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Risk of long-term benzodiazepine and Z-drug use following the first prescription among community-dwelling adults with anxiety/mood and sleep disorders: a retrospective cohort study

Jaden Brandt,[1] Donica Janzen,[1] Silvia Alessi-Severini,[1] Alexander Singer,[2] Dan Chateau,[3] Murray Enns,[4] Christine Leong [1,4]

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[1]College of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada
[2]Family Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[3]Manitoba Centre for Health Policy, Winnipeg, Manitoba, Canada
[4]Psychiatry, Univeristy of Manitoba, Winnipeg, Manitoba, Canada

Correspondence to
Dr Christine Leong;
christine.leong@umanitoba.ca

ABSTRACT

Objective To measure the incidence of long-term benzodiazepine receptor agonist (BZRA) use among individuals with anxiety, mood and/or sleep disorders. To identify factors associated with long-term use following the first prescription.

Methods This was a population-based retrospective cohort study using administrative databases in Manitoba, Canada. Individuals with anxiety/mood or sleep disorder who received their first BZRA between 1 April 2001 and 31 March 2015 were included. Long-term use was defined as ≥180 days. Logistic regression modelling was used to examine predictors of long-term use.

Results Among 206 933 individuals included, long-term BZRA use in the first episode of use was 4.5% (≥180 days) following their first prescription. Factors associated with ≥180 days of use included male sex (adjusted OR (aOR) 1.33, 95% CI 1.27 to 1.39), age ≥65 (aOR 5.15, 95% CI 4.81 to 5.52), income assistance (aOR 1.68, 95% CI 1.55 to 1.81), previous non-BZRA psychotropic (aOR 1.93, 95% CI 1.83 to 2.02) or opioid use (aOR 1.16, 95% CI 1.11 to 1.22), high comorbidity (aOR 1.43, 95% CI 1.32 to 1.55), high healthcare use (aOR 1.46, 95% CI 1.33 to 1.60) and psychiatrist prescriber (aOR 2.11, 95% CI 1.93 to 2.32).

Conclusions Less than 1 in 20 patients use BZRAs ≥180 days in their first treatment episode. Several factors were associated with long-term use following the first prescription and further investigation into whether these factors need to be considered at the point of prescribing is warranted. In light of these findings, future research should examine the predictors of cumulative repeat episodes of BZRA exposure.

Strengths and limitations of this study

- This study used administrative data from the Manitoba Centre for Health Policy, which is one of the most comprehensive datasets in North America containing >140 deidentified linked datasets on healthcare, education, social/families, justice and registries for all residents of Manitoba (population of 1.4 million people) not restricted by age or income.
- All diagnoses are identified through physician claims data or hospitalisations, which are dependent on people seeking treatment and may be prone to some misclassification. Drug information is also based on dispensing records from community pharmacies and does not confirm the patient actually took the drug. However, we performed multiple sensitivity analyses to address this.
- The databases do not capture participation in psychological interventions such as cognitive–behavioural therapy.

INTRODUCTION

The use of benzodiazepine receptor agonists (BZRAs), benzodiazepines (BZD) and Z-Drugs, in the treatment of anxiety and insomnia has shifted based on the evolving data on safety risks and limited efficacy on long-term use in the literature.[1–4] On their initial introduction into clinical practice in the late 1960s, BZD were considered to be a safer alternative to barbiturates.[5] However, safety concerns such as psychomotor impaired accidents (ie, falls and motor-vehicle accidents), dependency and misuse/abuse are now well known.[6–8] Recent studies have also raised concerns proposing possible links to dementia, recurrence of mood episode, respiratory disease exacerbation and suicide with long-term BZRA use.[9–13] However, the association of BZRA use for these newer harms is uncertain given conflicting evidence and confounding in previous studies.[14]

In spite of ongoing adverse effect concerns, justification for less restrictive BZRA use have stemmed from their clinical utility as rapidly effective anxiolytic sedatives.[15] Some view that limiting BZRA use is at times impractical.[16] Moreover, the use of alternative pharmacotherapy, including trazodone, atypical

antipsychotics, barbiturates, and tricyclic antidepressants are not without adverse effects. It should also be noted that the difficulties with de-prescribing BZRAs reported in the literature have added caution to the initiation of these agents in practice.[4 17]

Previous studies examining the pattern of BZRA use have found a decline in benzodiazepine (particularly lorazepam) incident use and an increase in the incidence of Z-drug use.[18 19] Limited studies have examined predictors of long-term use after a first prescription.[20 21] As such, this study sought (i) to measure the incidence of long-term BZRA use among a cohort of community-dwelling Canadian adults with anxiety, mood and/or sleep disorders, and (ii) to determine factors associated with progression to long-term BZD use following the first prescription in this population.

