BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046916
Article Type:	Original research
Date Submitted by the Author:	12-Nov-2020
Complete List of Authors:	Brandt, Jaden; University of Manitoba Alessi-Severini, Silvia; University of Manitoba Singer, Alexander; University of Manitoba Chateau, Dan; University of Manitoba Enns, Murray; University of Manitoba Leong, Christine; University of Manitoba
Keywords:	CLINICAL PHARMACOLOGY, PSYCHIATRY, Anxiety disorders < PSYCHIATRY, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running Title: Risk of long-term benzodiazepine receptor agonist use

Jaden Brandt, MSc BScPharm[1], Silvia Alessi-Severini, PhD[1,2], Alexander Singer, MB BAO BCh CCFP[3], Dan Chateau, PhD[2,4], Murray Enns, MD FRCPC[5], Christine Leong, PharmD BScPharm[1,5*]

[1]*College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[2]*Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, CAN*

[3]*Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[4]*Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[5]*Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

**Corresponding author: Dr. Christine Leong*

Apotex Centre, College of Pharmacy, Rady Faculty of Health Sciences

University of Manitoba

750 McDermot Avenue

Winnipeg, Manitoba R3E 0T5

P: (204) 318-5276

E: christine.leong@umanitoba.ca

Acknowledgements

The authors wish to acknowledge Dr. Sheryl Zelenitsky for her helpful comments on earlier drafts of this manuscript.

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under Research Ethic Board approval HS20498 (HIPC#2016/2017 – 062). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

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 April 1, 2001 to March 31, 2015 were included. Long-term use was defined as ≥180 days.

Results: Among 206,933 individuals included, long-term BZRA use in the first episode of use ranged from 4.5% (≥180 days) following their first prescription. Factors associated with ≥180 days of use included male sex (adjusted odds ratio (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 one in ten 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 BZRA exposure.

Key Words: *benzodiazepine, anxiety, insomnia, pharmacoepidemiology, clinical practice guidelines, z-drug hypnotics*

Strengths and Limitations of 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 de-identified 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 hospitalizations, 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 behavioral 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 safety and efficacy data on long-term use in the literature. [1–4] Upon their initial introduction into the clinical practice in the late 1950's, benzodiazepines were considered to be a safer alternative to barbiturates.[5] However, safety concerns such as psychomotor impaired accidents (i.e., falls and motor-vehicle accidents), dependency and misuse/abuse are now well known. [6–8] Benzodiazepine in combination with opioid prescription has also been reported to increase the risk of opioid-related death by 1.5 to 3.9-fold.[10-13] Opioid-related hospitalizations have ranged from 17.1% in British Columbia to 35.6% in Manitoba among individuals with a co-prescription of opioid and benzodiazepine.[12] Recent studies have raised concerns proposing possible links to dementia, recurrence of mood episode, respiratory disease exacerbation and suicide. [13–17] However, the association of BZRA use for these newer harms is uncertain given conflicting evidence and confounding in previous studies.[18,19]

In spite of ongoing adverse effect concerns, justification for less restrictive BZRA use have stemmed from their reputation as rapidly effective anxiolytic sedatives.[20] Some view that withholding BZRA is at times impractical and may increase psychiatric symptom burden and patient distress.[21] Moreover, the use of alternative pharmacotherapy, including trazodone, atypical antipsychotics, barbiturates, and tricyclic antidepressants are not without harm. Nevertheless, a patient-centered approach which carefully accounts for the benefits and risks of BZRA use is expected to yield the best outcomes for the patient.[22] It should also be noted that the difficulties

* ***Abbreviations****: BZRA, benzodiazepine receptor agonist; BZD, benzodiazepine*

with de-prescribing these agents reported in the literature and have added caution to the initiation of these agents in practice.

Clinical practice guidelines have attempted to provide general direction to practitioners and pharmacists on how these medications should be managed according to the best available evidence.[23-26] There are a small number of population-wide prescribing practice evaluations to determine the extent of adherence to guideline recommendations[27,28], and only one considered data on duration of use.[28] As such, this study sought to i) measure the incidence of long-term BZRA use among a cohort of community-dwelling Canadian adults with anxiety, mood and/or sleep disorders. ii) To determine factors associated with progression to long-term BZD use following the first prescription in this population.

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, hospitalization discharge abstracts, income assistance records and prescriber demographics (Table 1). All data used was extracted from the Manitoba Centre for Health Policy's Population Research Data Repository. The Repository provides comprehensive coverage of all Manitoba residents contact with the primary healthcare system. The Drug Program Information Network 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. 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 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.[29] All data was cleaned and analyzed using Base SAS v9.4©.

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 one year prior to the first prescription[30,31]) between April 1, 2001 to March 31, 2015, with no preceding dispensations from April 1, 2000 to March 31, 2001 (first year of the dataset) to avoid prevalent user bias (Figure 1). A ≥1-year of follow-up prior to and after the first prescription, as determined by insurance registry coverage, was required for cohort inclusion.

Eligibility was also based on diagnostic criteria for anxiety/mood related disorders and/or insomnia based on ICD-9-CM or ICD-10-CA medical claims, either at outpatient physician visits or hospitalizations, 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 (Table A1).[32-36] 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.[37]

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 program at any point in the 5 years preceding their first prescription for a BZRA (Table A2). 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 loss 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.[32] This duration is longer than clinical practice guideline duration recommendations and is believed to be of sufficient length, with repeated dosing, for some degree of dependency to arise in many users.[38] One-third of individuals who use BZDs for longer than six months have been previously reported to be unable to stop completely due to withdrawal symptoms (e.g., anxiety, insomnia, muscle spasms).[38] A sensitivity analysis, ranging from 60 to 365 days, was also used in our study to account for variances in dispensing patterns and to allow for a period long enough to develop tolerance.[32]

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 because we believed it was an acceptable compromise, in the absence of prescription use directions, because it allowed for clinically significant, but persistent, 'as needed' BZRA use while preventing more infrequent 'as needed' prescription fills from contributing to '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, hospitalization time was assumed to be a continuation of BZD use given that in-patient drug use data was limited.[39] The provincial drug program subsidizes 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 included age, sex, geographic residence, residential mobility, socioeconomic status, marriage, concurrent opioid or prescription psychotropic use, comorbidity burden, healthcare usage, time period of first prescription and prescriber characteristics (Table A3 and Table A4). 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 stabilizers).

Logistic Regression Modelling

Standard reporting criteria were followed in the approach to logistic regression modelling.[40] Univariate analysis was performed first in the form of simple logistic regression. The multi-variable 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.[32] Differences between models in their maximum log-likelihood estimation, likelihood ratios and other goodness-of-fit statistics enabled model discrimination.[40] Multicollinearity and effect-measure modification (i.e., interaction effects) were assessed when it was suspected that variables may be either correlated or non-independent.[40] 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 ≥ |0.8| or if any variance inflation factor was unreasonably high (≥10) while the corresponding tolerance factor was miniscule (≤0.1).[42] 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.[43] In this study, no claims were excluded on the basis of missing data fields. Only 1,568 claims (<0.01%) were excluded for being spurious (i.e '0' day/quantity supply or incredibly high dispensed quantity to day-supply ratio) Furthermore, observed missing data was believed to be missing at random. The

only variable with significant missing data was that of 'prescriber type' (~38,000 missing observations or 17.5% of final sample).

Sensitivity Analysis

To assess the robustness of the primary outcome, 6 sensitivity analyses (Tables A7 and Table A8) were conducted to determine how the proportion of long-term use changed under differing parameter assumptions.[43] The threshold duration for long-term use was adjusted to values ranging from 60 days to 365 days. Additionally, the episode lapse criteria (i.e., 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.

Ethical Approval

Access to the data for this project was approved by the University's Health Research Ethics Board (registration number H2017:052 (HS20498) and the Health Information Privacy Committee (no. 2016/2017-62) of the provincial government.

Results

Episodic BZD/Z-Drug Use

There were 206,933 patients in our cohort representing 931,271 unique BZRA dispensations over the 15-year study duration, accounting for a total of 337,341 person-years of BZRA use based upon our use-duration measurement method. 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%) (Table A7).

To evaluate treatment duration for insomnia, a sensitivity analysis was performed on only Z-Drugs (*n*=110,663). This was done to mitigate any effects of concurrent BZD use and to get a more specific estimate for insomnia treatment duration; however, the results were similar. All results for the Z-Drug cohort are provided in the supplemental appendix (Tables A8-A11).

Factors Predicting Long-term First Episode Use

Logistic regression analysis revealed that male sex (adjusted odds ratio (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 to <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 utilization 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 odds ratios are presented for the full cohort in Table 2.

A sub-analysis of the higher comorbidity scores in the long-term user groups shows that this relationship was mainly driven by cardiovascular diseases, diabetes and dementia (though nearly all diagnoses had statistically significant differences) (Table 3). Proportions for these particular diagnoses were 2 to 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%).

Discussion

This study demonstrates that 'first-episode' use appears to be largely consistent with current practice guideline recommendations in regards to usage duration among those with prior anxiety, depression, or insomnia. 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.[32] Restricting the analysis to Z-Drug use showed that the frequency of long-term use was higher than that of the main cohort. However, strictly in terms of practice guideline recommendations, the duration of use advocated for Z-Drugs in the treatment of primary insomnia is often shorter (range of ≤4-6 weeks) than that allowed for BZD in anxiety states.[45] 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 recognized 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.[46]

The proportion of patients who met criteria for 'long-term' use after accounting for all of their use-episodes was approximately 3.5 times higher than the proportion of patients meeting criteria after only their first episode of use. These results indicate that repeated episodes of BZRA use are associated with progression to longer-term use episodes. Though, the majority of repeat users still only take BZRAs for intermittent, short-term periods. Furthermore, confounding variables such as age and accrued comorbidity over time suggest a potentially legitimate requirement for future long-term use in some patients. Nonetheless, these results support the observed difficulty in de-prescribing once BZRA use has become chronic, which has also been reported in previous literature.[4,46,47] Lastly, other clinical considerations such as risk of protracted withdrawal symptoms, risk of rebound insomnia and/or anxiety, patient dissatisfaction, limited alternate drug and non-drug interventions, or interference with another prescriber's decisions likely undermine potential de-prescribing efforts.

Older age and female sex have also been identified in previous studies as being associated with long-term use.[48–55] 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. [56–58] As with almost all of the previously published studies, older age was strongly associated with long-term BZRA use.[55-59] It should be noted that older individuals may have had a greater opportunity to be exposed to BZRA use. Therefore, it is possible that age could be a

confounder if increased BZRA exposure is associated with decreased likelihood for BZRA cessation.

As supported by previous evidence, income assistance was associated with long-term BZRA use [51,60]. Our study also found frequent moving, unmarried status, and rural residence to be associated with increased odds of long-term use. Frequency of moving, income assistance, and marriage status could be a proxy for social or general life stability[53,65,62]. Rural residence may have a small effect on longer-term BZRA use due to the relative unavailability 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 .[61]

Healthcare consumption and the presence of various physical illnesses have been consistent predictors of long-term BZRA use [50,52,53,58,63]. In this study, as both of these variables increased, so did the odds of longer-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. Investigation of this link in future studies may better inform clinicians on prescribing of BZRA for such 'atypical' anxiety states.

The Charlson comorbidity score findings were not surprising given the relatively higher proportion of older adults in the long-term user group. Nonetheless, the greater degree of BZRA exposure among those patients with dementia is alarming given the ongoing controversy between dementia and BZD use [9,19]. This concern is echoed by a previous European study that found higher prevalence rates of long-term use of BZD in community dwelling elderly with Alzheimer's disease.[64]

In concordance with 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.[51,54,56,58,60,65] 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. Furthermore, certain antidepressants, namely SSRIs, may stimulate a greater need for a BZD due to their adverse pharmacology resulting in what has been termed "anxiety/jitteriness syndrome".[64] Therefore, undetected anxiogenic or sleep disrupting effects of other psychotropic medications may, in some cases, result in persisting BZD use.

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. Nevertheless, this trend may be partially explained by changes in the clinical selection of BZRA over the course of the 15-year study period and the corresponding evidence for the popularity of certain agents.[67] This finding may reflect the growing awareness that BZRAs should not be used as a first-line treatment resulting in only those with greater risk factors and fewer coping strategies to be more likely to receive BZRAs and who may be less likely to respond to other alternatives.

In regards to zopiclone, the relative absence of preferred alternative first-line pharmacotherapies in the Canadian prescriptive armamentarium may have resulted in the default selection of this agent by many prescribers to treat insomnia. Furthermore, a perception of lesser risk (compared to BZD) coupled with increases in population prevalence of insomnia over time (due to various factors such as population aging, increased technological screen time etc.) may

account for why the incidence of long-term use has increased. Lastly, long-term clonazepam usage was also observed in previous studies.[68,69] Some studies have shown greater abuse liability with clonazepam over other BZD.[70,71]

The present study has a number of strengths. This study used a large administrative data sources 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 BZD/Z-Drug 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. Firstly, administrative data is 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 hospitalizations 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 benzodiazepines 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 behavioral therapy. 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 generalizable to similar settings. Future research should aim to examine the association of repeat exposure to BZRA and risk of chronic use.

Conclusion

Prescribing of BZRAs was in accordance with clinical practice guideline recommendations on use 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.

References

1. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66 Suppl 2(suppl 2):28-33.

2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28(1):7-20. doi:10.1016/j.eurpsy.2011.11.003.

3. Moore N, Pariente A, Bégaud B. Why are benzodiazepines not yet controlled substances? *JAMA Psychiatry*. 2015;72(2):110-111. doi:10.1001/jamapsychiatry.2014.2190.

4. Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Fam Pract*. 2013;14:191.

doi:10.1186/1471-2296-14-191.

5. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562. doi:10.1016/j.janxdis.2011.01.002.

6. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19-34. doi:10.2165/0023210-200923010-00002.

7. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: A meta-analysis. *Osteoporos Int*. 2014;25(1):105-120. doi:10.1007/s00198-013-2446-y.

8. Rapoport MJ, Lanctôt KL, Streiner DL, et al. Benzodiazepine use and driving: A meta-analysis. *J Clin Psychiatry*. 2009;70(5):663-673. doi:10.4088/JCP.08m04325.

9. Leece P, Cavacuiti C, Macdonald EM, Gomes T, Kahan M, et al. Predictors of opioid-related death during methadone therapy. J Subst Abuse Treat. 2015 Oct;57:30-5.

10. Leece P, Chen C, Manson H, Orkin AM, Schwartz B, et al. One-year mortality after emergency department visit for nonfatal opioid poisoning: a population-based analysis. Ann Emerg Med 2020;75(1):20-28.

11. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 2015;350:h2698.

12. Gomes T, Khuu W, Craiovan D, Martins D, Hunt J, et al. Comparing the contribution of prescribed opioids to opioid-related hospitalizations across Canada: A multi-jurisdictional cross-sectional study. Drug Alcohol Depend 2018; 191:86-90.

13. Pariente A, De Gage SB, Moore N, Bégaud B. The Benzodiazepine-Dementia Disorders Link: Current State of Knowledge. *CNS Drugs*. 2016;30(1):1-7. doi:10.1007/s40263-015-0305-4.

14. Perlis RH, Ostacher MJ, Miklowitz DJ, et al. Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report. *J Clin Psychiatry*. 2010;71(2):194-200. doi:10.4088/JCP.09m05019yel.

