Received: 4 May 2023 | Accepted: 28 July 2023

DOI: 10.1111/head.14613

RESEARCH SUBMISSIONS

Trajectory of health care resources among adults stopping or reducing treatment frequency of botulinum toxin for chronic migraine treatment in Alberta, Canada

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Funding information
AbbVie Inc.

Abstract

Objective: Understand health resource, medication use, and cost of adults with chronic migraine who received guideline-recommended onabotulinumtoxinA (botulinum toxin) treatment frequency and then continued or reduced/stopped.

Background: Botulinum toxin may be a beneficial treatment for chronic migraine; the trajectory of health resources utilization among those with continued or reduced/stopped use is unclear.

Methods: A retrospective population-based cohort study utilizing administrative data from Alberta, Canada (2012–2020), was performed. A cohort of adults who received ≥5 botulinum toxin treatment cycles for chronic migraine over 18 months (6-month run-in; 1-year pre-index period) were grouped into those who (1) continued use (≥3 treatments/year), or (2) stopped or reduced use (stopped for 6 months then received 0 or 1–2 treatments/year, respectively) over a 1-year post-index period. Health resources and medication use were described, and pre–post costs were assessed. A second cohort that received ≥3 treatments/year immediately followed by 1 year of stopped or reduced use was considered in sensitivity analysis.

Results: Pre–post health resource, medication use, and costs were similar among those with continued use ($n = 3336$). Among those who stopped or reduced use ($n = 1099$; 756 stopped, 343 reduced), health resource, medication use, and costs were lower in the post- (total median per-person cost [IQR]: all-cause $4851 [$8090]; migraine-related $835 [$1915]) versus pre- (all-cause $6096 [$7207]; migraine-related $2995 [$1950]) index period (estimated cost ratios [95% CI]: total all-cause 0.86 [0.79, 0.95]; total migraine-related 0.44 [0.40, 0.48]). In the second cohort ($n = 3763$), return to

Abbreviations: AHCIP, Alberta Health Care Insurance Plan; CI, confidence intervals; CIHI, Canadian Institute for Health Information; CM, chronic migraine; DAD, Discharge Abstract Database; ED, emergency department; GEE, generalized estimating equations; ICD-10-CA, International Classification of Disease – Version 10 – Canadian Enhancement; ICD-9-CM, International Classification of Disease – Version 9 – Clinical Modification; IQR, interquartile ranges; NACRS, National Ambulatory Care Reporting System; PIN, Pharmaceutical Information Network; RIW, resource intensity weight; SD, standard deviations.

continued use (≥3 treatments/year) occurred in up to 70.4% in those with reduced use.

Conclusions: Of adults treated with botulinum toxin for chronic migraine, 75.2% had continued use, stable health resource and medication use, and costs over a 2 year period. In those that stopped/reduced use, the observed lower health resource and migraine medication use may indicate improved symptom control, but the resumption of guideline-recommended treatment intervals after reduced use was common.

KEYWORDS
administrative data, botulinum toxin, chronic migraine, onabotulinumtoxinA, retrospective

BACKGROUND

Chronic migraine (CM) imposes a significant burden of disease in terms of disability, health-related quality of life, comorbidities, use of health care resources, and economic impact on the health care system.[1–3] OnabotulinumtoxinA (botulinum toxin) is approved for prophylactic treatment of CM among adults, with demonstrated safety and efficacy.[4] While the Phase III Research Evaluating Migraine Prophylaxis Therapy protocol and the European Headache Federation guidelines recommend botulinum toxin be administered every 3 months among those that respond (defined as ≥30% reduction in headache days per month after two treatment cycles),[5,6] optimal duration of treatment is not well known. Among those that respond to botulinum toxin treatment for CM, it is recommended that treatment be stopped in those who become refractory (negative stopping); some recommend stopping in those whose condition either converts to episodic migraine or reduces to less than ten headache days per month for three consecutive months (positive stopping).[5,7] Others have recommended that increasing the amount of time between treatments may be a responsible strategy among people who have been stable responders to botulinum toxin treatment for at least 1 year[8]; however, it is possible that stopping an effective medication may lead to worsening symptoms and attendant consequences. Given that the consequences of poorly controlled migraine symptoms may lead to increased health care resource use, and that botulinum toxin treatment is costly, understanding health care resource use and associated costs in adults with continued use, as well as those who stop or reduce treatment frequency, is of importance.

The objectives of this study were to (1) describe the characteristics, health care resource utilization, and migraine medication use of adults with CM who were concordant with guideline-recommended botulinum toxin treatment frequency and either continued, or reduced or stopped treatment; and (2) assess the trajectory of total all-cause and migraine-related health care resources and costs among those with continued use, and those who reduced or stopped treatment. The resumption of guideline-recommended treatment frequency was also investigated among those who stopped or reduced use. It was hypothesized that among adults with CM who were concordant with guideline-recommended botulinum toxin treatment frequency, healthcare costs would not change among those that continued use and would be higher among those who reduced or stopped treatment. This study utilized population-based administrative health data in Alberta, Canada, where botulinum toxin treatment is available at three-month intervals to adults aged 18 to 65 years of age who meet the criteria for CM before initial treatment; this is a health care system where patients and/or providers determine botulinum toxin stopping decisions.