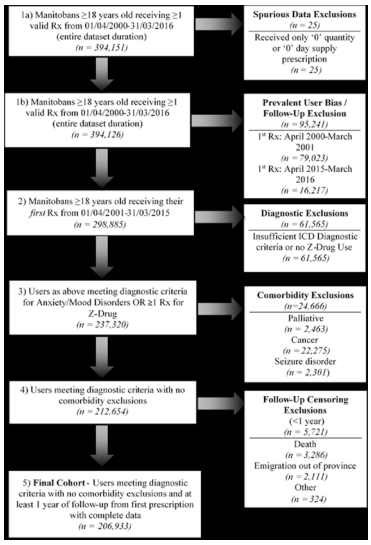

Figure 1 Flow chart of study population. ICD, International Classification of Diseases.

METHODS

Study design and data sources

This was a retrospective, cohort study using routinely collected administrative healthcare data pertaining to prescription drug dispensations, outpatient physician claims, hospitalisation discharge abstracts, income assistance records and prescriber demographics (online supplemental table A1). All data used was extracted from the Manitoba Centre for Health Policy Population Research Data Repository. The Repository provides comprehensive coverage of all Manitoba residents contact with the primary healthcare system. The Drug Programme Information Network (DPIN) provides information on outpatient prescription drugs dispensed in Manitoba with the exception of medications dispensed in hospital and nursing stations. In Manitoba, eligible outpatient prescriptions are 100% covered for residents after an income-based deductible is paid for each fiscal year. DPIN captures information on the drug name, strength, quantity, day-supply, and date of all outpatient prescriptions dispensed regardless of coverage. Merging of the various data sources was facilitated via linkage of unique de-identified Personal Health Information Numbers. The Charlson Comorbidity Score (0 (lowest risk), 1, ≥2 (high risk)) was also determined to examine the effects of comorbidity of duration of use. This was determined based on 17 categories of comorbidities using ICD-9-CM or ICD-10-CA equivalent codes in administrative data to provide the weight-based adjusted risk of death or resource use.[22]

Cohort inclusion/exclusion criteria

Eligible patients were adults age 18 years and older who initiated a new benzodiazepine or Z-drug prescription (defined as no use in the 1 year prior to the first prescription[20 21] between 1 April 2001 and 31 March 2015, with no preceding dispensations from 1 April 2000 to 31 March 2001 (first year of the dataset) to avoid prevalent user bias (figure 1). All individuals with at least 1 year of registry coverage prior to and after the first prescription was required for cohort inclusion. As such, individuals who received a benzodiazepine in the distant past could be included in the cohort as a new user, provided that the benzodiazepine was not used in the past 1 year. A sensitivity analysis was also performed in which incident use was defined as no prescription for a BZRA was received in the 3 years prior to the first prescription.[23]

Eligibility was also based on diagnostic criteria for anxiety/mood-related disorders and/or insomnia based on International Classification of Diseases 9, Clinical Modification (ICD-9-CM) or International Classification of Diseases 10, Canadian Enhancements (ICD-10-CA) medical claims, either at outpatient physician visits or hospitalisations, occurring within a 5-year period prior to the first prescription. The ICD diagnostic criteria chosen are a combination of the definitions from two sources; the Canadian Public Health Association on mental health surveillance and the MCHP concept dictionary, which listed the various past-case definitions employed in previous research within Manitoba for mood and anxiety disorders (online supplemental table A2).[24–28] Lastly, because reliance on ICD codes is expected (and has been previously shown) to underestimate capture of sleep disorder cases, we also accepted receipt of a Z-drug in the definition for insomnia as this was their sole approved indication.[29]

To reduce confounding, we established cohort exclusion criteria that otherwise may have justified long-term use of BZDs in clinical scenarios beyond the scope of general guideline recommendations for anxiety and insomnia. Namely, patients were excluded if they had ≥1 ICD code for cancer, a seizure disorder or if there was placement in the Manitoba palliative care drug programme at any point in the 5 years preceding their first prescription for a BZRA (online supplemental table A3). Where patients became palliative ≥1 year after the initial BZRA dispensation, their ongoing use of BZRA was

censored beginning from the date of their placement, but all use prior to their palliative status was retained. Clobazam use was excluded entirely from the evaluated drug claims because it is approved only as an adjunctive agent for epilepsy in Canada. Finally, patients were excluded if they lacked at least 1 year of registry coverage from their first-prescription index date. This was to eliminate any biasing effect from early mortality, moving out of province or other lost to follow-up.