15. Lai SW, Lai HC, Lin CL, Liao KF. Zopiclone use associated with increased risk of acute pancreatitis: A case-control study in Taiwan. *Int J Clin Pract*. 2015;69(11):1275-1280. doi:10.1111/ijcp.12689.

16. Dodds TJ. Prescribed benzodiazepines and suicide risk: A review of the literature. *Prim Care Companion CNS Discord*. 2017;19(2). doi:10.4088/PCC.16r02037.

17. Rodriguez-Roisin R, Garcia-Aymerich J. Should we exercise caution with benzodiazepine use in patients with COPD? *Eur Respir J*. 2014;44(2):284-286. doi:10.1183/09031936.00071014.

18. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017. doi:10.1007/s40268-017-0207-7.

19. Barbui C, Gastaldon C, Cipriani A, Barbui C. Benzodiazepines and risk of dementia: true association or reverse causation? *Epidemiol Psychiatr Sci*. 2013;22(04):307-308. doi:10.1017/S2045796013000358.

20. El-Guebaly N, Sareen J, Stein MB. Are There Guidelines for the Responsible Prescription of Benzodiazepines? *Can J Psychiatry*. 2010;55(11):709-714.

21. Bendtsen P, Hensing G, McKenzie L, Stridsman AK. Prescribing benzodiazepines - A critical incident study of a physician dilemma. *Soc Sci Med*. 1999;49(4):459-467. doi:10.1016/S0277-9536(99)00133-1.

22. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. *Expert Opin Drug Saf*. 2014;13(7):919-934. doi:10.1517/14740338.2014.925444.

23. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114.

24. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.

25. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

26. National Institute for Clinical Excellence. *Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia.*; 2004. https://www.nice.org.uk/guidance/ta77/resources/guidance-on-the-use-of-zaleplon-zolpidem-and-zopiclone-for-the-shortterm-management-of-insomnia-2294763557317.

27. Murphy KD, Sahm LJ, McCarthy S, Byrne S. Benzodiazepine prescribing guideline adherence and misuse potential in Irish minors. *Int J Clin Pharm*. 2015;37(5):749-752. doi:10.1007/s11096-015-0138-8.

28. Neutel CI, Skurtveit S, Berg C. What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population. *Sleep Med*. 2012;13(7):893-897. doi:10.1016/j.sleep.2011.12.014.

29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-383; Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology* 1992;45(6):613-619.

30. Takano A, Ono S, Yamana H, et al. Factors associated with long-term prescription benzodiazepine: a retrospective cohort study using a health insurance database in Japan. BMJ Open 2019;9:e029641.

31. Hata T, Kanazawa T, Hamada T, et al. What can predict and prevent the long-term use of benzodiazepines? J Psychiatric Research 2018;97:94-100.

32. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

33. Willems IAT, Gorgels WJMJ, Voshaar RCO, et al. Tolerance to benzodiazepines among long-term users in primary care. Family Practice 2013;30(4):404-410.

34. Public Health Agency of Canada. Government of Canada. *Report from the Canadian Chronic Disease Surveillance System: Mood and Anxiety Disorders in Canada*.; 2016. http://healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/mental-illness-2015-maladies-mentales/index-eng.php.

35. Manitoba Centre for Health Policy, Department of Community Health Sciences U of M. Concept: Mood and Anxiety Disorders - Measuring Prevalence. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1391#a_references. Published 2015. Accessed February 21, 2017.

36. MCHP. University of Manitoba - Manitoba Centre for Health Policy - Glossary: Anxiety /Anxiety States. http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102267. Published 2010. Accessed July 11, 2018.

37. Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, Kwok C-W. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med*. 2015;16(4):477-482. doi:10.1016/j.sleep.2014.10.018.

38. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295-301. doi:10.1111/j.1365-2125.2012.04418.x.

39. Palmaro A, Boucherie Q, Dupouy J, Micallef J, Lapeyre-Mestre M. Immeasurable time bias due to hospitalization in medico-administrative databases: which impact for pharmacoepidemiological studies? *Pharmacoepidemiol Drug Saf*. 2017;26(5):544-553. doi:10.1002/pds.4193.

40. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol*. 2001;54(10):979-985. doi:10.1016/S0895-4356(01)00372-9.

41. Rasouliyan L, Miller DP. The Logic and Logistics of Logistic Regression. In: *Western Users of SAS Software 2006*. Irvine, CA; 2006:1-14. https://www.lexjansen.com/wuss/2006/analytics/ANL-Rasouliyan.pdf.

42. Schreiber-Gregory DN. *Multicollinearity : What Is It , Why Should We Care , and How Can It Be Controlled ?*; 2017. https://analytics.ncsu.edu/sesug/2017/SESUG2017_Paper-160_Final_PDF.pdf.

43. Bennett D. How can I deal with missing data in my study? *Aust New Zeal J public ….* 2001;25(5):464-469. http://onlinelibrary.wiley.com/doi/10.1111/j.1467-842X.2001.tb00294.x/abstract.

44. Lash TL, Fox MP, Maclehose RF, Maldonado G, Mccandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149.

45. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175.

46. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(2):307-349.

47. Sirdifield C, Chipchase SY, Owen S, Siriwardena AN. A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. *Patient*. 2016:1-15. doi:10.1007/s40271-016-0182-z.

48. Simon GE, VonKorff M, Barlow W, Pabiniak C, Wagner E. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996;49(9):1067-1073. doi:10.1016/0895-4356(96)00139-4.

49. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related

drugs in Manitoba: a population-based study. *C open*. 2014;2(4):E208-16. doi:10.9778/cmajo.20130076.

50. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy (New York)*. 2010;97(2-3):122-129. doi:10.1016/j.healthpol.2010.03.008.

51. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

52. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *Br J Clin Pharmacol*. 2008;65(4):593-599. doi:10.1111/j.1365-2125.2007.03060.x.

53. Jorm AF, Grayson DA, Creasey H, Waite L, Broe GA. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health*. 2000;24(1):7-10. doi:10.1111/j.1467-842X.2000.tb00715.x.

54. Sakshaug S, Handal M, Hjellvik V, et al. Long-term Use of Z-Hypnotics and Co-Medication with Benzodiazepines and Opioids. *Basic Clin Pharmacol Toxicol*. 2016. doi:10.1111/bcpt.12684.

55. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf*. 2018;(October 2017):3-6. doi:10.1002/pds.4551.

56. Fride Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scand J Prim Health Care*. 2015;33(4):252-259. doi:10.3109/02813432.2015.1117282.

57. Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol*. 2012;68(3):311-319. doi:10.1007/s00228-011-1124-2.

58. Fang SY, Chen CY, Chang IS, Wu ECH, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: A population-based study. *Drug Alcohol Depend*. 2009;104(1-2):140-146. doi:10.1016/j.drugalcdep.2009.04.017.

59. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

60. Anderson ABT et al. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other

drugs. *Pharmacoepidemiol Drug Saf*. 2011;20:378-385. doi:10.1002/pds.

61. Mattos MK, Sereika SM, Naples JG, Albert SM. Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults. *Drugs - Real World Outcomes*. 2016;3(3):289-296. doi:10.1007/s40801-016-0080-7.

62. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. *Psychol Med*. 2010;40(9):1495-1505. doi:10.1017/S0033291709991942.

63. Manthey L, Van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: The Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71(2):263-272. doi:10.1111/j.1365-2125.2010.03818.x.

64. Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. Long-term use of benzodiazepines and related drugs among community-dwelling individuals with and without Alzheimer's disease. *Int Clin Psychopharmacol*. 2015;30(4):202-208. doi:http://dx.doi.org/10.1097/YIC.0000000000000080.

65. Patten SB, Williams JVA, Lavorato DH, Kassam A, Sabapathy CD. Sedative – Hypnotic Use in a Canadian General Population Cohort During 12 Years of Follow-up. *Can J Psychiatry*. 2010;55(12):792-799.

66. Sinclair LI, Christmas DM, Hood SD, et al. Antidepressant-induced jitteriness/anxiety syndrome: Systematic review. *Br J Psychiatry*. 2009;194(6):483-490. doi:10.1192/bjp.bp.107.048371.

67. Brandt J, Alessi-severini S, Singer A, Leong C. Novel Measures of Benzodiazepine and Z-Drug Utilisation in a Canadian Provincial Population (2001-2016). *J Popul Ther Clin Pharmacol*. 2018;in press.

68. Nardi AE, Freire RC, Mochcovitch MD, et al. A randomized, naturalistic, parallel-group study for the long-term treatment of panic disorder with clonazepam or paroxetine. *J Clin Psychopharmacol*. 2012;32(1):120-126. doi:10.1097/JCP.0b013e31823fe4bd.

69. Worthington JJ 3rd, Pollack MH, Otto MW, McLean RY, Moroz G, Rosenbaum JF. Long-term experience with clonazepam in patients with a primary diagnosis of panic disorder. *Psychopharmacol Bull*. 1998;34(2):199-205.

70. Wingård L, Taipale H, Reutfors J, et al. Initiation and long- - term use of benzodiazepines and Z- - drugs in bipolar disorder. *Bipolar Disord*. 2018;20:634-646. doi:10.1111/bdi.12626.

71. Arditti J, Thirion X, Lapeyre M. Evidence of clonazepam abuse liability : results of the tools developed by the French Centers for Evaluation and Information on

Pharmacodependence (CEIP) network. *Fundam Clin Pharmacol*. 2011;25:633-641. doi:10.1111/j.1472-8206.2010.00882.x.

Availability of Data and Materials

Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at MCHP. The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository.

Author Statement

All authors contributed to the original design, analysis, interpretation, and writing of this study and manuscript.

Conflict of Interest Disclosure

The authors declare no conflicts of interest related to any aspects of this work.

Funding

This work was supported by the College of Pharmacy at the University of Manitoba. Additional student funding for JB was granted by the Provincial Government of Manitoba in the form of a Manitoba Graduate Scholarship stipend. Funding sources had no role in the conduct of research and/or preparation of the article.

Patient and Public Involvement

We have a patient advisory group who provided feedback on the dissemination of research findings.

Table 1 –Raw Data Sources and Relevant Corresponding Data Elements

Database	Date Range of Data	Relevant Data Elements
Drug Program Information Network (DPIN)	Apr. 1/2000 – Mar. 31/2016	Prescriptions for benzodiazepines (ATC codes N03AE, N05BA, N05CD), Z-Drugs (N05CF), Antidepressants, Antipsychotics, Mood stabilisers, Lithium and Opioids -Drug, dosage strength, dosage type, metric quantity dispensed, day supply, date of dispensation
Manitoba Health Insurance Registry	Apr. 1/1996 – Mar. 31/2016	Birth date/age of patient; sex; location of residence, marital status, date of Manitoba Health coverage, date of coverage end, reason for coverage end (i.e death, emigration etc.)
Medical Claims (Physician Billings)	Apr. 1/1996 – Mar. 31/2016	Services - type of physician (e.g., psychiatrist); dates of services, specific diagnoses (ICD-9 or ICD-10 equivalent)
Hospital Separations Abstracts	Apr. 1/1996 – Mar. 31/2016	Diagnoses (ICD-9 or ICD-10 equivalent), length of stay, admission dates, discharge dates,
Provider Registry/Physician Master File	Apr. 1/1996 – Mar. 31/2016	Physician Age, Sex, Specialty
Social Allowances Management Information Network (SAMIN)	Apr. 1/2001– Mar. 31/2013	Receipt of income assistance

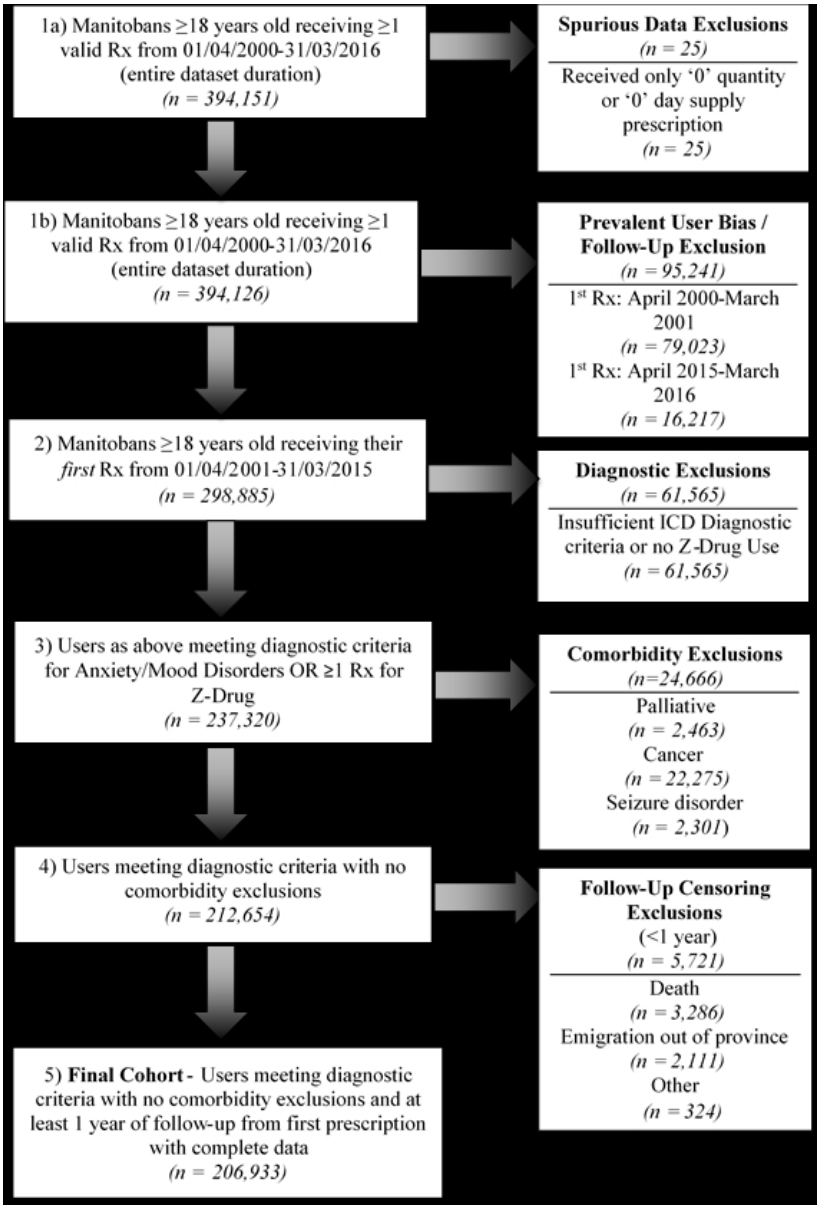
Table 2 – Statistical Associations between Predictor Variables and Long-term Use of BZRAs