METHODS

This retrospective population-based cohort study is reported according to STROBE guidelines.[9] The institutional review board at the University of Alberta (Pro00083495) approved this study. This is a study of administrative data without any intervention; no participants were placed at risk as a result of this study, and a waiver of consent was approved by the institutional review board.

Data sources

Administrative data from the period between April 1, 2012, and March 31, 2020, were obtained from several sources and linked to the Population Registry which contains demographic information for all Albertans with Alberta Health Care Insurance Plan (AHCIP) coverage, in which over 99% participate.[10] Hospital admissions were obtained from the Discharge Abstract Database (DAD) that contains primary and secondary diagnostic codes using the International Classification of Disease, Tenth Revision, Canadian Enhancement (ICD-10-CA). Ambulatory care visits were obtained from the National Ambulatory Care Reporting System (NACRS), which also contains primary and secondary ICD-10-CA diagnostic codes. Data from DAD and NACRS are recorded by health information management coding professionals who perform regular data quality reviews and assurance. Practitioner claims contain up to 3 ICD, Ninth Revision, Clinical Modification (ICD-9-CM; Alberta specific) diagnostic codes and physician specialty; the face validity of diagnostic codes has

been found to be substantially high.[11] The Pharmaceutical Information Network (PIN) contains information on dispensed prescription medications from community pharmacies; this is a primary dataset for community drug utilization reviews for quality improvement, research, and evaluations within Alberta Health Services. Additionally, all data are submitted to the Canadian Institute for Health Information (CIHI) who ensure the quality of the information within their data holdings.

Cohort selection

Adult (≥18-years of age) residents of Alberta who received ≥5 botulinum toxin treatments within an 18-month period (6-month run-in period followed by a 1-year pre-index observation period) for the treatment of CM (identified by the Alberta Health Services code 13.59O that is used for the injection of botulinum toxin for the prophylaxis of CM among eligible adults aged 18 to 65 years) were identified between 2014 and 2020; index date was the first date after the 18-month period. Individuals within this cohort were then grouped according to those who continued use (≥3 treatments/year) or stopped for a 6-month period and then either did not resume treatment (stopped; 0 treatments/year) or resumed at a reduced frequency (1–2 treatments/year) over a 1-year post-index observation period. Additional criteria included having AHCIP coverage for ≥2 years before the index date, and ≥1 year of coverage after the index date for those who continued use and ≥2 years for those who stopped or reduced treatment frequency. See Figure S1 for study design schematic.

A second cohort was created to determine resumption of guideline-recommended treatment frequency (≥3 treatments/year) among people with a period of stopped/reduced use. Adult residents of Alberta who received ≥3 botulinum toxin treatments within a 1-year period for the treatment of CM, immediately followed by 1 year of stopped or reduced treatment frequency (≤2 botulinum toxin treatment cycles), were identified between 2014 and 2020. Additional eligibility criteria included having AHCIP coverage that spanned the 3-year observation period. See Figure S2A for study design schematic.

Study measures

Demographic characteristics are presented overall and grouped according to those who continued use and those who stopped or reduced use. Age, sex, urban or rural residence, and socioeconomic status (social and material deprivation indices) were determined on the index date.[12,13] A Charlson Comorbidity Index score was determined during the 2-year pre-index period using ICD-10 and ICD-9 codes of 17 different specific medical conditions, which were weighted according to their potential for influencing mortality, to calculate the score[14]; average scores were presented, and categorized as 0 (no comorbid condition), 1–2 (mild comorbidity), 3–4 (moderate comorbidity), and ≥5 (severe comorbidity). The yearly average number of botulinum toxin treatments for CM was determined over the 18-month pre-index period.

Health care resource utilization and medication use were determined during the 1-year pre- and post-index observation periods. Health care resource utilization included all-cause and migraine-related (ICD-10 G43 from the most responsible diagnostic field; ICD-9 346 or 13.59O from any diagnostic field) hospitalizations, emergent (i.e., emergency department [ED]) and non-emergent ambulatory care visits, and physician visits. All-cause and migraine-related outpatient prescription medication dispensations were reported; migraine-related medications were reported overall and by type (i.e., acute and preventive including or not including CM-treatment-related botulinum toxin dispensations). Acute migraine medications included antiemetics, ergots, nonsteroidal anti-inflammatory drugs, triptans, and opioids, while preventative migraine medications included antidepressants, antiseizure, antihistamines, antihypertensives, and calcium antagonists; specific drug names have been previously listed.[15] Calcitonin gene-related peptide antibodies (erenumab and galcanezumab) were not available for the entirety of the observation period, and therefore are not included.