Main outcome measures

Long-term use was defined as ≥180 days based on the recommendation from a previous systematic review of similar studies.[24] This duration is longer than clinical practice guideline duration recommendations and is believed to be of sufficient length for risk of dependence to occur.[30] One-third of individuals who use BZDs for longer than 6 months have been previously reported to be unable to stop completely due to withdrawal symptoms (eg, anxiety, insomnia, muscle spasms).[30] A sensitivity analysis, ranging from 60 to 365 days, was also used in our study to account for varying definitions of long-term use reported in the literature.[24]

Patients were followed forward in time from the date of their first BZRA prescription. BZRA 'use episodes' were determined according to consecutive prescription overlap based on dispensation dates and coded day supply values. The allowable gap between prescriptions was the greater of either 30 days or 50% of the last prescription day supply after the prescription end date (end date=dispensation date+day-supply) of the prior prescription. This gap was chosen to account for those who regularly or frequently used 'as needed' BZRA in the 'use episode' duration. The episode end date was calculated as the date of the last prescription in a given 'use episode' plus its associated day-supply. To account for immeasurable time bias, hospitalisation time was assumed to be a continuation of BZD use given that in-patient drug use data was limited.[31] The provincial drug programme subsidises dispensations of up to a 100 day-supply.

Individuals were able to have multiple use episodes over the entire study duration. First episode duration and average episode duration were calculated for each user. If patients only had one use episode both of these values were the same. Patients were allowed to switch from one BZRA to another without it interrupting their 'use episodes'. This included switching from a BZD to a Z-drug and vice versa.

Independent variables

Variables used for statistical prediction of long-term use were determined a priori and included age, sex, geographical residence, residential mobility, socioeconomic status, marriage, concurrent opioid or prescription psychotropic use, comorbidity burden, healthcare usage, time period of first prescription and prescriber characteristics (online supplemental tables A4 and A5). Variables were assessed at baseline; either within 1 year before the index date, at the index date or up to 6 months past the index date (in the case of prescription opioids and other psychotropics, such as antidepressants, antipsychotics and mood stabilisers).

Statistical analysis

Standard reporting criteria were followed in the approach to logistic regression modelling (online supplemental tables A6 and A7).[32] Univariate analysis was performed first in the form of simple logistic regression. The multivariable model was constructed to determine the most parsimonious model for prediction of long-term BZRA use defined as ≥180 days in the first episode of use with adjustment of clinically relevant covariates based on previous literature.[24] Differences between models in their maximum log-likelihood estimation, likelihood ratios and other goodness-of-fit statistics enabled model discrimination.[32] Multicollinearity and effect-measure modification (ie, interaction effects) were assessed when it was suspected that variables may be either correlated or non-independent.[32] In order to perform these diagnostics, the binary dependent variable was first substituted for a linear variable (first-episode duration in days) to conduct a multiple linear regression. Specifically, collinearity was determined to be a model threat if any correlation coefficient in the independent variable correlation matrix was $\geq |0.8|$ or if any variance inflation factor was unreasonably high (≥10) while the corresponding tolerance factor was minuscule (≤0.1).[33] Analyses were assessed at $p<0.01$ threshold set a priori for statistical significance.

For the multiple logistic regression, 'complete-case analysis' was used because the extent of missing data was too small to justify the need for multiple imputation procedures.[34] In this study, no claims were excluded on the basis of missing data fields. Only 1568 claims (<0.01%) were excluded for being spurious (ie, '0' day/quantity supply or incredibly high dispensed quantity to day-supply ratio) Furthermore, observed missing data was believed to be missing at random.[35] The only variable with significant missing data was that of 'prescriber type' (~38 000 missing observations or 17.5% of final sample).

A subgroup analysis of each of the 17 categories of the Charlson Comorbidity Score was also performed using Z-test of two proportions to describe the specific comorbidities that may contribute to the relationship between Charlson Comorbidity Score and long-term use.

Sensitivity analysis

To assess the robustness of the primary outcome, six sensitivity analyses (online supplemental tables A8 and A9) were conducted to determine how the proportion of long-term use changed under differing parameter assumptions.[36] The threshold duration for long-term use was adjusted to values ranging from 60 days to 365 days. Additionally, the episode lapse criteria (ie, prescription gap rule) was changed. While the analysis was not exhaustive for every conceivable combination of these key parameters, the selected values were chosen because

they were judged to be representative of how peers in the international clinical community may have defined or measured 'long-term use' of BZRA. All data were cleaned and analysed using SAS V.9.4.