Independent Variable		Use Duration					
		≥180 Days		≥90 Days		≥60 Days	
		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 (1.35-1.47)	1.33 (1.27-1.39)	1.40 (1.35-1.45)	1.34 (1.29-1.40)	1.30 (1.26-1.34)	1.27 (1.23-1.31)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.82 (1.73-1.92)	2.24 (2.11-2.38)	1.77 (1.70-1.85)	2.00 (1.91-2.10)	1.81 (1.77-1.86)	1.89 (1.82-1.97)
	65+	4.06 (3.86-4.28)	5.15 (4.81-5.52)	3.56 (3.41-3.72)	4.11 (3.88-4.36)	3.34 (3.22-3.47)	3.52 (3.36-3.70)
Rural Residence		1.07 (1.02-1.11)	1.10 (1.04-1.15)	0.97 (0.93-1.00)	0.97 (0.94-1.02)	0.90 (0.87-0.92)	0.92 (0.88-0.95)
High Residential Mobility		1.52 (1.45-1.60)	1.14 (1.08-1.21)	1.35 (1.29-1.40)	1.06 (1.01-1.11)	1.14 (1.10-1.18)	1.01 (0.97-1.06)
Income Assistance		1.46 (1.37-1.55)	1.68 (1.55-1.81)	1.14 (1.08-1.21)	1.35 (1.26-1.45)	0.88 (0.84-0.93)	1.12 (1.06-1.20)
Socio-Economic Factor Index-2 (SEFI-2) Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.08 (1.00-1.15)	0.99 (0.92-1.07)	0.96 (0.91-1.02)	0.91 (0.86-0.97)	0.90 (0.87-0.95)	0.89 (0.85-0.94)
	0 to 1	1.16 (1.07-1.24)	1.02 (0.94-1.10)	0.98 (0.93-1.04)	0.92 (0.87-0.98)	0.87 (0.84-0.91)	0.89 (0.84-0.94)
	>1	1 (0.92-1.09)	0.93 (0.84-1.03)	0.78 (0.73-0.84)	0.80 (0.74-0.87)	0.63 (0.59-0.67)	0.73 (0.68-0.78)
Married		0.91 (0.87-0.95)	0.79 (0.76-0.83)	1.01 (0.98-1.05)	0.89 (0.85-0.92)	1.13 (1.10-1.16)	0.95 (0.92-0.99)
Opioid Use		1.19 (1.14-1.27)	1.16 (1.11-1.22)	1.08 (1.04-1.12)	1.09 (1.05-1.14)	0.99 (0.96-1.02)	1.05 (1.01-1.09)

Independent Variable		Use Duration					
		≥180 Days		≥90 Days		≥60 Days	
		Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Psychotropic Rx Use (non-BZRA)		1.82 (1.75-1.90)	1.93 (1.83-2.02)	1.62 (1.56-1.67)	1.75 (1.69-1.83)	1.34 (1.30-1.38)	1.49 (1.44-1.54)
Charlson Comorbidity Index Score	0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.44 (1.36-1.51)	1.11 (1.04-1.17)	1.33 (1.27-1.39)	1.08 (1.02-1.13)	1.24 (1.19-1.29)	1.04 (1.00-1.08)
	2+	2.96 (2.79-3.15)	1.43 (1.32-1.55)	2.41 (2.29-2.54)	1.33 (1.24-1.42)	2.01 (1.92-2.11)	1.23 (1.15-1.31)
Resource Utilization Band	0-3	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4	1.84 (1.73-1.95)	1.15 (1.07-1.23)	1.58 (1.50-1.66)	1.08 (1.01-1.14)	1.37 (1.31-1.43)	1.00 (0.94-1.05)
	5	3.48 (3.24-3.73)	1.46 (1.33-1.60)	2.73 (2.56-2.92)	1.31 (1.20-1.42)	2.21 (2.08-2.35)	1.17 (1.09-1.27)
Male Prescriber of First Prescription		1.07 (1.02-1.12)	1.03 (0.98-1.09)	1.07 (1.02-1.11)	1.04 (0.99-1.09)	1.01 (0.98-1.05)	0.98 (0.94-1.02)
Prescriber Age ≥50 Years		1.08 (1.03-1.12)	0.98 (0.94-1.03)	1.08 (1.04-1.12)	0.99 (0.95-1.03)	1.15 (1.11-1.18)	1.08 (1.04-1.11)
Type of Prescriber of First Prescription	GP	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	Psychiatrist	2.06 (1.89-2.25)	2.11 (1.93-2.32)	1.85 (1.72-2.00)	1.89 (1.75-2.05)	1.54 (1.44-1.65	1.63 (1.51-1.75)
	Other	1.09 (0.98-1.21)	0.92 (0.82-1.03)	1.07 (0.98-1.17)	0.92 (0.84-1.01)	1.16 (1.07-1.24)	1.03 (0.96-1.11)
Period of First Prescription	2001-2006	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	2006-2011	1.66 (1.58-1.75)	1.74 (1.64-1.85)	1.58 (1.51-1.65)	1.65 (1.57-1.7)	1.41 (1.36-1.46)	1.48 (1.42-1.54)
	2011-2015	2.93 (2.78-3.08)	2.99 (2.80-3.18)	2.59 (2.48-2.71)	2.71 (2.57-2.8)	1.97 (1.90-2.05)	2.07 (1.98-2.16)

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=9,327)*	Z-Test of Two Proportions
Myocardial Infarction	2,474 (1.3%)	281 (3.0%)	$p < 0.01$
Congestive Heart Failure	3,943 (2.0%)	628 (6.7%)	$p < 0.01$
Peripheral Vascular Disease	2,367 (1.2%)	256 (2.7%)	$p < 0.01$
Cerebrovascular Disease	3,690 (1.9%)	544 (5.8%)	$p < 0.01$
Dementia	2,928 (1.5%)	796 (8.5%)	$p < 0.01$
COPD	23,064 (11.7%)	1,163 (12.5%)	$p = 0.02$
Connective Tissue/Rheumatic Disease	2,793 (1.4%)	222 (2.4%)	$p < 0.01$
Peptic Ulcer Disease	2,140 (1.1%)	114 (1.2%)	$p = 0.20$
Mild Liver Disease	2,406 (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%)	1,099 (11.8%)	$p < 0.01$
Complicated Diabetes	1,611 (0.8%)	252 (2.7%)	$p < 0.01$
Paraplegia and Hemiplegia	794 (0.4%)	136 (1.5%)	$p < 0.01$
Renal Disease	1,858 (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%)	$p < 0.01$



Flowchart of study population

48x70mm (300 x 300 DPI)

Supplemental Appendix Tables

Table A1 – International Classification for Disease Coding for Mood/Anxiety/Sleep Disorders (Cohort Inclusion)

	Source 1 - CPHA	Source 2 - MCHP	Study Algorithm
ICD Codes	All Mental Health Disorders: 9-CM: 290-319 10-CA: F00-F99	Mood Disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety Disorders: 300 (ICD-9-CM) or F40-F42	Mood disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety disorders: 300 (ICD-9-CM) or F40-F43 (ICD-10-CA) Sleep disorders: 307, 780 or F51, G47 ICD-10-CA)
Case Definition	≥1 hospitalization or outpatient medical claim within 1 year	≥1 hospitalization or ≥1-3 outpatient medical claims within 3-5 years*	≥1 hospitalization or ≥3 outpatient medical claims within 5 years**

**Range of similar definitions between studies from 2000 to 2016*

***The decision to use a 5-year pre-exposure window was based on the fact that all patients received a BZRA, which itself increases specificity for anxiety/sleep disorder diagnoses.*

Table A2 – International Classification for Disease Coding Algorithms for Seizure, Cancer and Palliation (Cohort Exclusion)

	Seizure	**Cancer and other Neoplasms**	**Palliation**
ICD Codes	9-CM: 345 10-CA: G40	9-CM: 140-165, 170-176,179-195, 200-208 10-CA: C00-C99	N/A*
Case Definition	≥1 hospitalization or ≥3 outpatient medical claim within 5 years before index date	≥1 hospitalization or ≥3 outpatient medical claims within 5 years before index date	Carrier code indicating palliative drug program enrollment in DPIN

**While ICD codes do exist for palliation, the DPIN carrier code '04' is expected to be a reliable indicator of when patients become ill enough that community use of medication is required for symptom management.*

Table A3 – Independent 'Patient' Variables for Prediction of Long-Term BZRA Use

Baseline Patient Characteristics	Definition (Variable Type)	Measurement Period
Age	*3 age groups; 18-44, 45-64, 65+ (Ordinal)*	*Index Date*
Sex	*Male or Female (Dichotomous Categorical)*	*Index Date*
Region	*Urban; Winnipeg or Brandon postal-codes* *Rural; Any other Manitoba postal-code* *(Dichotomous Categorical)*	*Census Period closest in time to the index date*
Socioeconomic Status	*Socio-Economic Factor Index – Version 2 (SEFI-2) score composite of four variables based on geography;* *i) unemployment rate* *ii) average household income* *iii) proportion of single-parent households* *iv) proportion of population without high school education.* *Scores <0 indicate more favourable socioeconomic conditions* *Scores >0 indicate less ideal socioeconomic conditions* *(Ordinal Scale)*	*Census Period closest in time to the index date*
Income Assistance	*Record of income assistance (Dichotomous Categorical)*	*Up to 1-year before the Index Date*
Marriage Record	*Record of Marriage (Dichotomous Categorical)*	*Entire available registry period up to the Index Date*
Residential Mobility (i.e frequent mover)	*Average of 1 move every 3 years from beginning of registry coverage to index date (Dichotomous)*	*Entire available registry period up to the Index Date*
Comorbidity Burden	*Charlson Comorbidity Index (CCI) Score; 0, 1, 2+ (Ordinal Scale)*	*Up to 1-year before the Index Date*
Healthcare Resource Use	*Johns Hopkins Adjusted Clinical Groups Resource Utilization Band (Ordinal Scale); placement into a band (0 to 5) based on grouping of*	*Up to 1-year before the Index Date*

	ICD	
Prescription Psychotropic Use (non-BZRA)	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*
Prescription Opioid Use	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*

Table A4 - Independent 'First-Prescription' Variables for Prediction of Long-Term BZRA Use

Characteristics of First Consultation and Subsequent Prescription	**Definition**	**Measurement Period**
Fiscal Year Period	*Fiscal year of first prescription Assigned to 3 five-year intervals; 2001-2005, 2006-2010, 2011-2015 (Ordinal)*	*Index Date*
Prescriber	*10 Years or More (Dichotomous)*	*Index Date*
Sex of Prescriber	*Male or Female (Dichotomous)*	*Index Date*
Prescriber Specialty	*General Practitioner, Psychiatry or Other (Categorical)*	*Index Date*

Table A5 – Logistic Regression Methodology

Criteria	Approach
Variable Selection	-Informal selection via published literature -Simple logistic regression; β values ($p < 0.25$)
Variable Coding	-Dichotomous Categorical; 0 or 1 -Ordinal; discrete number scale starting at 1 -Polychotomous Categorical; 0 or 1 with auto-generated dummy variables -No continuous variables retained
Events-per-Variable	-Minimum 10 events per independent variable rule
Conformity of Linear Gradient	-Ordered categorical variables assessed for conformity of linear gradient; nonconformity handled by variable transformation or separation into additional (design) variables (i.e fiscal year was shown to be linear with respect to outcome so condensed variable into 5-year increments)
Interaction effects	-Assessed at $p < 0.01$. Suspected interactions included; age*sex, residential mobility*SEFI*income assistance, psychotropic use*opioid use, RUB*CCI
Collinearity	-Analysis of variance inflation factor, correlation coefficients, eigenvalues

	-Significant collinearity; combine variables or removal of inferior explanatory variable
Statistical Significance	-Wald 95% CI for β and OR's
Goodness-of-Fit Measures	-C-statistic, Log-Likelihood Ratio, Hosmer-Lemeshow Statistic
Fitting Procedure	-Stepwise addition/subtraction of variables -Assessment of clinical significance

Table A6 – Goodness of Fit for Final Logistic Regression Models Predicting Long-Term Use of BZRA

Model	Model Type	Independent Variables	Likelihood Ratio (higher is better)	C statistic	Hosmer-Lemeshow Chi-Square Statistic
1	Main-Effects	9 Variables; Age-Sex Category, Period of First Rx, Psychotropic Use, Opioid Use, Income Assistance, Marriage, RUB CCI Score, Residential Mobility	6932 ($p < 0.001$)	0.738	10.78 ($p = 0.215$)
2	Main-Effects + Interaction Effects	10 Variables: All from Model 1 + Residential Mobility*Income Assistance	6945 ($p < 0.001$)	0.739	11.02 ($p = 0.20$)

Table A7 – Proportion of Long-Term BZRA Use by Differing Parameters and Duration Thresholds

Scenario*	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Cohort
A1**	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	9,327	4.51%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	13,745	6.64%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	19,948	9.64%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	13,050	6.31%
A5	First-Use Episode ≥ 180 days	90 Days	16,831	8.13%
A6	First-Use Episode ≥ 270 days	90 Days	15,214	7.35%
A7	First-Use Episode ≥ 365 days	90 Days	14,219	6.87%
B1	Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	38,853	18.78%
B2	Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	58,442	28.24%
B3	Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	72,639	35.10%
B4	Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	44,593	21.55%
B5	Mean Episode Duration ≥ 180 days	90 Days	50,142	24.23%
B6	User Mean Episode Duration ≥ 270 days	90 Days	39,395	19.04%
B7	User Mean	90 Days	32,200	15.56%

	Episode Duration ≥ 365 days			

*A=First Episode Scenario; B=Mean Episode Duration Scenario
**Primary Scenario Used for Logistic Regression

Table A8 - Proportion of Long-Term Z-Drug Use by Differing Parameters and Duration Thresholds

Scenario	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Sub-Cohort
A1	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	8,206	7.41%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	12,155	11.0%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	17,126	15.5%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	10,437	9.43%
A5	First-Use Episode ≥ 180 days	90 Days	12,719	11.49%
A6	First-Use Episode ≥ 270 days	90 Days	11,117	10.04%
A7	First-Use Episode ≥ 365 days	90 Days	10,045	9.07%
B1	User Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	21,859	19.75%
B2	User Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	32,020	28.92%
B3	User Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	39,690	35.85%
B4	User Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	24,098	21.77%
B5	User Mean	90 Days	26,477	23.92%

	Episode Duration ≥ 180 days			
B6	User Mean Episode Duration ≥ 270 days	90 Days	21,040	19.01%
B7	User Mean Episode Duration ≥ 365 days	90 Days	17,358	15.68%

Table A9 – Patient Characteristics of Z-Drug Users by First Use Episode Duration

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Sex Distribution	*Male*	40,516 (39.5%)	3,473 (42.3%)	43,989 (39.8%)
	Female	61,943 (60.5%)	4,731 (57.7%)	66,674 (60.2%)
Age Category	*18-44*	42,663 (41.6%)	1,795 (21.9%)	44,458 (40.2%)
	45-64	39,817 (38.9%)	3,184 (38.8%)	43,001 (38.9%)
	65+	20,011 (19.5%)	3,227 (39.3%)	23,238 (21.0%)
SEFI-2 Score	*<-1*	13,678 (13.3%)	981 (12.0%)	14,659 (13.2%)
	-1 to 0	45,136 (44.1%)	3,674 (44.8%)	48,810 (44.1%)
	0 to 1	33,719 (32.9%)	2,885 (35.2%)	36,604 (33.1%)
	>1	9,958 (9.7%)	666 (8.1%)	10,624 (9.6%)
Residence Distribution	*Urban*	63,207 (61.7%)	3,313 (40.4%)	66,520 (60.1%)
	Rural	39,284 (38.3%)	4,893 (59.6%)	44,177 (39.9%)
High Residential Mobility		22,408 (21.9%)	2,523 (30.8%)	24,931 (22.5%)
Receipt of Income Assistance		8,351 (8.2%)	758 (9.2%)	9,109 (8.2%)
Marriage Record		57,308 (55.9%)	4,595 (56.0%)	61,903 (55.9%)