Hospitalization and ambulatory care visit costs were estimated by multiplying the associated resource intensity weight (RIW) with the CIHI standard cost for Alberta.[16] RIW is a measure to estimate hospital and ambulatory resource use and represents the relative value of resources that a given patient, contingent on diagnostic case-mix, would be expected to consume relative to a standard patient, and CIHI provides standardized average costs incurred from a standard visit. Physician visits were based on the amount paid. Drug costs were calculated using the drug product identification number and quantity dispensed, combined with the drug list price (from Alberta Blue Cross); a 3% per unit mark-up and a $12.15 dispensing fee were included. Botulinum toxin treatment-related costs for CM included the drug cost, the injection procedure fee, and the physician consultation fee (that can be claimed by a physician in addition to the injection procedure fee). Total all-cause and migraine-related costs included hospitalizations, ambulatory care visits (emergent and non-emergent), physician visits, and drug costs. Costs were adjusted to 2020 using the Consumer Price Index where appropriate and reported in Canadian dollars.

Among the second cohort of adults (received ≥3 treatments/year immediately followed by 1 year with ≤2 treatments), the proportion of those who resumed guideline-recommended treatment frequency in the following 1-year period (received ≥3 treatments/year) was quantified.

Statistical analyses

Descriptive statistics are reported as counts and percentages, and means and standard deviations (SDs) or medians and interquartile ranges (IQRs), where appropriate. An a priori cost analysis was conducted, and a two-sided significance level of 0.05 was applied for all statistical tests. Marginal models using generalized estimating

equations (GEE) were used to provide population-averaged estimates for pre–post differences (within-person comparisons) in health care costs, while comparing to group differences (between-person comparisons) and accounting for the correlation between pre- and post-index costs within people. As cost outcomes were non-negative highly skewed continuous data, GEE models using the log link function and gamma distribution were conducted. An exchangeable covariance structure was employed because intra-person pre–post outcomes were correlated. By-time interaction terms with the study group were included to evaluate differences in pre–post changes in health care resource costs between the continued use and stopped or reduced use groups.

Comparative results are presented as cost ratios with 95% confidence intervals (CIs), representing the study group's expected pre–post change in the mean health care costs with a multiplicative scale. Unadjusted estimates were computed from the GEE models with the main effects of time (post- versus pre-index) and the study group, and the interaction effect between time and the study group. Adjusted estimates were calculated with additional adjustments for differences between the study group that were associated with the cost outcomes, including age, sex, location of residence, and the Charlson Comorbidity Index score.

The data analysis represents the primary and a priori examination of the extracted data. Given that cohort size was based on the available population-based administrative data in Alberta, no statistical power calculation was conducted prior to the study. Minimal missing data were observed and reported. A two-sided significance level of 0.05 was applied for all statistical tests. Statistical Analysis Software, version 9.4 (SAS Institute; Cary North Carolina), was used for all statistical analyses and modeling.

RESULTS

Cohort selection

Among 17,102 adults who had ≥1 botulinum toxin treatment for CM between 2014 and 2020, 4435 met inclusion criteria for the main cohort, of which 3336 (75.2%) were included in the continued use group, and 1099 (24.8%) in the stopped or reduced use group (stopped use: 17.0%; reduced use 7.7%) (Figure 1). A total of 3763 adults met inclusion criteria for the second cohort, who received ≥3 treatments/year immediately followed by 1 year of ≤2 treatments (Figure S2B).

Characteristics

Overall, the mean age was 46 (SD 11) years, 89.7% were female, and the vast majority lived in urban areas (89.8%; Table 1). Socioeconomic status