RESULTS

Episodic BZD/Z-drug use

Study population demographics are presented in table 1. There were 206 933 patients in our cohort representing 931 271 unique BZRA dispensations over the 15-year study duration. Over the study period, cohort individuals had a median of three and average of 4.5 BZRA use episodes, respectively. First episodes of use were of a median duration of 20 days (IQR=10–30 days). For all use episodes, the median average use duration was 30 days (IQR=15–111 days). Evaluation of long-term use revealed that 4.51% of patients used a BZRA for ≥180-days in their 'first' episode of use. At most, this proportion increased to 9.64% when a sensitivity analysis of 60 days or greater was used for the definition of 'long-term use' for the first episode of use. However, the proportion of long-term users increased considerably after averaging for all episodes for each user (sensitivity analysis range: 15.6%–35.1%) (online supplemental table A7).

To evaluate treatment duration for insomnia, a sensitivity analysis was performed on only Z-drugs (n=1 10 663), which found similar results (online supplemental tables A9–A12).

Factors predicting long-term first episode use

Logistic regression analysis revealed that male sex (adjusted OR 1.33, 95% CI 1.27 to 1.39), older age (adjusted OR 2.24, 95% CI 2.11 to 2.38) and 5.15 (95% CI 4.81 to 5.52) for aged 45–64 years and ≥65 years, respectively, compared with <45 years), receipt of income assistance (adjusted OR 1.68, 95% CI 1.55 to 1.81), previous non-BZRA psychotropic (adjusted OR 1.93, 95% CI 1.83 to 2.02) or opioid use (adjusted OR 1.16, 95% CI 1.11 to 1.22), high comorbidity (Charlson Comorbidity Index 1 and ≥2, adjusted OR 1.11, 95% CI 1.04 to 1.17) and 1.43, 95% CI 1.32 to 1.55, respectively), high healthcare resource use (resource utilisation band of 4 and 5, adjusted OR 1.15, 95% CI 1.07 to 1.23 and 1.46, 95% CI 1.33 to 1.60, respectively), first prescription from psychiatrist (adjusted OR 2.11, 95% CI 1.93 to 2.32) and receipt of first prescription after 2006 (2006–2011, adjusted OR 1.74, 95% CI 1.64 to 1.85; 2011–2015, adjusted OR 2.99, 95% CI 2.80 to 3.18), were all predictive of long-term use of ≥180 days in the first episode. Rural residence (adjusted OR 1.10, 95% CI 1.04 to 1.15) and high residential mobility (adjusted OR 1.14, 95% CI 1.08 to 1.21) were also associated with a higher risk of long-term use in the first episode. Married status was associated with a lower risk of meeting the long-term use definition (adjusted OR 0.79, 95% CI 0.76 to 0.83). These findings were also replicated in the sensitivity analysis restricted to Z-drug users. Both the crude and adjusted ORs are presented for the full cohort in table 2.

A subanalysis of the higher comorbidity scores in the long-term user groups shows that this relationship was mainly driven by cardiovascular diseases, diabetes and dementia (table 3). Proportions for these particular diagnoses were 2–5 times higher in the long-term user group, with the greatest difference existing for dementia (long term; 8.5% vs short term; 1.5%). A sensitivity analysis was performed changing the definition of incident user to no receipt of BZRA prescription in the 3 years prior to the first BZRA prescription. No change in results were found.

DISCUSSION

This study found approximately 4.5% of the full cohort and 7.4% of the Z-drug cohort were 'long-term' first-episode users according to the best available evidence-based consensus definition of 180 days.[24] Restricting the analysis to Z-drug use showed that the frequency of long-term use was higher than that of the main cohort. Practice guidelines typically recommend a shorter duration of use for Z-drugs in the treatment of insomnia (range of ≤2–6 weeks)[37–39] compared with BZD for anxiety disorder (up to ≤12 weeks depending on indication).[40–42] Therefore, these results suggest greater disparity from practice guidelines in the case of Z-drug use for insomnia. Of note, more recent insomnia guidelines have recognised that while non-drug alternatives have a favourable safety profile, these interventions may be difficult to achieve for certain populations, which could explain the deviation between practice recommendations and real-world use of these agents.[38]