Johns Hopkins Healthcare Resource Utilization Band	*0 (no utilization)*	1,771 (1.7%)	234 (2.9%)	2,005 (1.8%)
	1	3,205 (3.1%)	175 (2.1%)	3,380 (3.1%)
	2	17,523 (17.1%)	1,012 (12.3%)	18,535 (16.7%)
	3	65,067 (63.5%)	4,699 (57.3%)	69,766 (63.0%)
	4	10,810 (10.6%)	1,259 (15.3%)	12,069 (10.9%)
	5 (high-utilization)	4,083 (4.0%)	825 (10.1%)	4,908 (4.4%)
		Short-term	**Long-term**	**Total**
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Charlson Comorbidity index Score	*0*	72,490 (70.8%)	4,528 (55.2%)	77,018 (69.6%)
	1	19,495 (19.0%)	1,905 (23.2%)	21,400 (19.3%)
	2+	10,506 (10.3%)	1,773 (21.6%)	12,279 (11.1%)
Non-BZRA Psychotropic Prescription Dispensations	*0*	27,797 (27.1%)	1,784 (21.7%)	29,581 (26.7%)
	1	36,939 (36.1%)	2,156 (26.3%)	39,095 (35.3%)
	2+	37,755 (36.8%)	4,266 (52.0%)	42,021 (38.0%)
Opioid Prescription Dispensations	*0*	47,427 (46.3%)	3,298 (40.2%)	50,725 (45.8%)
	1	34,505 (33.7%)	2,772 (33.8%)	37,277 (33.7%)
	2+	20,559 (20.1%)	2,136 (26.0%)	22,695 (20.5%)
Sex of Prescriber Issuing First Prescription	*Male*	71,485 (69.8%)	5,627 (68.6%)	77,112 (69.7%)
	Female	28,485 (27.8%)	2,273 (27.7%)	30,758 (27.8%)
Age of Prescriber Issuing First Prescription	*50+ Years*	47,871 (46.7%)	4,014 (48.9%)	51,885 (46.9%)
	<50 Years	49,257 (48.1%)	3,758 (45.8%)	53,015 (47.9%)

Type of Prescriber Issuing First Prescription	*General Practitioner*	78,610 (76.7%)	6,366 (77.6%)	84,976 (76.8%)
	Psychiatry	3,912 (3.8%)	475 (5.8%)	4,387 (4.0%)
	Other	3,881 (3.8%)	381 (4.6%)	4,262 (3.9%)
Period of First Prescription	*2001-2006*	34,360 (33.5%)	1,526 (18.6%)	35,886 (32.4%)
	2006-2011	37,752 (36.8%)	2,808 (34.2%)	40,560 (36.7%)
	2011-2016	30,379 (29.6%)	3,872 (47.2%)	34,251 (31.0%)

Table A10 – Frequency of Charlson Comorbidity Group Diagnoses by First Use Episode Duration for Z-Drug Cohort

Charlson Diagnosis	**Short-Term 'First-Episode' Users** *(n=102,459)*	**Long-Term 'First-Episode' Users** *(n=8,204)*	**Z-Test of Two Proportions**
Myocardial Infarction	1,836 (1.8%)	306 (3.7%)	$p < 0.01$
Congestive Heart Failure	3,174 (3.1%)	700 (8.5%)	$p < 0.01$
Peripheral Vascular Disease	1,772 (1.7%)	284 (3.5%)	$p < 0.01$
Cerebrovascular Disease	2,321 (2.3%)	550 (6.7%)	$p < 0.01$
Dementia	1,925 (1.9%)	865 (10.5%)	$p < 0.01$
COPD	12,357 (12.1%)	1,171 (14.3%)	$p < 0.01$
Connective Tissue/Rheumatic Disease	1,906 (1.9%)	243 (3.0%)	$p < 0.01$
Peptic Ulcer Disease	1,111 (1.1%)	123 (1.5%)	$p < 0.01$
Mild Liver Disease	1,672 (1.6%)	139 (1.7%)	$p = 0.33$
Moderate/Severe Liver Disease	275 (0.2%)	38 (0.4%)	$p < 0.01$
Uncomplicated Diabetes	9,317 (9.1%)	1,150 (14.0%)	$p < 0.01$
Complicated Diabetes	1,639 (1.6%)	328 (4.0%)	$p < 0.01$
Paraplegia and Hemiplegia	508 (0.5%)	136 (1.7%)	$p < 0.01$
Renal Disease	1,543 (1.5%)	293 (3.6%)	$p < 0.01$
Cancer	2,109 (2.1%)	247 (3.0%)	$p < 0.01$
Metastatic Carcinoma	429 (0.4%)	45 (0.5%)	$p = 0.04$
HIV/AIDS	118 (0.1%)	16 (0.2%)	$p = 0.02$

Table A11 – Statistical Associations between Predictor Variables and Long-term Use of Z-Drugs

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		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		1.12 (1.07-1.18)	1.04 (0.99-1.09)	1.13 (1.08-1.17)	1.05 (1.01-1.10)	1.08 (1.05-1.12)	1.04 (1.00-1.08)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.90 (1.79-2.02)	2.02 (1.89-2.17)	1.74 (1.66-1.82)	1.78 (1.68-1.88)	1.71 (1.64-1.78)	1.68 (1.60-1.76)
	65+	3.83 (3.61-4.07)	3.71 (3.44-4.00)	3.24 (3.08-3.40)	3.08 (2.90-3.28)	2.99 (2.87-3.12)	2.78 (2.64-2.93)
Rural Residence		0.92 (0.88-0.96)	1.13 (1.07-1.19)	0.99 (0.96-1.03)	1.02 (0.98-1.07)	1.08 (1.04-1.11)	0.95 (0.91-0.99)
High Residential Mobility		1.59 (1.51-1.67)	1.26 (1.19-1.33)	1.53 (1.46-1.59)	1.21 (1.15-1.27)	1.30 (1.26-1.35)	1.12 (1.07-1.17)
Income Assistance		1.15 (1.06-1.24)	1.47 (1.34-1.61)	1.02 (0.95-1.09)	1.29 (1.19-1.40)	0.82 (0.77-0.87)	1.08 (1.00-1.17)
SEFI-2 Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.14 (1.06-1.22)	1.07 (0.99-1.16)	1.03 (0.97-1.09)	0.98 (0.92-1.04)	0.95 (0.91-1.00)	0.94 (0.89-0.99)
	0 to 1	1.19 (1.11-1.29)	1.08 (0.99-1.17)	1.04 (0.98-1.11)	0.99 (0.93-1.06)	0.92 (0.87-0.97)	0.93 (0.88-0.99)
	>1	0.93 (0.84-1.03)	0.84 (0.75-0.94)	0.80 (0.73-0.87)	0.77 (0.70-0.85)	0.68 (0.63-0.73)	0.72 (0.66-0.78)
Married		1.00 (0.96-1.05)	0.86 (0.82-0.91)	1.07 (1.03-1.10)	0.93 (0.89-0.98)	1.13 (1.10-1.17)	0.98 (0.94-1.01)
		1.28	1.15	1.26	1.15	1.18	1.11

Opioid Use		(1.22-1.34)	(1.09-1.21)	(1.21-1.31)	(1.11-1.20)	(1.14-1.21)	(1.07-1.15)
Independent Variable		***Use Duration***					
		≥180 days		***≥90 days***		***≥60 days***	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Psychotropic Rx Use (Non-BZRA)		1.34 (1.27-1.41)	1.24 (1.17-1.32)	1.35 (1.29-1.41)	1.27 (1.20-1.33)	1.22 (1.17-1.27)	1.19 (1.14-1.24)
Charlson Comorbidity Index Score	*0*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.56 (1.48-1.65)	1.25 (1.18-1.33)	1.45 (1.39-1.52)	1.21 (1.15-1.27)	1.33 (1.28-1.38)	1.13 (1.08-1.19)
	2+	2.70 (2.55-2.87)	1.46 (1.36-1.58)	2.34 (2.22-2.46)	1.38 (1.29-1.47)	2.02 (1.93-2.12)	1.30 (1.22-1.37)
Resource Utilization Band	*0-3 (≤Moderate)*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4 (High)	1.67 (1.56-1.78)	1.16 (1.08-1.25)	1.47 (1.39-1.56)	1.09 (1.01-1.16)	1.30 (1.24-1.37)	1.00 (0.95-1.07)
	5 (Very High)	2.89 (2.67-3.13)	1.55 (1.41-1.70)	2.43 (2.26-2.61)	1.42 (1.30-1.55)	1.97 (1.85-2.11)	1.22 (1.12-1.32)
Male Prescriber of First Prescription		0.99 (0.94-1.04)	0.97 (0.92-1.03)	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.94 (0.90-0.97)	0.93 (0.90-0.97)
Prescriber Age ≥50 Years		1.10 (1.05-1.15)	0.98 (0.93-1.03)	1.10 (1.06-1.15)	0.98 (0.94-1.02)	1.15 (1.11-1.19)	1.05 (1.01-1.09)
Prescriber of First Prescription	*GP*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Psychiatrist	1.50 (1.36-1.66)	1.96 (1.76-2.17)	1.36 (1.25-1.49)	1.72 (1.57-1.89)	1.41 (1.02-1.20)	1.38 (1.27-1.51)
	Other	1.21 (1.09-1.35)	0.92 (0.82-1.03)	1.18 (1.07-1.29)	0.91 (0.83-1.00)	1.19 (1.10-1.29)	0.98 (0.91-1.07)
Period of First Prescription	*2001-2006*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	2006-2011	1.68 (1.57-1.79)	1.57 (1.46-1.68)	1.67 (1.59-1.76)	1.56 (1.47-1.66)	1.53 (1.46-1.60)	1.46 (1.39-1.54)

	2011-2015	2.87 (2.70-3.05)	2.45 (2.28-2.65)	2.83 (2.69-2.97)	2.44 (2.30-2.59)	2.20 (2.10-2.29)	1.96 (1.86-2.07)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7, fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*12-13*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046916.R1
Article Type:	Original research
Date Submitted by the Author:	18-May-2021
Complete List of Authors:	Brandt, Jaden; University of Manitoba Janzen, Donica; University of Manitoba Alessi-Severini, Silvia; University of Manitoba Singer, Alexander; University of Manitoba Chateau, Dan; University of Manitoba Enns, Murray; University of Manitoba Leong, Christine; University of Manitoba
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, PSYCHIATRY, Anxiety disorders < PSYCHIATRY, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running Title: Risk of long-term benzodiazepine receptor agonist use

Jaden Brandt, MSc BScPharm[1], Donica Janzen, PhD Candidate BSP[1], Silvia Alessi-Severini, PhD[1,2], Alexander Singer, MB BAO BCh CCFP[3], Dan Chateau, PhD[2,4], Murray Enns, MD FRCPC[5], Christine Leong, PharmD BScPharm[1,5*]

[1]*College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[2]*Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, CAN*

[3]*Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[4]*Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[5]*Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

**Corresponding author: Dr. Christine Leong*

Apotex Centre, College of Pharmacy, Rady Faculty of Health Sciences

University of Manitoba

750 McDermot Avenue

Winnipeg, Manitoba R3E 0T5

P: (204) 318-5276

E: christine.leong@umanitoba.ca

Acknowledgements

The authors wish to acknowledge Dr. Sheryl Zelenitsky for her helpful comments on earlier drafts of this manuscript.

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under Research Ethic Board approval HS20498 (HIPC#2016/2017 – 062). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

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 April 1, 2001 to March 31, 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 odds ratio (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 one in twenty 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.

Key Words: *benzodiazepine, anxiety, insomnia, pharmacoepidemiology, clinical practice guidelines, z-drug hypnotics*

Strengths and Limitations of 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 de-identified 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 hospitalizations, 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 behavioral 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] Upon their initial introduction into clinical practice in the late 1960s, benzodiazepines were considered to be a safer alternative to barbiturates.[5] However, safety concerns such as psychomotor impaired accidents (i.e., 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

* ***Abbreviations****: BZRA, benzodiazepine receptor agonist; BZD, benzodiazepine*

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.

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, hospitalization discharge abstracts, income assistance records and prescriber demographics (Table 1). 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 Program 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 one year prior to the first prescription[20,21]) between April 1, 2001 to March 31, 2015, with no preceding dispensations from April 1, 2000 to March 31, 2001 (first year of the dataset) to avoid prevalent user bias (Figure 1). All individuals with at least one 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 one year. A sensitivity analysis was also performed in which incident use was defined as no prescription for a BZRA was received in the three years prior to the first prescription.[23]

Eligibility was also based on diagnostic criteria for anxiety/mood related disorders and/or insomnia based on ICD-9-CM or ICD-10-CA medical claims, either at outpatient physician visits or hospitalizations, 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 (Table A1).[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 program at any point in the 5 years preceding their first prescription for a BZRA (Table A2). 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 loss 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 (Figure 2).[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 six months have been previously reported to be unable to stop completely due to withdrawal symptoms (e.g., 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

(Figure 3). 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, hospitalization time was assumed to be a continuation of BZD use given that in-patient drug use data was limited.[31] The provincial drug program subsidizes 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, geographic residence, residential mobility, socioeconomic status, marriage, concurrent opioid or prescription psychotropic use, comorbidity burden, healthcare usage, time period of first prescription and prescriber characteristics (Table A3 and Table A4). 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 stabilizers).

Statistical Analysis

Standard reporting criteria were followed in the approach to logistic regression modelling (Table A5 and A6).[32] Univariate analysis was performed first in the form of simple logistic regression. The multi-variable 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 (i.e., 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 ≥ |0.8| or if any variance inflation factor was unreasonably high (≥10) while the corresponding tolerance factor was miniscule (≤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 1,568 claims (<0.01%) were excluded for being spurious (i.e '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, 6 sensitivity analyses (Tables A7 and Table A8) 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 (i.e., 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 was cleaned and analyzed using SAS v9.4©.

Ethical Approval

Access to the data for this project was approved by the University's Health Research Ethics Board (HREB, registration number H2017:052 (HS20498) and the Health Information Privacy Committee (HIPC, no. 2016/2017-62) of the provincial government. Consent for this study was not required by HREB given the retrospective nature of the study and data agreements in place through HIPC.

Results

Episodic BZD/Z-Drug Use

Study population demographics are presented in Table 2. 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%) (Table A7).

To evaluate treatment duration for insomnia, a sensitivity analysis was performed on only Z-Drugs (*n*=110,663), which found similar results (Tables A8-A11).

Factors Predicting Long-term First Episode Use

Logistic regression analysis revealed that male sex (adjusted odds ratio (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 to <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 utilization 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 odds ratios are presented for the full cohort in Table 3.

A sub-analysis 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 4). Proportions for these particular diagnoses were 2 to 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 three 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 to 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 recognized 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 (i.e., 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 de-prescribing 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 interference with another prescriber's decisions likely undermine potential de-prescribing 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.

The present 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. Firstly, administrative data is 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 hospitalizations 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 benzodiazepines 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 behavioral 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 generalizable 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 six 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.