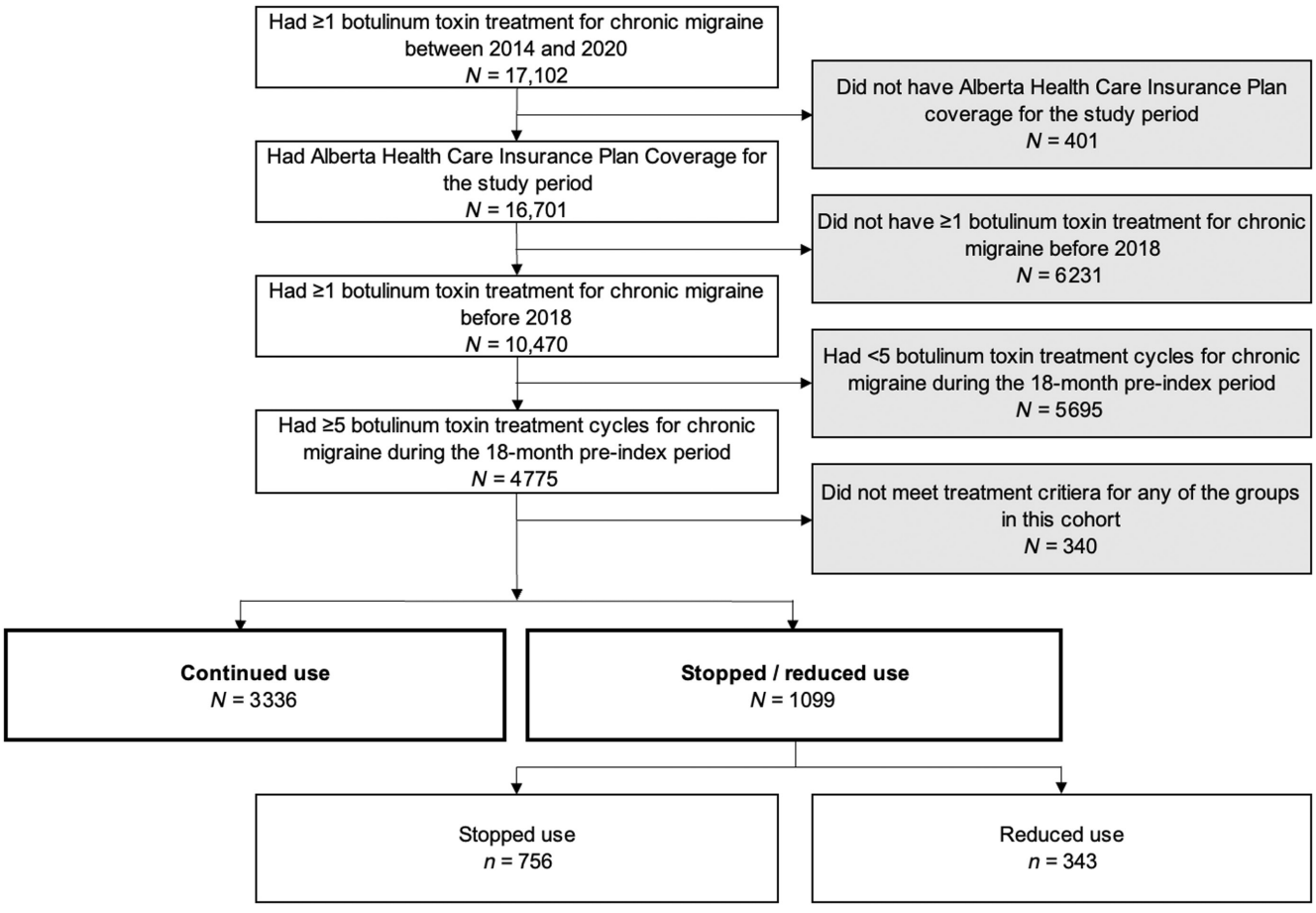

FIGURE 1 Cohort selection flow diagram. Years shown are fiscal years (April 1 to March 31).

TABLE 1 Baseline characteristics.

Characteristics	All (*N* = 4435)	Continued use (*N* = 3336)	Stopped or reduced use		
			Stopped or reduced (*N* = 1099)	Stopped (*N* = 756)	Reduced (*N* = 343)
Demographic					
Age (years)					
Mean (SD)	46 (11)	46 (10)	45 (12)	46 (12)	44 (11)
Median (IQR)	47 (16)	47 (15)	45 (19)	46 (20)	44 (17)
Sex, *n* (%)					
Female	3978 (89.7)	3030 (90.8)	948 (86.3)	639 (84.5)	309 (90.1)
Male	457 (10.3)	306 (9.2)	151 (13.7)	117 (15.5)	34 (9.9)
Residence					
Urban	3983 (89.8)	3009 (90.2)	974 (88.6)	671 (88.8)	303 (88.3)
Rural	452 (10.2)	327 (9.8)	125 (11.4)	85 (11.2)	40 (11.7)
Socioeconomic					
Material deprivation, *n* (%)					
1 (most well off)	1016 (22.9)	787 (23.6)	229 (20.8)	161 (21.3)	68 (19.8)
2	998 (22.5)	768 (23.0)	230 (20.9)	152 (20.1)	78 (22.7)
3	871 (19.6)	644 (19.3)	227 (20.7)	160 (21.2)	67 (19.5)
4	764 (17.2)	562 (16.9)	202 (18.4)	143 (18.9)	59 (17.2)
5 (most deprived)	630 (14.2)	469 (14.1)	161 (14.7)	107 (14.2)	54 (15.7)
Missing	156 (3.5)	106 (3.2)	50 (4.6)	33 (4.4)	17 (5.0)
Social deprivation, *n* (%)					
1 (most well off)	898 (20.3)	689 (20.7)	209 (19.0)	143 (18.9)	66 (19.2)
2	773 (17.4)	591 (17.7)	182 (16.6)	120 (15.9)	62 (18.1)
3	847 (19.1)	642 (19.2)	205 (18.7)	140 (18.5)	65 (19.0)
4	890 (20.1)	666 (20.0)	224 (20.4)	157 (20.8)	67 (19.5)
5 (most deprived)	871 (19.6)	642 (19.2)	229 (20.8)	163 (21.6)	66 (19.2)
Missing	156 (3.5)	106 (3.2)	50 (4.6)	33 (4.4)	17 (5.0)
Charlson Comorbidity Index					
Overall score					
Mean (SD)	0.4 (0.9)	0.4 (1.0)	0.4 (0.9)	0.4 (1.0)	0.3 (0.8)
Median (IQR)	0 (0)	0 (1)	0 (0)	0 (0)	0 (0)
Category, *n* (%)					
0; no comorbidity	3339 (75.3)	2495 (74.8)	844 (76.8)	575 (76.1)	269 (78.4)
1–2; mild comorbidity	951 (21.4)	730 (21.9)	221 (20.1)	155 (20.5)	66 (19.2)
3–4; moderate comorbidity	110 (2.5)	84 (2.5)	<30 (N/A)	<20 (N/A)	<10 (N/A)
≥5; severe comorbidity	35 (0.8)	27 (0.8)	<10 (N/A)	<10 (N/A)	<10 (N/A)
Yearly number of botulinum toxin treatments for CM during the 18 month pre-index period					
Mean (SD)	3.6 (0.5)	3.6 (0.5)	3.5 (0.5)	3.6 (0.5)	3.4 (0.5)
Median (IQR)	3.6 (0.6)	3.6 (0.6)	3.5 (0.6)	3.6 (0.6)	3.4 (0.6)