The proportion of patients who met criteria for 'long-term' use after accounting for all of their use-episodes (ie, rather than just the first episode of use) was approximately 3.5 times higher than the proportion of patients meeting criteria after only their first episode of use. These results may indicate that repeated episodes of BZRA use may be associated with a higher risk of being exposed to a BZRA for a duration of ≥180 days in one episode. An area of future research is to examine whether repeated episodes of BZRA use is associated with progression to long-term use as demonstrated in a previous study that observed the number of episodes of dispensing in the first month was a significant predictor of the total duration of dispensing in the later period.[43] Of note, the majority of people with repeated use still only take BZRAs for intermittent, short-term periods. Furthermore, confounding variables such as age and accrued comorbidity over time may influence the risk of future long-term use in some patients. Nonetheless, these results support the observed difficulty in deprescribing once BZRA use has become chronic, which has also been reported in previous literature.[4 44] Lastly, other clinical considerations such as risk of protracted withdrawal symptoms, risk of rebound insomnia and/or anxiety, severity of indication, patient dissatisfaction, limited alternate drug and non-drug interventions, or

Table 1 Characteristics of BZRA users by first use episode duration

No of users		Short term	Long term	Total
		197 606 (100%)	**9327 (100%)**	**206 933 (100%)**
Sex distribution*	Male	74 487 (37.7%)	4295 (46.1%)	78 782 (38.1%)
	Female	123 057 (62.3%)	5029 (53.9%)	128 086 (61.9%)
Age category	18–44	101 709 (51.5%)	2776 (29.8%)	104 487 (50.5%)
	45–64	66 752 (33.8%)	3320 (35.6%)	70 072 (33.9%)
	65+	29 143 (14.7%)	3231 (34.6%)	32 374 (15.6%)
SEFI-2 score	≤1	24 955 (12.6%)	1089 (11.7%)	26 044 (12.6%)
	−1 to 0	81 718 (41.4%)	3835 (41.1%)	85 553 (41.3%)
	0 to 1	64 967 (32.9%)	3274 (35.1%)	68 241 (33.0%)
	>1	25 966 (13.1%)	1129 (12.1%)	27 095 (13.1%)
Residence distribution	Urban	125 950 (63.7%)	5802 (62.2%)	131 752 (63.7%)
	Rural	71 656 (36.3%)	3525 (37.8%)	75 181 (36.3%)
High residential mobility		36 392 (18.4%)	2385 (25.6%)	38 777 (18.7%)
Receipt of income assistance		18 530 (9.4%)	1222 (13.1%)	19 752 (9.5%)
Marriage record		102 461 (51.9%)	4618 (49.5%)	107 079 (51.8%)
Johns Hopkins Healthcare Resource Utilisation Band††	0 (no utilisation)	3001 (1.5%)	349 (3.7%)	3350 (1.6%)
	1	5798 (2.9%)	182 (2.0%)	5980 (2.9%)
	2	33 974 (17.2%)	1192 (12.8%)	35 166 (17.0)
	3	127 824 (64.7%)	5151 (55.2%)	132 975 (64.3%)
	4	20 065 (10.2%)	1486 (15.9%)	21 551 (10.4%)
	5 (high utilisation)	6882 (3.5%)	964 (10.3%)	7846 (3.8%)
Charlson Comorbidity Index Score	0	148 257 (75.0%)	5783 (62.0%)	154 040 (74.4%)
	1	36 261 (18.4%)	2031 (21.8%)	38 292 (18.5%)
	2+	13 088 (6.6%)	1513 (16.2%)	14 601 (7.1%)
Non-BZRA psychotropic prescription dispensations	0	111 216 (56.3%)	3862 (41.4%)	115 078 (55.6%)
	1	17 661 (8.9%)	518 (5.6%)	18 179 (8.8%)
	2+	68 729 (34.8%)	4947 (53.0%)	73 676 (35.6%)
Opioid prescription dispensations	0	132 027 (66.8%)	5855 (62.8%)	137 882 (66.6%)
	1	30 530 (15.5%)	1011 (10.8%)	169 423 (15.2%)
	2+	35 049 (17.7%)	2461 (26.4%)	37 510 (18.2%)
Sex of prescriber issuing first prescription††*	Male	143 619 (75.3%)	6928 (76.5%)	150 547 (75.3%)
	Female	47 128 (24.7%)	2126 (23.5%)	49 254 (24.7%)
Age of prescriber issuing first prescription‡‡	50+ years	95 629 (52.1%)	4775 (53.9%)	100 404 (52.2%)
	<50 years	87 833 (47.9%)	4.076 (46.1%)	91 909 (47.8%)
Type of prescriber issuing first prescription§§	General practitioner	146 823 (91.6%)	7013 (87.5%)	153 836 (91.4%)
	Psychiatry	6338 (4.1%)	624 (7.8%)	6962 (4.1%)
	Other	7183 (4.5%)	375 (4.7%)	7558 (4.5%)
Period of first prescription	2001–2006	90 008 (45.5%)	2608 (28.0%)	92 616 (44.8%)
	2006–2011	65 750 (33.3%)	3170 (34.0%)	68 920 (33.3%)
	2011–2016	41 848 (21.2%)	3549 (38.1%)	45 397 (21.9%)