References

1. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66 Suppl 2(suppl 2):28-33.

2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28(1):7-20. doi:10.1016/j.eurpsy.2011.11.003.

3. Moore N, Pariente A, Bégaud B. Why are benzodiazepines not yet controlled substances? *JAMA Psychiatry*. 2015;72(2):110-111. doi:10.1001/jamapsychiatry.2014.2190.

4. Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Fam Pract*. 2013;14:191. doi:10.1186/1471-2296-14-191.

5. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562. doi:10.1016/j.janxdis.2011.01.002.

6. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19-34. doi:10.2165/0023210-200923010-00002.

7. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: A meta-analysis. *Osteoporos Int*. 2014;25(1):105-120. doi:10.1007/s00198-013-2446-y.

8. Rapoport MJ, Lanctôt KL, Streiner DL, et al. Benzodiazepine use and driving: A meta-analysis. *J Clin Psychiatry*. 2009;70(5):663-673. doi:10.4088/JCP.08m04325.

9. Pariente A, De Gage SB, Moore N, Bégaud B. The Benzodiazepine-Dementia Disorders Link: Current State of Knowledge. *CNS Drugs*. 2016;30(1):1-7. doi:10.1007/s40263-015-0305-4.

10. Perlis RH, Ostacher MJ, Miklowitz DJ, et al. Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report. *J Clin Psychiatry*. 2010;71(2):194-200. doi:10.4088/JCP.09m05019yel.

11. Lai SW, Lai HC, Lin CL, Liao KF. Zopiclone use associated with increased risk of acute pancreatitis: A case-control study in Taiwan. *Int J Clin Pract*. 2015;69(11):1275-1280. doi:10.1111/ijcp.12689.

12. Dodds TJ. Prescribed benzodiazepines and suicide risk: A review of the literature. *Prim Care Companion CNS Discord*. 2017;19(2). doi:10.4088/PCC.16r02037.

13. Rodriguez-Roisin R, Garcia-Aymerich J. Should we exercise caution with benzodiazepine use in patients with COPD? *Eur Respir J*. 2014;44(2):284-286. doi:10.1183/09031936.00071014.

14. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017. doi:10.1007/s40268-017-0207-7.

15. El-Guebaly N, Sareen J, Stein MB. Are There Guidelines for the Responsible Prescription of Benzodiazepines? *Can J Psychiatry*. 2010;55(11):709-714.

16. Bendtsen P, Hensing G, McKenzie L, Stridsman AK. Prescribing benzodiazepines - A critical incident study of a physician dilemma. *Soc Sci Med*. 1999;49(4):459-467. doi:10.1016/S0277-9536(99)00133-1.

17. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. *Expert Opin Drug Saf*. 2014;13(7):919-934. doi:10.1517/14740338.2014.925444.

18. Alessi-Severini S, Bolton JM, Enns MW, Dahl M, Collins DM, Chateau D, Sareen J. Use of benzodiazepines and related drugs in Manitoba: a population-based study. CMAJ Open 2014;2(4):E208-16.

19. Berman E, Eyal S, Marom E. Trends in utilization of benzodiazepine and z-drug in Israel. Pharmacoepidemiol Drug Saf 2017;26(12):1555-1560.

20. Takano A, Ono S, Yamana H, et al. Factors associated with long-term prescription benzodiazepine: a retrospective cohort study using a health insurance database in Japan. BMJ Open 2019;9:e029641.

21. Hata T, Kanazawa T, Hamada T, et al. What can predict and prevent the long-term use of benzodiazepines? J Psychiatric Research 2018;97:94-100.

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-383; Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology* 1992;45(6):613-619.

23. Bramness, JG, Sexton, JA. The basic pharmacoepidemiology of benzodiazepine use in Norway 2004-9. Nor Epidemiol. 2011;21(1):35- 41.

24. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

25. Willems IAT, Gorgels WJMJ, Voshaar RCO, et al. Tolerance to benzodiazepines among long-term users in primary care. Family Practice 2013;30(4):404-410.

26. Public Health Agency of Canada. Government of Canada. *Report from the Canadian Chronic Disease Surveillance System: Mood and Anxiety Disorders in Canada*.; 2016. http://healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/mental-illness-2015-maladies-mentales/index-eng.php.

27. Manitoba Centre for Health Policy, Department of Community Health Sciences U of M. Concept: Mood and Anxiety Disorders - Measuring Prevalence. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1391#a_references. Published 2015. Accessed February 21, 2017.

28. MCHP. University of Manitoba - Manitoba Centre for Health Policy - Glossary: Anxiety /Anxiety States. http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102267. Published 2010. Accessed July 11, 2018.

29. Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, Kwok C-W. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med*. 2015;16(4):477-482. doi:10.1016/j.sleep.2014.10.018.

30. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295-301. doi:10.1111/j.1365-2125.2012.04418.x.

31. Palmaro A, Boucherie Q, Dupouy J, Micallef J, Lapeyre-Mestre M. Immeasurable time bias due to hospitalization in medico-administrative databases: which impact for pharmacoepidemiological studies? *Pharmacoepidemiol Drug Saf*. 2017;26(5):544-553. doi:10.1002/pds.4193.

32. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol*. 2001;54(10):979-985. doi:10.1016/S0895-4356(01)00372-9.

33. Rasouliyan L, Miller DP. The Logic and Logistics of Logistic Regression. In: *Western Users of SAS Software 2006*. Irvine, CA; 2006:1-14. https://www.lexjansen.com/wuss/2006/analytics/ANL-Rasouliyan.pdf.

34. Schreiber-Gregory DN. *Multicollinearity : What Is It , Why Should We Care , and How Can It Be Controlled ?*; 2017. https://analytics.ncsu.edu/sesug/2017/SESUG2017_Paper-160_Final_PDF.pdf.

35. Bennett D. How can I deal with missing data in my study? *Aust New Zeal J public ….* 2001;25(5):464-469. http://onlinelibrary.wiley.com/doi/10.1111/j.1467-842X.2001.tb00294.x/abstract.

36. Lash TL, Fox MP, Maclehose RF, Maldonado G, Mccandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149.

37. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia

disorder in adults: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175.

38. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(2):307-349

39. National Institute for Clinical Excellence. *Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia*.; 2004. https://www.nice.org.uk/guidance/ta77/resources/guidance-on-the-use-of-zaleplon-zolpidem-and-zopiclone-for-the-shortterm-management-of-insomnia-2294763557317.

40. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114.

41. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.

42. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

43. Islam MM. Pattern and probability of dispensing of prescription opioids and benzodiazepines among the new users in Australia: a retrospective cohort study. BMJ Open 2019;9:e030803.

44. Sirdifield C, Chipchase SY, Owen S, Siriwardena AN. A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. *Patient*. 2016:1-15. doi:10.1007/s40271-016-0182-z.

45. Simon GE, VonKorff M, Barlow W, Pabiniak C, Wagner E. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996;49(9):1067-1073. doi:10.1016/0895-4356(96)00139-4.

46. Alessi-Severini S, Bolton JM, Enns MW, et al. Sustained use of benzodiazepines and escalation to high doses in a Canadian population. *Psychiatr Serv*. 2016;67(9):1012-8.

47. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy (New York)*. 2010;97(2-3):122-129.

doi:10.1016/j.healthpol.2010.03.008.

48. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

49. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *Br J Clin Pharmacol*. 2008;65(4):593-599. doi:10.1111/j.1365-2125.2007.03060.x.

50. Jorm AF, Grayson DA, Creasey H, Waite L, Broe GA. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health*. 2000;24(1):7-10. doi:10.1111/j.1467-842X.2000.tb00715.x.

51. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf*. 2018;(October 2017):3-6. doi:10.1002/pds.4551.

52. Fride Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scand J Prim Health Care*. 2015;33(4):252-259. doi:10.3109/02813432.2015.1117282.

53. Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol*. 2012;68(3):311-319. doi:10.1007/s00228-011-1124-2.

54. Fang SY, Chen CY, Chang IS, Wu ECH, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: A population-based study. *Drug Alcohol Depend*. 2009;104(1-2):140-146. doi:10.1016/j.drugalcdep.2009.04.017.

55. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

56. Anderson ABT et al. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other drugs. *Pharmacoepidemiol Drug Saf*. 2011;20:378-385. doi:10.1002/pds.

57. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. *Psychol Med*. 2010;40(9):1495-1505. doi:10.1017/S0033291709991942.

58. Patten SB, Williams JVA, Lavorato DH, Kassam A, Sabapathy CD. Sedative – Hypnotic Use in a Canadian General Population Cohort During 12 Years of Follow-up. *Can J Psychiatry*. 2010;55(12):792-799.

59. Mattos MK, Sereika SM, Naples JG, Albert SM. Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults. *Drugs - Real World Outcomes*. 2016;3(3):289-296. doi:10.1007/s40801-016-0080-7.

60. Manthey L, Van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: The Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71(2):263-272. doi:10.1111/j.1365-2125.2010.03818.x.

61. Sakshaug S, Handal M, Hjellvik V, et al. Long-term Use of Z-Hypnotics and Co-Medication with Benzodiazepines and Opioids. *Basic Clin Pharmacol Toxicol*. 2016. doi:10.1111/bcpt.12684.

Availability of Data and Materials

Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at MCHP. The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository.

Author Statement

Jaden Brandt contributed to the conception, design, acquisition of data, analysis, and writing of the manuscript. Donica Janzen contributed to the analysis, interpretation, and writing of the manuscript. Silvia Alessi-Severini contributed to the interpretation and writing of the manuscript. Dan Chateau contributed to the interpretation and analysis of the study. Murray Enns contributed to the interpretation and writing of the study. Alexander Singer contributed to the interpretation and writing of the study. Christine Leong contributed to the conception, design, interpretation, and writing of the manuscript.

Conflict of Interest Disclosure

The authors declare no conflicts of interest related to any aspects of this work.

Funding

This work was supported by the College of Pharmacy at the University of Manitoba. Additional student funding for JB was granted by the Provincial Government of Manitoba in the form of a Manitoba Graduate Scholarship stipend. Funding sources had no role in the conduct of research and/or preparation of the article.

Patient and Public Involvement

We have a patient advisory group who provided feedback on the dissemination of research findings.

Table 1 –Raw Data Sources and Relevant Corresponding Data Elements

Database	Date Range of Data	Relevant Data Elements
Drug Program Information Network (DPIN)	Apr. 1/2000 – Mar. 31/2016	Prescriptions for benzodiazepines (ATC codes N03AE, N05BA, N05CD), Z-Drugs (N05CF), Antidepressants, Antipsychotics, Mood stabilisers, Lithium and Opioids -Drug, dosage strength, dosage type, metric quantity dispensed, day supply, date of dispensation
Manitoba Health Insurance Registry	Apr. 1/1996 – Mar. 31/2016	Birth date/age of patient; sex; location of residence, marital status, date of Manitoba Health coverage, date of coverage end, reason for coverage end (i.e death, emigration etc.)
Medical Claims (Physician Billings)	Apr. 1/1996 – Mar. 31/2016	Services - type of physician (e.g., psychiatrist); dates of services, specific diagnoses (ICD-9 or ICD-10 equivalent)
Hospital Separations Abstracts	Apr. 1/1996 – Mar. 31/2016	Diagnoses (ICD-9 or ICD-10 equivalent), length of stay, admission dates, discharge dates,

Provider Registry/Physician Master File	Apr. 1/1996 – Mar. 31/2016	Physician Age, Sex, Specialty
Social Allowances Management Information Network (SAMIN)	Apr. 1/2001– Mar. 31/2013	Receipt of income assistance

Table 2. **Characteristics of BZRA Users by First Use Episode Duration**

		Short-term	Long-term	Total
Number of Users		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
*Sex Distribution**	*Male*	74,487 (37.7%)	4,295 (46.1%)	78,782 (38.1%)
	Female	123,057 (62.3%)	5,029 (53.9%)	128,086 (61.9%)
Age Category	*18-44*	101,709 (51.5%)	2,776 (29.8%)	104,487 (50.5%)
	45-64	66,752 (33.8%)	3,320 (35.6%)	70,072 (33.9%)
	65+	29,143 (14.7%)	3,231 (34.6%)	32,374 (15.6%)
SEFI-2 Score	*<-1*	24,955 (12.6%)	1,089 (11.7%)	26,044 (12.6%)
	-1 to 0	81,718 (41.4%)	3,835 (41.1%)	85,553 (41.3%)
	0 to 1	64,967 (32.9%)	3,274 (35.1%)	68,241 (33.0%)
	>1	25,966 (13.1%)	1,129 (12.1%)	27,095 (13.1%)
Residence Distribution	*Urban*	125,950 (63.7%)	5,802 (62.2%)	131,752 (63.7%)
	Rural	71,656 (36.3%)	3,525 (37.8%)	75,181 (36.3%)
High Residential Mobility		36,392 (18.4%)	2,385 (25.6%)	38,777 (18.7%)

Receipt of Income Assistance		18,530 (9.4%)	1,222 (13.1%)	19,752 (9.5%)
Marriage Record		102,461 (51.9%)	4,618 (49.5%)	107,079 (51.8%)
*Johns Hopkins Healthcare Resource Utilization Band***	*0* *(no utilization)*	3,001 (1.5%)	349 (3.7%)	3,350 (1.6%)
	1	5,798 (2.9%)	182 (2.0%)	5,980 (2.9%)
	2	33,974 (17.2%)	1,192 (12.8%)	35,166 (17.0)
	3	127,824 (64.7%)	5,151 (55.2%)	132,975 (64.3%)
	4	20,065 (10.2%)	1,486 (15.9%)	21,551 (10.4%)
	5 *(high-utilization)*	6,882 (3.5%)	964 (10.3%)	7,846 (3.8%)
		Short-term	**Long-term**	**Total**
Number of Users		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
Charlson Comorbidity index Score	*0*	148,257 (75.0%)	5,783 (62.0%)	154,040 (74.4%)
	1	36,261 (18.4%)	2,031 (21.8%)	38,292 (18.5%)
	2+	13,088 (6.6%)	1,513 (16.2%)	14,601 (7.1%)
Non-BZRA Psychotropic Prescription Dispensations	*0*	111,216 (56.3%)	3,862 (41.4%)	115,078 (55.6%)
	1	17,661 (8.9%)	518 (5.6%)	18,179 (8.8%)
	2+	68,729 (34.8%)	4,947 (53.0%)	73,676 (35.6%)
Opioid Prescription Dispensations	*0*	132,027 (66.8%)	5,855 (62.8%)	137,882 (66.6%)

	1	30,530 (15.5%)	1,011 (10.8%)	169,423 (15.2%)
	2+	35,049 (17.7%)	2,461 (26.4%)	37,510 (18.2%)
*Sex of Prescriber Issuing First Prescription****	*Male*	143,619 (75.3%)	6,928 (76.5%)	150,547 (75.3%)
	Female	47,128 (24.7%)	2,126 (23.5%)	49,254 (24.7%)
Age of Prescriber Issuing First Prescription†	*50+ Years*	95,629 (52.1%)	4,775 (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%)	7,013 (87.5%)	153,836 (91.4%)
	Psychiatry	6,338 (4.1%)	624 (7.8%)	6,962 (4.1%)
	Other	7,183 (4.5%)	375 (4.7%)	7,558 (4.5%)
Period of First Prescription	*2001-2006*	90,008 (45.5%)	2,608 (28.0%)	92,616 (44.8%)
	2006-2011	65,750 (33.3%)	3,170 (34.0%)	68,920 (33.3%)
	2011-2016	41,848 (21.2%)	3,549 (38.1%)	45,397 (21.9%)