Note: In accordance with Alberta Health Services privacy standards, results containing 1–9 individuals were presented as <10 and associated results suppressed to prevent calculation of the exact number of individuals less than 10.

Abbreviations: CM, chronic migraine; IQR, interquartile range; N/A, not applicable; SD, standard deviation.

was evenly distributed among the quintiles, except for those most materially deprived, which was relatively low (14.2% overall; Table 1). The average Charlson Comorbidity Index was 0.4 (SD 0.9) overall, with 75.3% having a Charlson Comorbidity Index of zero (Table 1).

Health care resource utilization

Health care resource utilization was similar between the pre–post periods among those who continued use (Table 2). Those

who stopped or reduced treatment frequency were more likely to have had a lower proportion with ≥1 health care visit in the 1-year post-index observation period (≤2 botulinum toxin treatments/year) versus the pre-index period (≥3 botulinum toxin treatments/year) for ED visits (all-cause: 39.2% vs. 43.0%; migraine-related: 5.6% vs. 9.5%), ambulatory care visits (all-cause: 59.3% vs. 64.5%; migraine-related: 4.6% vs. 10.6%), and physician visits (all-cause: 96.4% vs. 100%; migraine-related: 64.4% vs. 100%); all-cause hospitalizations were higher in the post- versus pre-index period (13.0% vs. 8.7%; Table 2). Those who stopped treatment consistently had the largest differences in all-cause and migraine-related ED visits, non-emergent ambulatory visits, and physician visits (lower in the post- compared with the pre-index period; Table 2).

TABLE 2 Health care resource utilization and medication use during the 1-year pre-index and post-index observation periods.

	Continued use		Stopped or reduced use					
	(*N* = 3336)		Stopped or reduced (*N* = 1099)		Stopped (*N* = 756)		Reduced (*N* = 343)	
Treatments/year	≥3	≥3	≥3	≤2	≥3	0	≥3	1–2
Time period	*Pre-index*	*Post-index*	*Pre-index*	*Post-index*	*Pre-index*	*Post-index*	*Pre-index*	*Post-index*
Health care resource utilization								
Had ≥1 encounter, *n* (%)								
Hospitalization								
All-cause	265 (7.9)	261 (7.8)	96 (8.7)	143 (13.0)	67 (8.9)	95 (12.6)	29 (8.5)	48 (14.0)
Migraine-related	<10 (N/A)	<10 (N/A)	<10 (N/A)	<10 (N/A)	<10 (N/A)	<10 (N/A)	<10 (N/A)	0 (0)
Emergency department visit								
All-cause	1192 (35.7)	1175 (35.2)	472 (43.0)	431 (39.2)	322 (42.6)	284 (37.6)	150 (43.7)	147 (42.9)
Migraine-related	201 (6.0)	181 (5.4)	104 (9.5)	61 (5.6)	82 (10.9)	45 (6.0)	22 (6.4)	16 (4.7)
Ambulatory care visit								
All-cause	2058 (61.7)	1889 (56.6)	709 (64.5)	652 (59.3)	481 (63.6)	434 (57.4)	228 (66.5)	218 (63.6)
Migraine-related	305 (9.1)	240 (7.2)	116 (10.6)	50 (4.6)	85 (11.2)	34 (4.5)	31 (9.0)	16 (4.7)
Physician visits								
All-cause	3336 (100)	3336 (100)	1099 (100)	1059 (96.4)	756 (100)	716 (94.7)	343 (100)	343 (100)
Migraine-related	3336 (100)	3336 (100)	1099 (100)	708 (64.4)	756 (100)	365 (48.3)	343 (100)	343 (100)
Outpatient medication dispensations								
Had ≥1 dispensation, *n* (%)								
All-cause	3328 (99.8)	3328 (99.8)	1096 (99.7)	1045 (95.1)	754 (99.7)	706 (93.4)	342 (99.7)	339 (98.8)
Migraine-related								
Overall								
Including botulinum toxin	3260 (97.7)	3261 (97.8)	1068 (97.2)	922 (83.9)	733 (97.0)	590 (78.0)	335 (97.7)	332 (96.8)
Excluding botulinum toxin	2825 (84.7)	2818 (84.5)	904 (82.3)	840 (76.4)	630 (83.3)	573 (75.8)	274 (79.9)	267 (77.8)
Acute								
Overall	2563 (76.8)	2544 (76.3)	839 (76.3)	743 (67.6)	581 (76.9)	505 (66.8)	258 (75.2)	238 (69.4)
Prophylactic								
Including botulinum toxin	3170 (95.0)	3179 (95.3)	1035 (94.2)	709 (64.5)	707 (93.5)	388 (51.3)	328 (95.6)	321 (93.6)
Excluding botulinum toxin	1768 (53.0)	1710 (51.3)	582 (53.0)	486 (44.2)	427 (56.5)	329 (43.5)	155 (45.2)	157 (45.8)

Note: In accordance with Alberta Health Services privacy standards, results containing 1–9 individuals were presented as <10.
Abbreviation: N/A, not applicable.