*N=197 544 (short-term users); N=9324 (long-term users); N=206 868 (total users).
†N=197 544 (short-term users); N=9324 (long-term users); N=206 868 (total users).
‡N=183 462 (short-term users); N=8851 (long-term users); N=192 313 (total users).
§N=160 344 (short-term users); N=8012 (long-term users); N=168 356 (total users).
BZRA, benzodiazepine receptor agonist; SEFI-2, socioeconomic factor index.

Table 2 Statistical associations between predictor variables and long-term use of BZRAs

		Use duration					
		≥180 days		≥90 days		≥60 days	
Independent variable		Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Male		1.41 (1.35 to 1.47)	1.33 (1.27 to 1.39)	1.40 (1.35 to 1.45)	1.34 (1.29 to 1.40)	1.30 (1.26 to 1.34)	1.27 (1.23 to 1.31)
Age	18–44	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45–64	1.82 (1.73 to 1.92)	2.24 (2.11 to 2.38)	1.77 (1.70 to 1.85)	2.00 (1.91 to 2.10)	1.81 (1.75 to 1.86)	1.89 (1.82 to 1.97)
	65+	4.06 (3.86 to 4.28)	5.15 (4.81 to 5.52)	3.56 (3.41 to 3.72)	4.11 (3.88 to 4.36)	3.34 (3.22 to 3.47)	3.52 (3.36 to 3.70)
Rural residence		1.07 (1.02 to 1.11)	1.10 (1.04 to 1.15)	0.97 (0.93 to 1.00)	0.97 (0.94 to 1.02)	0.90 (0.87 to 0.92)	0.92 (0.88 to 0.95)
High residential mobility		1.52 (1.45 to 1.60)	1.14 (1.08 to 1.21)	1.35 (1.29 to 1.40)	1.06 (1.01 to 1.11)	1.14 (1.10 to 1.18)	1.01 (0.97 to 1.06)
Income assistance		1.46 (1.37 to 1.55)	1.68 (1.55 to 1.81)	1.14 (1.08 to 1.21)	1.35 (1.26 to 1.45)	0.88 (0.84 to 0.93)	1.12 (1.06 to 1.20)
Socio-Economic Factor Index-2 Score	≤1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	−1 to 0	1.08 (1.00 to 1.15)	0.99 (0.92 to 1.07)	0.96 (0.91 to 1.02)	0.91 (0.86 to 0.97)	0.90 (0.87 to 0.95)	0.89 (0.85 to 0.94)
	0 to 1	1.16 (1.07 to 1.24)	1.02 (0.94 to 1.10)	0.98 (0.93 to 1.04)	0.92 (0.87 to 0.98)	0.87 (0.83 to 0.91)	0.89 (0.84 to 0.94)
	>1	1 (0.92 to 1.09)	0.93 (0.84 to 1.03)	0.78(0.73 to 0.84)	0.80 (0.74 to 0.87)	0.63 (0.59 to 0.67)	0.73 (0.68 to 0.78)
Married		0.91 (0.87 to 0.95)	0.79 (0.76 to 0.83)	1.01 (0.98 to 1.05)	0.89 (0.85 to 0.92)	1.13 (1.10 to 1.16)	0.95 (0.92 to 0.99)
Opioid use		1.19 (1.14 to 1.27)	1.16 (1.11 to 1.22)	1.08 (1.04 to 1.12)	1.09 (1.05 to 1.14)	0.99 (0.96 to 1.02)	1.05 (1.01 to 1.09)
Psychotropic Rx Use (non-BZRA)		1.82 (1.75 to 1.90)	1.93 (1.83 to 2.02)	1.62 (1.56 to 1.67)	1.75 (1.69 to 1.83)	1.34 (1.30 to 1.38)	1.49 (1.44 to 1.54)
Charlson Comorbidity Index Score	0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.44 (1.36 to 1.51)	1.11 (1.04 to 1.17)	1.33 (1.27 to 1.39)	1.08 (1.02 to 1.13)	1.24 (1.19 to 1.29)	1.04 (1.00 to 1.08)
	2+	2.96 (2.79 to 3.15)	1.43 (1.32 to 1.55)	2.41 (2.29 to 2.54)	1.33 (1.24 to 1.42)	2.01 (1.92 to 2.11)	1.23 (1.15 to 1.31)
Resource Utilisation Band	0–3	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4	1.84 (1.73 to 1.95)	1.15 (1.07 to 1.23)	1.58 (1.50 to 1.66)	1.08 (1.01 to 1.14)	1.37 (1.31 to 1.43)	1.00 (0.94 to 1.05)
	5	3.48 (3.24 to 3.73)	1.46 (1.33 to 1.60)	2.73 (2.56 to 2.92)	1.31 (1.20 to 1.42)	2.21 (2.08 to 2.35)	1.17 (1.09 to 1.27)
Male prescriber of first prescription		1.07 (1.02 to 1.12)	1.03 (0.98 to 1.09)	1.07 (1.02 to 1.11)	1.04 (0.99 to 1.09)	1.01 (0.98 to 1.05)	0.98 (0.94 to 1.02)
Prescriber age ≥50 years		1.08 (1.03 to 1.12)	0.98 (0.94 to 1.03)	1.08 (1.04 to 1.12)	0.99 (0.95 to 1.03)	1.15 (1.11 to 1.18)	1.08 (1.04 to 1.11)
Type of prescriber of first prescription	GP	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	Psychiatrist	2.06 (1.89 to 2.25)	2.11 (1.93 to 2.32)	1.85 (1.72 to 2.00)	1.89 (1.75 to 2.05)	1.54 (1.44 to 1.65	1.63 (1.51 to 1.75)
	Other	1.09 (0.98 to 1.21)	0.92 (0.82 to 1.03)	1.07 (0.98 to 1.17)	0.92 (0.84 to 1.01)	1.16 (1.07 to 1.24)	1.03 (0.96 to 1.11)
Period of first prescription	2001–2006	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	2006–2011	1.66 (1.58 to 1.75)	1.74 (1.64 to 1.85)	1.58 (1.51 to 1.65)	1.65 (1.57 to 1.7)	1.41 (1.36 to 1.46)	1.48 (1.42 to 1.54)
	2011–2015	2.93 (2.78 to 3.08)	2.99 (2.80 to 3.18)	2.59 (2.48 to 2.71)	2.71 (2.57 to 2.8)	1.97 (1.90 to 2.05)	2.07 (1.98 to 2.16)