*N=197,544 (short-term users); N=9,324 (long-term users); N=206,868 (total users)
**N=197,544 (short-term users); N=9,324 (long-term users); N=206,868 (total users)
***N=190,747 (short-term users); N=9,054 (long-term users); N=199,801 (total users)
†N=183,462 (short-term users); N=8,851 (long-term users); N=192,313 (total users)
‡N=160,344 (short-term users); N=8,012 (long-term users); N=168,356 (total users)

Table 3 – Statistical Associations between Predictor Variables and Long-term Use of BZRAs

Independent Variable		Use Duration					
		≥180 Days		≥90 Days		≥60 Days	
		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 (1.35-1.47)	1.33 (1.27-1.39)	1.40 (1.35-1.45)	1.34 (1.29-1.40)	1.30 (1.26-1.34)	1.27 (1.23-1.31)
Age	18-44	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.82 (1.73-1.92)	2.24 (2.11-2.38)	1.77 (1.70-1.85)	2.00 (1.91-2.10)	1.81 (1.77-1.86)	1.89 (1.82-1.97)
	65+	4.06 (3.86-4.28)	5.15 (4.81-5.52)	3.56 (3.41-3.72)	4.11 (3.88-4.36)	3.34 (3.22-3.47)	3.52 (3.36-3.70)
Rural Residence		1.07 (1.02-1.11)	1.10 (1.04-1.15)	0.97 (0.93-1.00)	0.97 (0.94-1.02)	0.90 (0.87-0.92)	0.92 (0.88-0.95)
High Residential Mobility		1.52 (1.45-1.60)	1.14 (1.08-1.21)	1.35 (1.29-1.40)	1.06 (1.01-1.11)	1.14 (1.10-1.18)	1.01 (0.97-1.06)
Income Assistance		1.46 (1.37-1.55)	1.68 (1.55-1.81)	1.14 (1.08-1.21)	1.35 (1.26-1.45)	0.88 (0.83-0.93)	1.12 (1.06-1.20)
Socio-Economic Factor Index-2 (SEFI-2) Score	<-1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.08 (1.00-1.15)	0.99 (0.92-1.07)	0.96 (0.91-1.02)	0.91 (0.86-0.97)	0.90 (0.87-0.95)	0.89 (0.85-0.94)
	0 to 1	1.16 (1.07-1.24)	1.02 (0.94-1.10)	0.98 (0.93-1.04)	0.92 (0.87-0.98)	0.87 (0.83-0.91)	0.89 (0.84-0.94)
	>1	1 (0.92-1.09)	0.93 (0.84-1.03)	0.78 (0.73-0.84)	0.80 (0.74-0.87)	0.63 (0.59-0.67)	0.73 (0.68-0.78)
Married		0.91 (0.87-0.95)	0.79 (0.76-0.83)	1.01 (0.98-1.05)	0.89 (0.85-0.92)	1.13 (1.10-1.16)	0.95 (0.92-0.99)
Opioid Use		1.19 (1.14-1.27)	1.16 (1.11-1.22)	1.08 (1.04-1.12)	1.09 (1.05-1.14)	0.99 (0.96-1.02)	1.05 (1.01-1.09)
Independent Variable		Use Duration					

		≥180 Days		≥90 Days		≥60 Days	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Psychotropic Rx Use (non-BZRA)		1.82 (1.75-1.90)	1.93 (1.83-2.02)	1.62 (1.56-1.67)	1.75 (1.69-1.83)	1.34 (1.30-1.38)	1.49 (1.44-1.54)
Charlson Comorbidity Index Score	*0*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.44 (1.36-1.51)	1.11 (1.04-1.17)	1.33 (1.27-1.39)	1.08 (1.02-1.13)	1.24 (1.19-1.29)	1.04 (1.00-1.08)
	2+	2.96 (2.79-3.15)	1.43 (1.32-1.55)	2.41 (2.29-2.54)	1.33 (1.24-1.42)	2.01 (1.92-2.11)	1.23 (1.15-1.31)
Resource Utilization Band	*0-3*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4	1.84 (1.73-1.95)	1.15 (1.07-1.23)	1.58 (1.50-1.66)	1.08 (1.01-1.14)	1.37 (1.31-1.43)	1.00 (0.94-1.05)
	5	3.48 (3.24-3.73)	1.46 (1.33-1.60)	2.73 (2.56-2.92)	1.31 (1.20-1.42)	2.21 (2.08-2.35)	1.17 (1.09-1.27)
Male Prescriber of First Prescription		1.07 (1.02-1.12)	1.03 (0.98-1.09)	1.07 (1.02-1.11)	1.04 (0.99-1.09)	1.01 (0.98-1.05)	0.98 (0.94-1.02)
Prescriber Age ≥50 Years		1.08 (1.03-1.12)	0.98 (0.94-1.03)	1.08 (1.04-1.12)	0.99 (0.95-1.03)	1.15 (1.11-1.18)	1.08 (1.04-1.11)
Type of Prescriber of First Prescription	*GP*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	Psychiatrist	2.06 (1.89-2.25)	2.11 (1.93-2.32)	1.85 (1.72-2.00)	1.89 (1.75-2.05)	1.54 (1.44-1.65	1.63 (1.51-1.75)
	Other	1.09 (0.98-1.21)	0.92 (0.82-1.03)	1.07 (0.98-1.17)	0.92 (0.84-1.01)	1.16 (1.07-1.24)	1.03 (0.96-1.11)
Period of First Prescription	*2001-2006*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	2006-2011	1.66 (1.58-1.75)	1.74 (1.64-1.85)	1.58 (1.51-1.65)	1.65 (1.57-1.7)	1.41 (1.36-1.46)	1.48 (1.42-1.54)
	2011-2015	2.93 (2.78-3.08)	2.99 (2.80-3.18)	2.59 (2.48-2.71)	2.71 (2.57-2.8)	1.97 (1.90-2.05)	2.07 (1.98-2.16)

Table 4 – 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=9,327)*	Z-Test of Two Proportions
Myocardial Infarction	2,474 (1.3%)	281 (3.0%)	$p < 0.01$
Congestive Heart Failure	3,943 (2.0%)	628 (6.7%)	$p < 0.01$
Peripheral Vascular Disease	2,367 (1.2%)	256 (2.7%)	$p < 0.01$
Cerebrovascular Disease	3,690 (1.9%)	544 (5.8%)	$p < 0.01$
Dementia	2,928 (1.5%)	796 (8.5%)	$p < 0.01$
COPD	23,064 (11.7%)	1,163 (12.5%)	$p = 0.02$
Connective Tissue/Rheumatic Disease	2,793 (1.4%)	222 (2.4%)	$p < 0.01$
Peptic Ulcer Disease	2,140 (1.1%)	114 (1.2%)	$p = 0.20$
Mild Liver Disease	2,406 (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%)	1,099 (11.8%)	$p < 0.01$
Complicated Diabetes	1,611 (0.8%)	252 (2.7%)	$p < 0.01$
Paraplegia and Hemiplegia	794 (0.4%)	136 (1.5%)	$p < 0.01$
Renal Disease	1,858 (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%)	$p < 0.01$

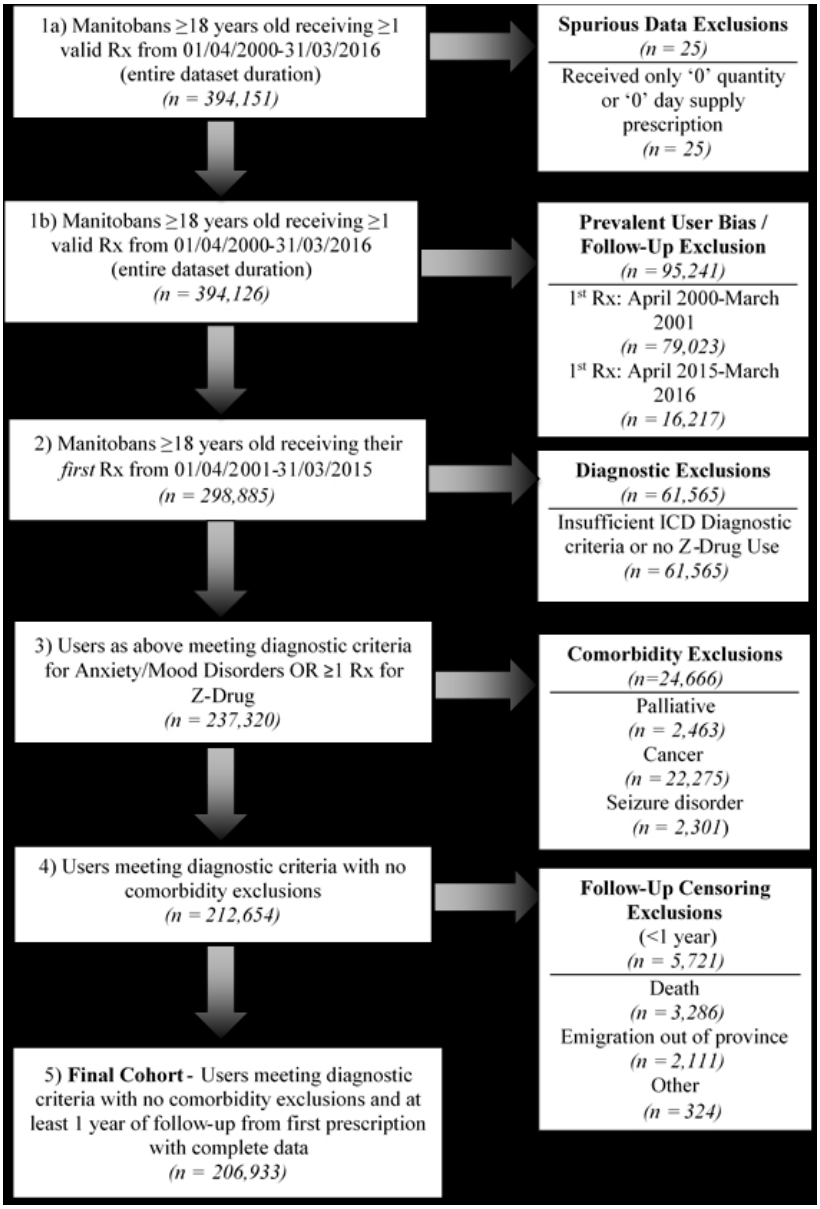
Figure Legend/Caption

Figure 1. Flowchart of study population

Figure 2. Definition of long-term use (≥180 days)

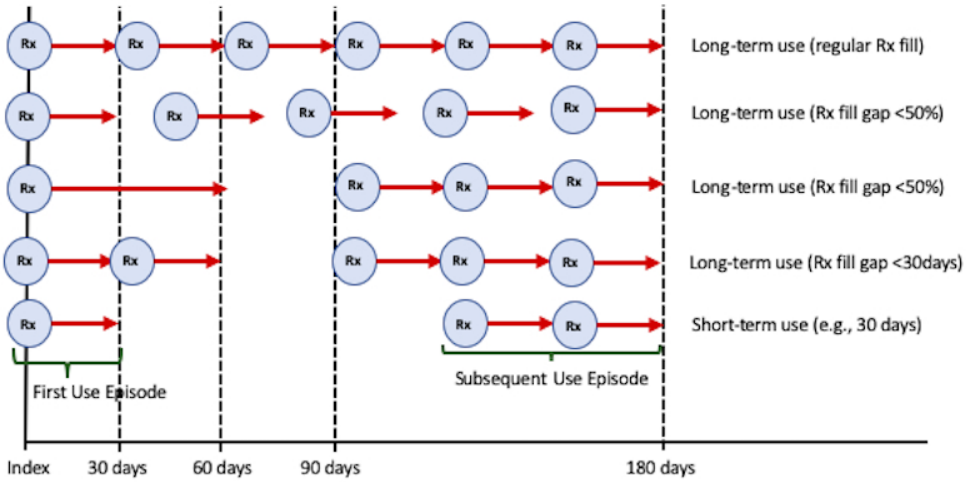
Figure 3a. Duration of use determination

Figure 3b. Legend



Flowchart of study population

48x70mm (300 x 300 DPI)



Definition of long-term use (≥180 days)

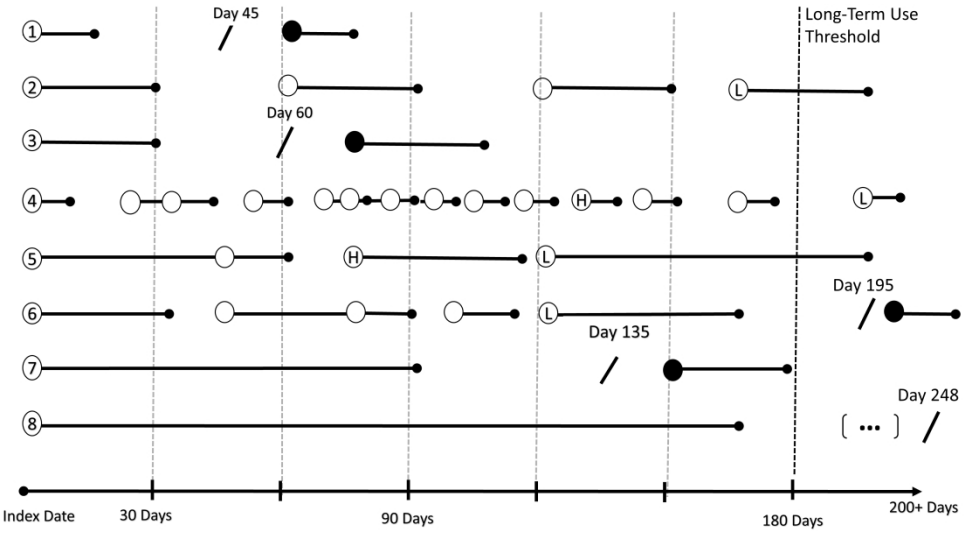


Figure 3a. Duration of use determination

338x190mm (300 x 300 DPI)

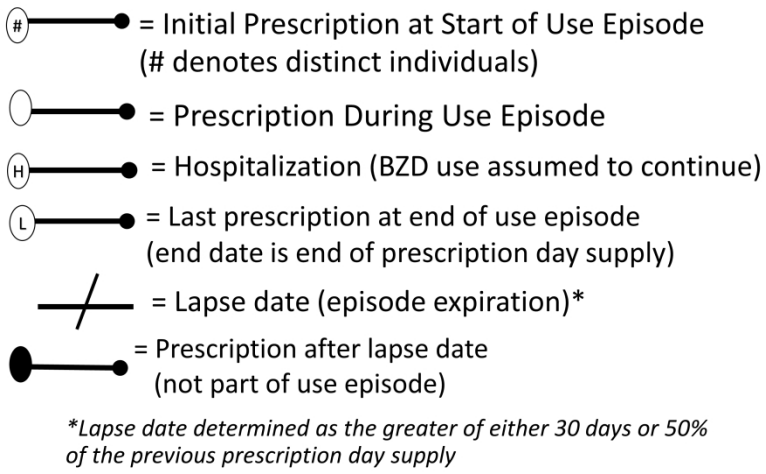


Figure 3b. Legend

338x190mm (300 x 300 DPI)