Medication dispensation

All-cause and migraine-related outpatient medication dispensations were similar between the 1-year pre- and post-index periods among those who continued use (Table 2). Those who stopped or reduced treatment frequency were more likely to have had a lower proportion with ≥1 all-cause (95.1% vs. 99.7%) or migraine-related medication dispensation overall (including botulinum toxin: 83.9% vs. 97.2%; excluding botulinum toxin: 76.4% vs. 82.3%), as well as by classification type (acute: 67.6% vs. 76.3%; prophylactics including botulinum toxin: 64.5% vs. 94.2%, and not including botulinum toxin: 44.2% vs. 53.0%) in the 1-year post-index period versus the pre-index period (Table 2). Individuals who stopped treatment consistently had the largest differences in the proportion who received ≥1 all-cause or migraine-related medication dispensation (lower in the post-index compared with pre-index period; Table 2). Among those who reduced use, oral prophylactic migraine-related medication use was similar between the 1-year pre- (45.2%) and post-index (45.8%) periods (Table 2).

Health care costs

Among those who continued use, pre–post costs were not different across measured categories, with the exception of a 5.0% reduction in total migraine-related costs (estimated cost ratio: 0.95; 95% CI 0.94, 0.96; Table 3). Among those who stopped or reduced use overall, total all-cause costs were 14.0% lower (0.86; 95% CI 0.79, 0.95), and total migraine-related costs were 56.0% lower (0.44; 95% CI 0.40, 0.48) in the 1-year post- versus pre-index observation period; migraine-related costs were not different when CM-related botulinum toxin costs (drug cost, the injection procedure fee, and the physician consultation fee) were removed (0.89; 95% CI 0.80, 1.00) compared with the 1-year pre-index period; the cost of acute migraine-related prescription drugs was not different in the post-index observation period versus the pre-index period (0.90; 95% CI 0.76, 1.08) (Table 3). Table S1 shows health care costs during the 1-year pre- and post-index observation periods, and Table S2 shows unadjusted cost ratios.

Among those who stopped treatment, all measured costs were significantly lower in the 1-year post-index observation period compared to the pre-index year (Table 3). Total all-cause costs were 11.0% lower (0.89; 95% CI 0.79, 0.99) and total all-cause migraine-related costs were 61.0% lower (0.39; 95% CI 0.34, 0.45) in the 1-year post-index observational period (versus the pre-index year); total migraine-related costs remained lower during the 1-year post-index observation period when CM-related botulinum toxin costs were removed (0.78; 95% CI 0.68, 0.89) (Table 3). Acute migraine-related drug costs were 20.0% lower (0.80; 95% CI 0.70, 0.91) in the 1-year post-index observation period compared with the pre-index year (Table 3). Among those who reduced treatment frequency, total all-cause costs were not different in the 1-year post-index observation period compared with the pre-index year (1.01; 95% CI 0.90, 1.14) (Table 3). Total migraine-related costs were 35.0% lower (0.65; 95% CI 0.62, 0.69) in the 1-year post-index observation period, but were not different when CM-related botulinum toxin costs were removed (0.98; 95% CI 0.88, 1.09) compared with the 1-year pre-index period (Table 3). Acute migraine-related prescription drug costs were not different in the observation period versus the pre-index period (0.99; 95% CI 0.78, 1.25) (Table 3).

Resumption of botulinum toxin treatment

Overall, among the 3763 adults with CM who received guideline-concordant botulinum toxin treatments for ≥1 year, 34.1% ($n=1284$) resumed this treatment frequency after ≥1 year of stopped or reduced treatment frequency (Table 4). Specifically, 3.6% ($n=57$) of those who stopped use ($n=1595$), 16.9% ($n=95$) of those who reduced use to 1 treatment ($n=561$), and 70.4% ($n=1132$) of those who reduced use to 2 treatments ($n=1607$) over a 1-year period resumed guideline-recommended botulinum toxin treatment frequency for at least 1 year (Table 4).

TABLE 3 Adjusted per-person health care cost ratios (95% confidence interval) compared between the 1-year pre-index and post-index observation periods.