BZRA, benzodiazepine receptor agonist; GP, general practitioner; SEFI-2, Socio-Economic Factor Index-2.

Table 3 Frequency of Charlson Comorbidity Group diagnoses by first use episode duration for BZD/Z-Drug cohort

Charlson diagnosis	Short-term 'first-episode' users **(n=197 606)**	Long-term 'first-episode' users **(n=9327)**	Z-test of two proportions
Myocardial infarction	2474 (1.3%)	281 (3.0%)	P<0.01
Congestive heart failure	3943 (2.0%)	628 (6.7%)	P<0.01
Peripheral vascular disease	2367 (1.2%)	256 (2.7%)	P<0.01
Cerebrovascular disease	3690 (1.9%)	544 (5.8%)	P<0.01
Dementia	2928 (1.5%)	796 (8.5%)	P<0.01
COPD	23 064 (11.7%)	1163 (12.5%)	P=0.02
Connective tissue/rheumatic disease	2793 (1.4%)	222 (2.4%)	P<0.01
Peptic ulcer disease	2140 (1.1%)	114 (1.2%)	P=0.20
Mild liver disease	2406 (1.2%)	135 (1.4%)	P=0.05
Moderate/severe liver disease	341 (0.1%)	28 (0.0%)	P<0.01
Uncomplicated diabetes	14 131 (7.2%)	1099 (11.8%)	P<0.01
Complicated diabetes	1611 (0.8%)	252 (2.7%)	P<0.01
Paraplegia and hemiplegia	794 (0.4%)	136 (1.5%)	P<0.01
Renal disease	1858 (0.9%)	238 (2.6%)	P<0.01
Cancer	829 (0.4%)	64 (0.1%)	P<0.01
Metastatic carcinoma	64 (0.0%)	13 (0.0%)	P<0.01
HIV/AIDS	50 (0.0%)	10 (0.0%)	P<0.01

BZD, benzodiazepines; COPD, chronic obstructive pulmonary disease.

interference with another prescriber's decisions likely undermine potential deprescribing efforts.

