic and episodic migraine.

Regarding patient satisfaction with their primary migraine treatment, the Canadian Women and Migraine Survey reported that 37% of women currently taking medication for migraine were very satisfied, 46% were somewhat satisfied, 9% were somewhat unsatisfied, and 5% were very unsatisfied.[8] Another study utilizing CCHS data noted that individuals with migraines were 1.42 times more likely to use alternative medicine than individuals without migraines.[41] These findings regarding satisfaction with and choice of treatment, together with the varied use of triptans and infrequent use of preventive medications described in these studies, suggest that there may be an unmet need in the medical management of migraines in Canada.

Discussion

Migraines impose a substantial burden on both patients and the health care system in Canada, including a detrimental impact on patients' quality of life, ability to work and/or care for others, as well as increased HCRU and costs. Notably, the summarized evidence indicates that individuals with chronic migraine use more health care services and have poorer labor force outcomes than individuals with episodic migraine. These results are similar to observations in Europe, with a survey in five European countries finding significantly higher HRU and work productivity impairment among individuals with migraine.[52] Additionally, our review showed that prevalence estimates vary widely across Canada and by data source. However, a prevalence of comorbid mental health conditions among patients with migraine was commonly reported, highlighting a key challenge in devising effective treatment strategies. These studies found serious psychiatric symptoms and suicidal ideation occurring with comorbid migraine and mental health conditions. Beyond increasing comorbid occurrence, the multi-fold increase in the risk of suicide attempts based strictly on migraine diagnosis shows an urgent need to improve treatment strategies for this population.

The studies included in this review show a substantial decrease in HRQoL, particularly for patients with chronic migraine. Migraine has also been shown to have detrimental impacts on workforce productivity in Canada. Taken together, the included studies highlight a substantial burden of illness, with impacts ranging from missed work to unemployment, with the greatest impact seen in patients with comorbid mental health conditions. Comorbid mental health conditions have been observed in other regions, with a study in the US finding that depression and anxiety were the most commonly reported.[53] Importantly, the peak occurrence of migraine is also during prime working years, indicating a potentially larger impact than what is visible from the headline unemployment rate in Canada, which covers individuals over the age of 15 years. A similar impact on missed work has also been seen in the US and Europe, where migraine is the cause of an estimated 250,000,000 missed workdays every year.[54] Although the included studies noted negative impacts on labor force participation, such as employment rates and absenteeism, there was a lack of data regarding presenteeism. This is a key area for future research. Specifically, there is a need to understand the real-world impact of newer therapies such as CGPR monoclonal antibodies on employment rates, absenteeism,

and presenteeism among patients with migraine in Canada.

Additionally, we found increased HCRU among individuals with migraine compared with those who did not have migraine,[20] with the highest rates observed for chronic migraine.[21,22] Notably, one study reported a median of 24 GP visits over a 2-year period among people with migraine (12 GP visits per year).[50] In contrast, the Organisation for Economic Co-operation and Development (OECD) reported that the average Canadian had an estimated 7.2 physician visits per capita in 2008.[55] The costs associated with migraine are related to increased HCRU compared with the general population, with higher costs associated with chronic migraine. In the US, direct annual health care costs related to migraine have been estimated to reach CAD 17 billion.[56] Whereas the literature on direct costs is limited in Canada, these costs can be expected to be higher for people with migraine based on the increased HCRU, including additional resource use among patients with chronic migraines, with medications likely being the largest cost driver. The frequent health care interactions, including ED visits, experienced by these patients suggests that current long-term medical management and treatment strategies may not be effective.

Notably, our review included RWE studies that reported inconsistencies in how patients with migraine are managed in clinical practice. For example, a study among patients referred to a tertiary care pain clinic for migraine reported that under half of patients had not been prescribed a triptan whereas nearly three-quarters of patients were taking an opiate.[45] In the ED setting, an Ontario survey study found that 69% of ED physicians reported that fewer than half of patients with migraine had tried triptans, and approximately 66% of ED physicians reported that they did not use triptans in treating patients with migraine.[44]

The literature included in this review also reveals unmet needs in the management and treatment of migraine in Canada. The included studies highlighted that the proportion of patients taking OTC and prescription medications is variable, with patients often utilizing a variety of medications (different classes), and those with chronic migraine tend to have increased medication use compared with those who have episodic migraine. The review also found that effective acute medications (e.g., triptans) were underutilized among Canadian patients with migraine, despite strong recommendations for the use of triptans by the Canadian Headache Society. Although only two included studies examined the use of preventive medications, both reported that only a small number of patients had used preventive medications, indicating that this is an area for improving the treatment landscape of migraine in Canada. Until recently, onabotulinumtoxinA was the only approved treatment for the prevention of chronic migraine in the country. However, a novel class of medications, CGPR monoclonal antibodies, have recently received Canadian regulatory approval for episodic and chronic migraine prevention.[28]

In summary, the evidence demonstrates that the burden of disease of migraine, particularly chronic migraine, in Canada is substantial, leading to higher unemployment, lower quality of life, increased HCRU and costs, as well as variable medication use. Furthermore, these findings illustrate that despite the availability of effective treatment options, the underutilization of these therapies requires new approaches for the management of migraine.

In future research, further RWE (observational or retrospective) studies are needed to examine the burden of migraine to better understand the unmet needs and how new

treatments are utilized by the health care system and patients. Whereas this review identified several studies regarding migraine in Canada, most of these studies were secondary analyses of national, population-based surveys, such as the CCHS. Outside of self-reported survey data, there is limited evidence available in Canadian populations regarding the burden of disease of migraine, providing only a partial picture of Canadian care. RWE studies utilizing administrative health system data are imperative to provide a clearer picture of how patients with migraine in Canada are treated and how they interact with the health system. Additional research on the impact of CGPR monoclonal antibodies on comorbid mental health conditions, quality of life, reductions in the burden of disease, and the economic impact for patients with migraine is needed.

Strengths and limitations

This literature review provided a synopsis of the substantial burden of disease according to existing RWE studies of patients with migraine in Canada. Whereas this review involved a comprehensive search and screening process, some limitations should be considered. There may be selection bias because the title/abstract and full-text screening as well as data extraction processes were performed by a single reviewer, and quality appraisal was not conducted. There may be publication bias because only peer-reviewed, full-text publications were included (e.g., conference abstracts were excluded). Additionally, only studies published during the past 10 years and in the English language were considered for inclusion. Four studies had small sample sizes with fewer than 400 participants.[23,44,45,51] The large differences in sample size could have affected the overall interpretation of the studies. It should also be noted that several studies had the same data source (mainly the Canadian Community Health Survey), which may have resulted in redundancy of data among studies. Finally, synthesis of the findings was limited owing to substantial variation in study design, which is common in RWE reviews.

Conclusion

The burden of disease among patients with migraine in Canada is substantial. The findings of the current review demonstrate reduced quality of life, poorer labor force outcomes, and increased utilization of health care services and associated costs, especially among patients with chronic migraine in Canada. Paired with the underutilization of available migraine medications, particularly triptans, and the limited use of preventive medications, the findings of this review suggest that there is an important gap in the medical management of migraine in the country. Addressing this gap requires the development of more effective treatment strategies focused on improving patient outcomes and reducing HCRU. Future RWE studies using health system data are needed to better understand the epidemiology, treatment patterns, and HCRU among the large and diverse populations of Canada to inform and improve care for Canadians with migraine.

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Author contributions

EG: study design, literature screening, data extraction, results interpretation, manuscript

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Supplemental material

Supplemental material for this article is available online.

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