		Stopped or reduced use		
	Continued use	Stopped or reduced	Stopped	Reduced
All-cause				
Total cost	1.02 [0.98; 1.06]	**0.86 [0.79; 0.95]**	**0.89 [0.79; 0.99]**	1.01 [0.90; 1.14]
Migraine-related				
Total cost	**0.95 [0.94; 0.96]**	**0.44 [0.40; 0.48]**	**0.39 [0.34; 0.45]**	**0.65 [0.62; 0.69]**
Excluding CM-related botulinum toxin treatment costs[a]	0.99 [0.96; 1.01]	0.89 [0.80; 1.00]	**0.78 [0.68; 0.89]**	0.98 [0.88; 1.09]
Acute migraine-related drug cost	0.97 [0.93; 1.02]	0.90 [0.76; 1.08]	**0.80 [0.70; 0.91]**	0.99 [0.78; 1.25]

Note: Cost ratio is a non-intercept parameter quantifying the ratio between natural logarithms of cost that are exponentiated. Adjusted for age, location of residence, and Charlson Comorbidity Index score. Bolded numbers indicate significance ($p<0.05$).

Abbreviation: CM, chronic migraine.

[a]CM-related botulinum toxin treatment costs included the drug cost, the injection procedure fee, and the physician consultation fee.

TABLE 4 Resumption of guideline-recommended botulinum toxin treatment frequency among those who stopped or reduced use in the second cohort.

	Stopped or reduced use			
			Reduced ($N = 2168$)	
	Stopped or reduced ($N = 3763$)	Stopped ($N = 1595$)	1 treatment ($N = 561$)	2 treatments ($N = 1607$)
Resumed ≥3 treatments/year of botulinum toxin for the treatment of chronic migraine, *n* (%)	1284 (34.1)	57 (3.6)	95 (16.9)	1132 (70.4)

DISCUSSION

In this population-based retrospective, observational cohort study of adults with CM in Alberta who were concordant with guideline-recommended botulinum toxin treatment intervals for CM (for at least 18 months), the trajectory of health care resources was determined in those who continued this treatment frequency and those who stopped or reduced use. Patient characteristics were consistent with other reports; individuals were middle aged and the vast majority were females.[17–23] Results of this study showed that in a health care system where patients and/or providers determined botulinum toxin treatment decisions, the majority of adults treated with botulinum toxin for CM maintained the guideline-recommended treatment interval long-term (75.2% received ≥3 treatments/year for ≥2 years); health care resource utilization, medication use, and costs were largely consistent among these individuals. Among the 24.8% of adults who stopped or reduced use of botulinum toxin treatment, we observed lower health care resource utilization (with the exception of all-cause hospitalizations), medication use, and associated costs; those who stopped treatment consistently showed the largest differences (lower in the post- versus pre-index period). While the majority of those who stopped botulinum toxin treatment did not resume guideline-recommended treatment intervals after a 1-year period, up to 70.4% of those who reduced use returned to 3 or more treatments/year.

Other real-world studies have shown sustained long-term improvements in symptoms, and reductions in health care resource utilization and acute migraine-related medication use among adults with CM who responded to botulinum toxin treatment and received treatment cycles every 3 months compared with baseline.[17–21] For example, Kollewe et al. evaluated adults with CM who initiated botulinum toxin and continued to receive treatment every 3 months for 2 years.[21] A significant improvement in patient-reported number of headache days per month, acute pain medication use, quality of life, and health care resource utilization occurred, starting after the second treatment and was maintained throughout the treatment period compared with beforehand. We found that health care resource utilization and medication use, including acute and prophylactic migraine medication, was consistent among those who continued guideline-recommended botulinum toxin treatment frequency, and speculate that these individuals had a stable symptom burden that was sustained.

While botulinum toxin for the treatment of CM has demonstrated safety and efficacy, the optimal duration of treatment is not well known. Recent real-world studies have investigated long-term outcomes when positive stopping criteria or increasing the amount of time between botulinum toxin treatment was employed.[19,22,23] Cernuda-Morollón et al. increased the amount of time between botulinum toxin treatment cycles among adults with CM who had responded to botulinum toxin and received treatment every 3 months for a 1-year period (81.8% of the starting cohort).[23] They found that among 108 adults, 3.7% were able to stop treatment because of a sustained response and 41.7% maintained an increased amount of time between treatment cycles (every 4–6 months); 45.4% experienced symptom worsening and returned to treatment every 3 months, and 9.3% stopped due to the development of treatment resistance.[23] Andreou et al. prospectively followed 200 adults with CM, of whom 127 responded to the first two treatments of botulinum toxin.[19] Among responders, 42.5% converted to episodic migraine and were willing to stop or reduce treatment frequency; of these, 9.3% were able to discontinue treatment after maintaining a sustained response, 70.3% maintained an increased amount of time between treatment cycles (every 4–8 months), and 20.3% relapsed to CM after 6 months and returned to continued treatment. Similarly, Ahmed et al. prospectively followed 655 patients for at least 2 years, of whom 380 (58.0%) responded to the first two treatments of botulinum toxin and 353 remained in the study.[22] Among these individuals, 49.0% converted to episodic migraine and stopped treatment; 112 maintained a sustained response and 61 relapsed after an average of 9 months and returned to treatment. Over the study period, 7.9% stopped due to the development of treatment resistance. Collectively, these studies show that just under half of adults with CM who respond to the initiation of botulinum toxin treatment achieve positive stopping criteria or conditions for extending the time between treatments, but the length of response varies and return to continued treatment is common.