Supplemental Appendix Tables

Table A1 – International Classification for Disease Coding for Mood/Anxiety/Sleep Disorders (Cohort Inclusion)

	Source 1 - CPHA	Source 2 - MCHP	Study Algorithm
ICD Codes	All Mental Health Disorders: 9-CM: 290-319 10-CA: F00-F99	Mood Disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety Disorders: 300 (ICD-9-CM) or F40-F42	Mood disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety disorders: 300 (ICD-9-CM) or F40-F43 (ICD-10-CA) Sleep disorders: 307, 780 or F51, G47 ICD-10-CA)
Case Definition	≥1 hospitalization or outpatient medical claim within 1 year	≥1 hospitalization or ≥1-3 outpatient medical claims within 3-5 years*	≥1 hospitalization or ≥3 outpatient medical claims within 5 years**

**Range of similar definitions between studies from 2000 to 2016*

***The decision to use a 5-year pre-exposure window was based on the fact that all patients received a BZRA, which itself increases specificity for anxiety/sleep disorder diagnoses.*

Table A2 – International Classification for Disease Coding Algorithms for Seizure, Cancer and Palliation (Cohort Exclusion)

	Seizure	Cancer and other Neoplasms	Palliation
ICD Codes	9-CM: 345 10-CA: G40	9-CM: 140-165, 170-176,179-195, 200-208 10-CA: C00-C99	N/A*
Case Definition	≥1 hospitalization or ≥3 outpatient medical claim within 5 years before index date	≥1 hospitalization or ≥3 outpatient medical claims within 5 years before index date	Carrier code indicating palliative drug program enrollment in DPIN

**While ICD codes do exist for palliation, the DPIN carrier code '04' is expected to be a reliable indicator of when patients become ill enough that community use of medication is required for symptom management.*

Table A3 – Independent 'Patient' Variables for Prediction of Long-Term BZRA Use

Baseline Patient Characteristics	Definition (Variable Type)	Measurement Period
Age	*3 age groups; 18-44, 45-64, 65+ (Ordinal)*	*Index Date*
Sex	*Male or Female (Dichotomous Categorical)*	*Index Date*
Region	*Urban; Winnipeg or Brandon postal-codes* *Rural; Any other Manitoba postal-code* *(Dichotomous Categorical)*	*Census Period closest in time to the index date*
Socioeconomic Status	*Socio-Economic Factor Index – Version 2 (SEFI-2) score composite of four variables based on geography;* *i) unemployment rate* *ii) average household income* *iii) proportion of single-parent households* *iv) proportion of population without high school education.* *Scores <0 indicate more favourable socioeconomic conditions* *Scores >0 indicate less ideal socioeconomic conditions* *(Ordinal Scale)*	*Census Period closest in time to the index date*
Income Assistance	*Record of income assistance (Dichotomous Categorical)*	*Up to 1-year before the Index Date*
Marriage Record	*Record of Marriage (Dichotomous Categorical)*	*Entire available registry period up to the Index Date*
Residential Mobility (i.e frequent mover)	*Average of 1 move every 3 years from beginning of registry coverage to index date (Dichotomous)*	*Entire available registry period up to the Index Date*
Comorbidity Burden	*Charlson Comorbidity Index (CCI) Score; 0, 1, 2+ (Ordinal Scale)*	*Up to 1-year before the Index Date*
Healthcare Resource Use	*Johns Hopkins Adjusted Clinical Groups Resource Utilization Band (Ordinal Scale); placement into a band (0 to 5) based on grouping of*	*Up to 1-year before the Index Date*

	ICD	
Prescription Psychotropic Use (non-BZRA)	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*
Prescription Opioid Use	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*

Table A4 - Independent 'First-Prescription' Variables for Prediction of Long-Term BZRA Use

Characteristics of First Consultation and Subsequent Prescription	**Definition**	**Measurement Period**
Fiscal Year Period	*Fiscal year of first prescription Assigned to 3 five-year intervals; 2001-2005, 2006-2010, 2011-2015 (Ordinal)*	*Index Date*
Prescriber	*10 Years or More (Dichotomous)*	*Index Date*
Sex of Prescriber	*Male or Female (Dichotomous)*	*Index Date*
Prescriber Specialty	*General Practitioner, Psychiatry or Other (Categorical)*	*Index Date*

Table A5 – Logistic Regression Methodology

Criteria	Approach
Variable Selection	-Informal selection via published literature -Simple logistic regression; β values ($p < 0.25$)
Variable Coding	-Dichotomous Categorical; 0 or 1 -Ordinal; discrete number scale starting at 1 -Polychotomous Categorical; 0 or 1 with auto-generated dummy variables -No continuous variables retained
Events-per-Variable	-Minimum 10 events per independent variable rule
Conformity of Linear Gradient	-Ordered categorical variables assessed for conformity of linear gradient; nonconformity handled by variable transformation or separation into additional (design) variables (i.e fiscal year was shown to be linear with respect to outcome so condensed variable into 5-year increments)
Interaction effects	-Assessed at $p < 0.01$. Suspected interactions included; age*sex, residential mobility*SEFI*income assistance, psychotropic use*opioid use, RUB*CCI
Collinearity	-Analysis of variance inflation factor, correlation coefficients, eigenvalues -Significant collinearity; combine variables or

	removal of inferior explanatory variable
Statistical Significance	-Wald 95% CI for β and OR's
Goodness-of-Fit Measures	-C-statistic, Log-Likelihood Ratio, Hosmer-Lemeshow Statistic
Fitting Procedure	-Stepwise addition/subtraction of variables -Assessment of clinical significance

Table A6 – Goodness of Fit for Final Logistic Regression Models Predicting Long-Term Use of BZRA

Model	Model Type	Independent Variables	Likelihood Ratio (higher is better)	C statistic	Hosmer-Lemeshow Chi-Square Statistic
1	Main-Effects	9 Variables; Age-Sex Category, Period of First Rx, Psychotropic Use, Opioid Use, Income Assistance, Marriage, RUB CCI Score, Residential Mobility	6932 ($p < 0.001$)	0.738	10.78 ($p = 0.215$)
2	Main-Effects + Interaction Effects	10 Variables: All from Model 1 + Residential Mobility*Income Assistance	6945 ($p < 0.001$)	0.739	11.02 ($p = 0.20$)

Table A7 – Proportion of Long-Term BZRA Use by Differing Parameters and Duration Thresholds

Scenario*	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Cohort
A1**	First-Use Episode ≥ 180 days	Greater of either 30 days or 50% of previous Day Supply	9,327	4.51%
A2	First-Use Episode ≥ 90 days	Greater of either 30 days or 50% of previous Day Supply	13,745	6.64%
A3	First-Use Episode ≥ 60 days	Greater of either 30 days or 50% of previous Day Supply	19,948	9.64%
A4	First-Use Episode ≥ 180 days	Greater of either 60 Days or 50% of previous Day Supply	13,050	6.31%
A5	First-Use Episode ≥ 180 days	90 Days	16,831	8.13%
A6	First-Use Episode ≥ 270 days	90 Days	15,214	7.35%
A7	First-Use Episode ≥ 365 days	90 Days	14,219	6.87%
B1	Mean Episode Duration ≥ 180 days	Greater of either 30 days or 50% of previous Day Supply	38,853	18.78%
B2	Mean Episode Duration ≥ 90 days	Greater of either 30 days or 50% of previous Day Supply	58,442	28.24%
B3	Mean Episode Duration ≥ 60 days	Greater of either 30 days or 50% of previous Day Supply	72,639	35.10%
B4	Mean Episode Duration ≥ 180 days	Greater of either 60 Days or 50% of previous Day Supply	44,593	21.55%
B5	Mean Episode Duration ≥ 180 days	90 Days	50,142	24.23%
B6	User Mean Episode Duration ≥ 270 days	90 Days	39,395	19.04%
B7	User Mean Episode Duration	90 Days	32,200	15.56%

	≥ 365 days			

*A=First Episode Scenario; B=Mean Episode Duration Scenario
**Primary Scenario Used for Logistic Regression

Table A8 - Proportion of Long-Term Z-Drug Use by Differing Parameters and Duration Thresholds

Scenario	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Sub-Cohort
A1	First-Use Episode ≥ 180 days	Greater of either 30 days or 50% of previous Day Supply	8,206	7.41%
A2	First-Use Episode ≥ 90 days	Greater of either 30 days or 50% of previous Day Supply	12,155	11.0%
A3	First-Use Episode ≥ 60 days	Greater of either 30 days or 50% of previous Day Supply	17,126	15.5%
A4	First-Use Episode ≥ 180 days	Greater of either 60 Days or 50% of previous Day Supply	10,437	9.43%
A5	First-Use Episode ≥ 180 days	90 Days	12,719	11.49%
A6	First-Use Episode ≥ 270 days	90 Days	11,117	10.04%
A7	First-Use Episode ≥ 365 days	90 Days	10,045	9.07%
B1	User Mean Episode Duration ≥ 180 days	Greater of either 30 days or 50% of previous Day Supply	21,859	19.75%
B2	User Mean Episode Duration ≥ 90 days	Greater of either 30 days or 50% of previous Day Supply	32,020	28.92%
B3	User Mean Episode Duration ≥ 60 days	Greater of either 30 days or 50% of previous Day Supply	39,690	35.85%
B4	User Mean Episode Duration	Greater of either 60 Days or 50% of	24,098	21.77%

	≥ 180 days	previous Day Supply		
B5	User Mean Episode Duration ≥ 180 days	90 Days	26,477	23.92%
B6	User Mean Episode Duration ≥ 270 days	90 Days	21,040	19.01%
B7	User Mean Episode Duration ≥ 365 days	90 Days	17,358	15.68%

Table A9 – Patient Characteristics of Z-Drug Users by First Use Episode Duration

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Sex Distribution	*Male*	40,516 (39.5%)	3,473 (42.3%)	43,989 (39.8%)
	Female	61,943 (60.5%)	4,731 (57.7%)	66,674 (60.2%)
Age Category	*18-44*	42,663 (41.6%)	1,795 (21.9%)	44,458 (40.2%)
	45-64	39,817 (38.9%)	3,184 (38.8%)	43,001 (38.9%)
	65+	20,011 (19.5%)	3,227 (39.3%)	23,238 (21.0%)
SEFI-2 Score	*<-1*	13,678 (13.3%)	981 (12.0%)	14,659 (13.2%)
	-1 to 0	45,136 (44.1%)	3,674 (44.8%)	48,810 (44.1%)
	0 to 1	33,719 (32.9%)	2,885 (35.2%)	36,604 (33.1%)
	>1	9,958 (9.7%)	666 (8.1%)	10,624 (9.6%)
Residence Distribution	*Urban*	63,207 (61.7%)	3,313 (40.4%)	66,520 (60.1%)
	Rural	39,284 (38.3%)	4,893 (59.6%)	44,177 (39.9%)
High Residential Mobility		22,408 (21.9%)	2,523 (30.8%)	24,931 (22.5%)
Receipt of Income Assistance		8,351 (8.2%)	758 (9.2%)	9,109 (8.2%)

Marriage Record		57,308 (55.9%)	4,595 (56.0%)	61,903 (55.9%)
Johns Hopkins Healthcare Resource Utilization Band	*0 (no utilization)*	1,771 (1.7%)	234 (2.9%)	2,005 (1.8%)
	1	3,205 (3.1%)	175 (2.1%)	3,380 (3.1%)
	2	17,523 (17.1%)	1,012 (12.3%)	18,535 (16.7%)
	3	65,067 (63.5%)	4,699 (57.3%)	69,766 (63.0%)
	4	10,810 (10.6%)	1,259 (15.3%)	12,069 (10.9%)
	5 (high-utilization)	4,083 (4.0%)	825 (10.1%)	4,908 (4.4%)
		Short-term	**Long-term**	**Total**
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Charlson Comorbidity index Score	*0*	72,490 (70.8%)	4,528 (55.2%)	77,018 (69.6%)
	1	19,495 (19.0%)	1,905 (23.2%)	21,400 (19.3%)
	2+	10,506 (10.3%)	1,773 (21.6%)	12,279 (11.1%)
Non-BZRA Psychotropic Prescription Dispensations	*0*	27,797 (27.1%)	1,784 (21.7%)	29,581 (26.7%)
	1	36,939 (36.1%)	2,156 (26.3%)	39,095 (35.3%)
	2+	37,755 (36.8%)	4,266 (52.0%)	42,021 (38.0%)
Opioid Prescription Dispensations	*0*	47,427 (46.3%)	3,298 (40.2%)	50,725 (45.8%)
	1	34,505 (33.7%)	2,772 (33.8%)	37,277 (33.7%)
	2+	20,559 (20.1%)	2,136 (26.0%)	22,695 (20.5%)
Sex of Prescriber Issuing First Prescription	*Male*	71,485 (69.8%)	5,627 (68.6%)	77,112 (69.7%)
	Female	28,485 (27.8%)	2,273 (27.7%)	30,758 (27.8%)
Age of Prescriber Issuing First	*50+ Years*	47,871 (46.7%)	4,014 (48.9%)	51,885 (46.9%)

Prescription	*<50 Years*	49,257 (48.1%)	3,758 (45.8%)	53,015 (47.9%)
Type of Prescriber Issuing First Prescription	*General Practitioner*	78,610 (76.7%)	6,366 (77.6%)	84,976 (76.8%)
	Psychiatry	3,912 (3.8%)	475 (5.8%)	4,387 (4.0%)
	Other	3,881 (3.8%)	381 (4.6%)	4,262 (3.9%)
Period of First Prescription	*2001-2006*	34,360 (33.5%)	1,526 (18.6%)	35,886 (32.4%)
	2006-2011	37,752 (36.8%)	2,808 (34.2%)	40,560 (36.7%)
	2011-2016	30,379 (29.6%)	3,872 (47.2%)	34,251 (31.0%)

Table A10 – Frequency of Charlson Comorbidity Group Diagnoses by First Use Episode Duration for Z-Drug Cohort

Charlson Diagnosis	**Short-Term 'First-Episode' Users** *(n=102,459)*	**Long-Term 'First-Episode' Users** *(n=8,204)*	**Z-Test of Two Proportions**
Myocardial Infarction	1,836 (1.8%)	306 (3.7%)	$p < 0.01$
Congestive Heart Failure	3,174 (3.1%)	700 (8.5%)	$p < 0.01$
Peripheral Vascular Disease	1,772 (1.7%)	284 (3.5%)	$p < 0.01$
Cerebrovascular Disease	2,321 (2.3%)	550 (6.7%)	$p < 0.01$
Dementia	1,925 (1.9%)	865 (10.5%)	$p < 0.01$
COPD	12,357 (12.1%)	1,171 (14.3%)	$p < 0.01$
Connective Tissue/Rheumatic Disease	1,906 (1.9%)	243 (3.0%)	$p < 0.01$
Peptic Ulcer Disease	1,111 (1.1%)	123 (1.5%)	$p < 0.01$
Mild Liver Disease	1,672 (1.6%)	139 (1.7%)	$p = 0.33$
Moderate/Severe Liver Disease	275 (0.2%)	38 (0.4%)	$p < 0.01$
Uncomplicated Diabetes	9,317 (9.1%)	1,150 (14.0%)	$p < 0.01$
Complicated Diabetes	1,639 (1.6%)	328 (4.0%)	$p < 0.01$
Paraplegia and Hemiplegia	508 (0.5%)	136 (1.7%)	$p < 0.01$
Renal Disease	1,543 (1.5%)	293 (3.6%)	$p < 0.01$
Cancer	2,109 (2.1%)	247 (3.0%)	$p < 0.01$
Metastatic Carcinoma	429 (0.4%)	45 (0.5%)	$p = 0.04$
HIV/AIDS	118 (0.1%)	16 (0.2%)	$p = 0.02$