Older age and female sex have also been identified in previous studies as being associated with long-term use.[45–51] While we found females to have greater representation in all patterns of BZRA use, we found males were more specifically predictive of long-term use after the first episode of use.[52–54] As with almost all of the previously published studies, older age was strongly associated with long-term BZRA use.[51–55] It should be noted that older individuals may have had a greater opportunity to be exposed to BZRA use.

As supported by previous evidence, income assistance was associated with long-term BZRA use.[48 56] Our study also found frequent moving, unmarried status and rural residence to be associated with increased odds of long-term use. Frequency of moving and income assistance could be a proxy for general life stability.[50 57 58] Rural residence may have a small effect on longer-term BZRA use due to the relative limitations of timely scheduled follow-up, which may necessitate prescriptions of greater quantity or for longer periods. Another study also found rural adults to be at higher odds of inappropriate BZD use .[59]

Healthcare use and the presence of various physical illnesses have been consistent predictors of long-term BZRA use.[47 49 50 60] In this study, as both of these variables increased, so did the odds of long-term use. We speculate that the positive relationship between these two indices and long-term use may be partially explained by unmeasured 'health' anxiety or associated mental health issues arising secondary to physical comorbidities or by additional disruptive effects of physical illness on sleep.

The Charlson Comorbidity Score findings were not surprising given the relatively higher proportion of older adults in the long-term use group. Nonetheless, the greater degree of BZRA exposure among those patients with dementia is of concern given the risk of BZD use in this population.[9] Similar to previous studies, prescriptions for an opioid or a psychotropic agent, such as antidepressants, antipsychotics or mood stabilisers, during the baseline period were modestly predictive for future long-term use.[48 52 54 56 58 61] Those having received a non-BZD prescription agent for a psychiatric disorder could be expected to have had greater disease severity on average than those BZRA users who did not receive such treatment early on.

An unexpected finding was the increased odds of long-term use associated with the more recent time period of the first prescription. This is contrary to what may be expected from cumulative knowledge on BZRA and the long-standing emphasis on short-term use advised in guidelines and clinical literature. This finding may reflect the growing awareness that BZRAs should not be used as a first-line treatment resulting in only those who have not responded to other alternatives to be more likely to receive BZRAs long-term.

This study has a number of strengths. This study used a large administrative data source that were near complete in their coverage of the study population's prescription

drug dispensations and healthcare contact. Application of cohort inclusion and exclusion criteria in a carefully constructed new user longitudinal design limited confounding and bias to the extent possible. Multiple sensitivity analyses on the main outcome measure, the duration of BZRA use measurement method and the association between the independent and dependent variables for two cohorts reduced quantitative bias to increase confidence in the results.

A few important limitations should be acknowledged. First, administrative data are prone to some misclassification of variables. For instance, diagnostic criteria for cohort case inclusion and exclusion will differ in their true sensitivity and specificity, regardless of prior validation of case definitions. Drugs used during any hospitalisations were not available and was assumed to be continued BZD exposure. As all independent variables were only measured cross-sectionally before or at the time of the first prescription of the first use episode, the logistic regression model was only predictively valid for the first use episode duration and not users' average episode duration. Since DPIN only captures the days supply provided, it is possible that not all of the medication was actually taken by the patient. However, this study was able to provide insight into the prescribing practices of BZD that are filled in the pharmacy in this population. Our study did not evaluate the extent of concurrent use of multiple BZD or other psychiatric diagnoses such as substance use disorder. The databases also do not capture participation in psychological interventions such as cognitive behavioural therapy. Moreover, while the databases are able to link several data on health information regardless of age and coverage, they do not capture other potential confounding factors such as education status and ethnicity. This study was done in a setting where there is a universal healthcare system and medication costs are covered for all Manitobans after an income-based deductible is met every year. As a result, findings may be generalisable to similar settings. Future research should aim to examine the association of repeat exposure to BZRA and risk of chronic use. Future research could also examine specific benzodiazepine type and formulations on risk of long-term use.

CONCLUSION

Prescribing of BZRAs was used for less than 6 months duration for the majority of individuals with a prior history of anxiety, depression or insomnia. However, the proportion of long-term use among new users was up to one in three based on the average of all episodes of use, warranting future research in this area. Patients who are male, of older age, are socially or financially deprived, have poor physical health, use opioids or other psychotropic agents and are frequent consumers of healthcare resources are more likely to use BZRA long-term after their first prescription. Future research could be done to explore whether these factors need to be considered at the point of prescribing in clinical practice.

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ORCID iD

Christine Leong http://orcid.org/0000-0003-0033-6877

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