While we did not have patient-level data on migraine frequency, symptoms, or reasons for the treatment change among those who stopped or reduced use of botulinum toxin, a plausible hypothesis for the observed reduction in health care resource utilization, medication use, and cost is that they had improved migraine symptom control and health status. Consistent with this explanation is the observed reduction in acute and prophylactic migraine medication use in the follow-up period. It is also possible that individuals who

stopped use developed treatment resistance and found no other viable treatment options; they may have reduced their health care resource utilization and migraine medication use of their own accord, but continued to experience significant symptom burden; however, this may be less likely as the development of treatment resistance is not common,[22,23] and there were no observed changes in other use of health care resources that may be associated with this (such as migraine-related ED visits).

This study has several important strengths, including the large size and population-based design; however, this study is also subject to a number of limitations that should be taken into consideration when interpreting the results. Retrospective administrative claims-based studies use administrative data as opposed to medical records, and therefore there is a potential for misclassification of the study groups or measures. With that said, the Health Service code 13.59O is specific for the injection of botulinum toxin for the prophylaxis of CM headaches for eligible adults 18–65 years of age. This study cannot account for the possible changes in the natural history of CM, as well as the reasons for continued use, stopped, or reduced use of botulinum toxin. The PIN database only provides information on prescription medication dispensations from community pharmacies, and therefore may not represent actual medication uptake by individuals. Additionally, it is not known whether oral migraine-related medications were taken specifically for migraine or other conditions such as arthritis, depression, hypertension, or epilepsy. Use of over-the-counter medications, drug samples, and non-pharmacotherapy self-management techniques are not captured within provincial administrative data, and therefore not reported. Generalization of findings should be considered within the Alberta context, and similar health care and medication insurance systems.

CONCLUSIONS

In a health care system where patients and/or providers determined botulinum toxin treatment decisions for CM, continued use of guideline-recommended botulinum toxin treatment frequency was associated with stable health care resource utilization, medication use, and costs over a 2 year period. Stopping or reducing use of botulinum toxin was associated with lower health care resource use and migraine-related medication use, suggesting CM symptoms were reduced; the patient or provider's decision to stop or reduce use may be in keeping with appropriate symptom management. Most patients who stopped treatment did not resume, but up to 70.4% of those with reduced use returned to guideline-recommended treatment intervals after 1 year. Findings highlight the importance of closely monitoring symptoms in these individuals and providing readily available access to botulinum toxin treatment, as drug-related extended relief from symptoms appears temporary for most. Future population-based real-world evidence studies that consider emerging treatments for CM as they become available, and patient level data on CM symptoms from electronic medical records, are needed to confirm or refute our proposed explanation for the reduced health care utilization and medication use after stopping botulinum toxin.

AUTHOR CONTRIBUTIONS

Conception and design: Huong Luu, Karen J. B. Martins, Khanh Vu, Alexis Guigue, Kai On Wong, and Scott W. Klarenbach. *Acquisition of data*: Huong Luu. *Analysis and interpretation of data*: Huong Luu and Khanh Vu contributed to analysis; all authors contributed to interpretation of data. *Drafting the manuscript*: Karen J. B. Martins prepared the initial manuscript. *Revising it for intellectual content*: All authors. *Final approval of the completed manuscript*: All authors.

ACKNOWLEDGMENTS

This study is based in part on anonymized raw data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta/Alberta Health nor Alberta Health Services express any opinion in relation to this study. SK was supported by the Kidney Health Research Chair and the Division of Nephrology at the University of Alberta.

FUNDING INFORMATION

This research study was funded by AbbVie Inc. to Lawrence Richer. The funders had no role in the study design, analysis, interpretation of the data, drafting of the manuscript, or in the decision to submit for publication. The funders had the right to comment on the manuscript prior to submission, but the final decision regarding content and submission of the manuscript remained with Lawrence Richer and Scott W. Klarenbach.

CONFLICT OF INTEREST STATEMENT

The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: **Lawrence Richer, Huong Luu, Karen J. B. Martins, Khanh Vu, Phuong Uyen Nguyen, Tyler Williamson,** and **Scott W. Klarenbach** are members (**Kai On Wong** and **Alexis Guigue** were previous members) of the Alberta Real World Evidence Consortium, an academic entity at the University of Alberta and University of Calgary that conducts research including investigator-initiated industry-funded studies. **Thilinie Rajapakse** is an assistant professor at the University of Alberta, received no research or direct funding for this study; they have received an advisory board honorarium from Teva Pharmaceuticals. No other conflict of interest has been declared. All authors of this study had complete autonomy over the content and submission of the manuscript, as well as the design and execution of the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Richer L, Luu H, Martins KJB, et al. Trajectory of health care resources among adults stopping or reducing treatment frequency of botulinum toxin for chronic migraine treatment in Alberta, Canada. *Headache*. 2023;63:1285-1294. doi:10.1111/head.14613