Table A11 – Statistical Associations between Predictor Variables and Long-term Use of Z-Drugs

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		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		1.12 (1.07-1.18)	1.04 (0.99-1.09)	1.13 (1.08-1.17)	1.05 (1.01-1.10)	1.08 (1.05-1.12)	1.04 (1.00-1.08)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.90 (1.79-2.02)	2.02 (1.89-2.17)	1.74 (1.66-1.82)	1.78 (1.68-1.88)	1.71 (1.64-1.78)	1.68 (1.60-1.76)
	65+	3.83 (3.61-4.07)	3.71 (3.44-4.00)	3.24 (3.08-3.40)	3.08 (2.90-3.28)	2.99 (2.87-3.12)	2.78 (2.64-2.93)
Rural Residence		0.92 (0.88-0.96)	1.13 (1.07-1.19)	0.99 (0.96-1.03)	1.02 (0.98-1.07)	1.08 (1.04-1.11)	0.95 (0.91-0.99)
High Residential Mobility		1.59 (1.51-1.67)	1.26 (1.19-1.33)	1.53 (1.46-1.59)	1.21 (1.15-1.27)	1.30 (1.26-1.35)	1.12 (1.07-1.17)
Income Assistance		1.15 (1.06-1.24)	1.47 (1.34-1.61)	1.02 (0.95-1.09)	1.29 (1.19-1.40)	0.82 (0.77-0.87)	1.08 (1.00-1.17)
SEFI-2 Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.14 (1.06-1.22)	1.07 (0.99-1.16)	1.03 (0.97-1.09)	0.98 (0.92-1.04)	0.95 (0.91-1.00)	0.94 (0.89-0.99)
	0 to 1	1.19 (1.11-1.29)	1.08 (0.99-1.17)	1.04 (0.98-1.11)	0.99 (0.93-1.06)	0.92 (0.87-0.97)	0.93 (0.88-0.99)
	>1	0.93 (0.84-1.03)	0.84 (0.75-0.94)	0.80 (0.73-0.87)	0.77 (0.70-0.85)	0.68 (0.63-0.73)	0.72 (0.66-0.78)
Married		1.00 (0.96-1.05)	0.86 (0.82-0.91)	1.07 (1.03-1.10)	0.93 (0.89-0.98)	1.13 (1.10-1.17)	0.98 (0.94-1.01)
Opioid Use		1.28 (1.22-1.34)	1.15 (1.09-1.21)	1.26 (1.21-1.31)	1.15 (1.11-1.20)	1.18 (1.14-1.21)	1.11 (1.07-1.15)

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Psychotropic Rx Use (Non-BZRA)		1.34 (1.27-1.41)	1.24 (1.17-1.32)	1.35 (1.29-1.41)	1.27 (1.20-1.33)	1.22 (1.17-1.27)	1.19 (1.14-1.24)
Charlson Comorbidity Index Score	0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.56 (1.48-1.65)	1.25 (1.18-1.33)	1.45 (1.39-1.52)	1.21 (1.15-1.27)	1.33 (1.28-1.38)	1.13 (1.08-1.19)
	2+	2.70 (2.55-2.87)	1.46 (1.36-1.58)	2.34 (2.22-2.46)	1.38 (1.29-1.47)	2.02 (1.93-2.12)	1.30 (1.22-1.37)
Resource Utilization Band	0-3 (≤Moderate)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4 (High)	1.67 (1.56-1.78)	1.16 (1.08-1.25)	1.47 (1.39-1.56)	1.09 (1.01-1.16)	1.30 (1.24-1.37)	1.00 (0.95-1.07)
	5 (Very High)	2.89 (2.67-3.13)	1.55 (1.41-1.70)	2.43 (2.26-2.61)	1.42 (1.30-1.55)	1.97 (1.85-2.11)	1.22 (1.12-1.32)
Male Prescriber of First Prescription		0.99 (0.94-1.04)	0.97 (0.92-1.03)	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.94 (0.90-0.97)	0.93 (0.90-0.97)
Prescriber Age ≥50 Years		1.10 (1.05-1.15)	0.98 (0.93-1.03)	1.10 (1.06-1.15)	0.98 (0.94-1.02)	1.15 (1.11-1.19)	1.05 (1.01-1.09)
Prescriber of First Prescription	GP	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Psychiatrist	1.50 (1.36-1.66)	1.96 (1.76-2.17)	1.36 (1.25-1.49)	1.72 (1.57-1.89)	1.11 (1.02-1.20)	1.38 (1.27-1.51)
	Other	1.21 (1.09-1.35)	0.92 (0.82-1.03)	1.18 (1.07-1.29)	0.91 (0.83-1.00)	1.19 (1.10-1.29)	0.98 (0.91-1.07)
Period of First Prescription	2001-2006	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	2006-2011	1.68 (1.57-1.79)	1.57 (1.46-1.68)	1.67 (1.59-1.76)	1.56 (1.47-1.66)	1.53 (1.46-1.60)	1.46 (1.39-1.54)
	2011-2015	2.87 (2.70-3.05)	2.45 (2.28-2.65)	2.83 (2.69-2.97)	2.44 (2.30-2.59)	2.20 (2.10-2.29)	1.96 (1.86-2.07)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7, fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*12-13*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046916.R2
Article Type:	Original research
Date Submitted by the Author:	13-Oct-2021
Complete List of Authors:	Brandt, Jaden; University of Manitoba Janzen, Donica; University of Manitoba Alessi-Severini, Silvia; University of Manitoba Singer, Alexander; University of Manitoba Chateau, Dan; University of Manitoba Enns, Murray; University of Manitoba Leong, Christine; University of Manitoba
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, PSYCHIATRY, Anxiety disorders < PSYCHIATRY, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Running Title: Risk of long-term benzodiazepine receptor agonist use

Jaden Brandt, MSc BScPharm[1], Donica Janzen, PhD Candidate BSP[1], Silvia Alessi-Severini, PhD[1,2], Alexander Singer, MB BAO BCh CCFP[3], Dan Chateau, PhD[2,4], Murray Enns, MD FRCPC[5], Christine Leong, PharmD BScPharm[1,5*]

[1]*College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[2]*Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, CAN*

[3]*Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[4]*Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

[5]*Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, CAN*

**Corresponding author: Dr. Christine Leong*

Apotex Centre, College of Pharmacy, Rady Faculty of Health Sciences

University of Manitoba

750 McDermot Avenue

Winnipeg, Manitoba R3E 0T5

P: (204) 318-5276

E: christine.leong@umanitoba.ca

Acknowledgements

The authors wish to acknowledge Dr. Sheryl Zelenitsky for her helpful comments on earlier drafts of this manuscript.

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under Research Ethic Board approval HS20498 (HIPC#2016/2017 – 062). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

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 April 1, 2001 to March 31, 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 odds ratio (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 one in twenty 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.

Key Words: *benzodiazepine, anxiety, insomnia, pharmacoepidemiology, clinical practice guidelines, z-drug hypnotics*

Strengths and Limitations of 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 de-identified 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 hospitalizations, 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 behavioral 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] Upon their initial introduction into clinical practice in the late 1960s, benzodiazepines were considered to be a safer alternative to barbiturates.[5] However, safety concerns such as psychomotor impaired accidents (i.e., 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

* ***Abbreviations****: BZRA, benzodiazepine receptor agonist; BZD, benzodiazepine*

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.

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, hospitalization discharge abstracts, income assistance records and prescriber demographics (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 Program 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 one year prior to the first prescription[20,21]) between April 1, 2001 to March 31, 2015, with no preceding dispensations from April 1, 2000 to March 31, 2001 (first year of the dataset) to avoid prevalent user bias (Figure 1). All individuals with at least one 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 one year. A sensitivity analysis was also performed in which incident use was defined as no prescription for a BZRA was received in the three years prior to the first prescription.[23]

Eligibility was also based on diagnostic criteria for anxiety/mood related disorders and/or insomnia based on ICD-9-CM or ICD-10-CA medical claims, either at outpatient physician visits or hospitalizations, 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 (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 program at any point in the 5 years preceding their first prescription for a BZRA (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 loss 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 six months have been previously reported to be unable to stop completely due to withdrawal symptoms (e.g., 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, hospitalization time was assumed to be a continuation of BZD use given that in-patient drug use data was limited.[31] The provincial drug program subsidizes 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, geographic residence, residential mobility, socioeconomic status, marriage, concurrent opioid or prescription psychotropic use, comorbidity burden, healthcare usage, time period of first prescription and prescriber characteristics (Table A4 and Table 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 stabilizers).

Statistical Analysis

Standard reporting criteria were followed in the approach to logistic regression modelling (Table A6 and A7).[32] Univariate analysis was performed first in the form of simple logistic regression. The multi-variable 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 (i.e., 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 ≥ |0.8| or if any variance inflation factor was unreasonably high (≥10) while the corresponding tolerance factor was miniscule (≤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 1,568 claims (<0.01%) were excluded for being spurious (i.e '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, 6 sensitivity analyses (Tables A8 and Table 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 (i.e., 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 was cleaned and analyzed using SAS v9.4©.

Ethical Approval

Access to the data for this project was approved by the University's Health Research Ethics Board (HREB, registration number H2017:052 (HS20498) and the Health Information Privacy Committee (HIPC, no. 2016/2017-62) of the provincial government. Consent for this study was not required by HREB given the retrospective nature of the study and data agreements in place through HIPC.

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%) (Table A7).

To evaluate treatment duration for insomnia, a sensitivity analysis was performed on only Z-Drugs (*n*=110,663), which found similar results (Tables A9-A12).

Factors Predicting Long-term First Episode Use

Logistic regression analysis revealed that male sex (adjusted odds ratio (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 to <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 utilization 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 odds ratios are presented for the full cohort in Table 2.

A sub-analysis 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 to 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 three 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 to 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 recognized 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 (i.e., 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 de-prescribing 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 interference with another prescriber's decisions likely undermine potential de-prescribing 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.

The present 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. Firstly, administrative data is 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 hospitalizations 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 benzodiazepines 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 behavioral 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 generalizable 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 six 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.

References

1. O'Brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66 Suppl 2(suppl 2):28-33.

2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry*. 2013;28(1):7-20. doi:10.1016/j.eurpsy.2011.11.003.

3. Moore N, Pariente A, Bégaud B. Why are benzodiazepines not yet controlled substances? *JAMA Psychiatry*. 2015;72(2):110-111. doi:10.1001/jamapsychiatry.2014.2190.

4. Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC Fam Pract*. 2013;14:191. doi:10.1186/1471-2296-14-191.

5. López-Muñoz F, Álamo C, García-García P. The discovery of chlordiazepoxide and the clinical introduction of benzodiazepines: Half a century of anxiolytic drugs. *J Anxiety Disord*. 2011;25(4):554-562. doi:10.1016/j.janxdis.2011.01.002.

6. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23(1):19-34. doi:10.2165/0023210-200923010-00002.

7. Xing D, Ma XL, Ma JX, Wang J, Yang Y, Chen Y. Association between use of benzodiazepines and risk of fractures: A meta-analysis. *Osteoporos Int*. 2014;25(1):105-120. doi:10.1007/s00198-013-2446-y.

8. Rapoport MJ, Lanctôt KL, Streiner DL, et al. Benzodiazepine use and driving: A meta-analysis. *J Clin Psychiatry*. 2009;70(5):663-673. doi:10.4088/JCP.08m04325.

9. Pariente A, De Gage SB, Moore N, Bégaud B. The Benzodiazepine-Dementia Disorders Link: Current State of Knowledge. *CNS Drugs*. 2016;30(1):1-7. doi:10.1007/s40263-015-0305-4.

10. Perlis RH, Ostacher MJ, Miklowitz DJ, et al. Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report. *J Clin Psychiatry*. 2010;71(2):194-200. doi:10.4088/JCP.09m05019yel.

11. Lai SW, Lai HC, Lin CL, Liao KF. Zopiclone use associated with increased risk of acute pancreatitis: A case-control study in Taiwan. *Int J Clin Pract*. 2015;69(11):1275-1280. doi:10.1111/ijcp.12689.

12. Dodds TJ. Prescribed benzodiazepines and suicide risk: A review of the literature. *Prim Care Companion CNS Discord*. 2017;19(2). doi:10.4088/PCC.16r02037.

13. Rodriguez-Roisin R, Garcia-Aymerich J. Should we exercise caution with benzodiazepine use in patients with COPD? *Eur Respir J*. 2014;44(2):284-286. doi:10.1183/09031936.00071014.

14. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017. doi:10.1007/s40268-017-0207-7.

15. El-Guebaly N, Sareen J, Stein MB. Are There Guidelines for the Responsible Prescription of Benzodiazepines? *Can J Psychiatry*. 2010;55(11):709-714.

16. Bendtsen P, Hensing G, McKenzie L, Stridsman AK. Prescribing benzodiazepines - A critical incident study of a physician dilemma. *Soc Sci Med*. 1999;49(4):459-467. doi:10.1016/S0277-9536(99)00133-1.

17. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. *Expert Opin Drug Saf*. 2014;13(7):919-934. doi:10.1517/14740338.2014.925444.

18. Alessi-Severini S, Bolton JM, Enns MW, Dahl M, Collins DM, Chateau D, Sareen J. Use of benzodiazepines and related drugs in Manitoba: a population-based study. CMAJ Open 2014;2(4):E208-16.

19. Berman E, Eyal S, Marom E. Trends in utilization of benzodiazepine and z-drug in Israel. Pharmacoepidemiol Drug Saf 2017;26(12):1555-1560.

20. Takano A, Ono S, Yamana H, et al. Factors associated with long-term prescription benzodiazepine: a retrospective cohort study using a health insurance database in Japan. BMJ Open 2019;9:e029641.

21. Hata T, Kanazawa T, Hamada T, et al. What can predict and prevent the long-term use of benzodiazepines? J Psychiatric Research 2018;97:94-100.

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-383; Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology* 1992;45(6):613-619.

23. Bramness, JG, Sexton, JA. The basic pharmacoepidemiology of benzodiazepine use in Norway 2004-9. Nor Epidemiol. 2011;21(1):35- 41.

24. Kurko TAT, Saastamoinen LK, Tahkapaa S, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - A systematic review of register-based studies. *Eur Psychiatry*. 2015;30(8):1037-1047. doi:10.1016/j.eurpsy.2015.09.003.

25. Willems IAT, Gorgels WJMJ, Voshaar RCO, et al. Tolerance to benzodiazepines among long-term users in primary care. Family Practice 2013;30(4):404-410.

26. Public Health Agency of Canada. Government of Canada. *Report from the Canadian Chronic Disease Surveillance System: Mood and Anxiety Disorders in Canada*.; 2016. http://healthycanadians.gc.ca/publications/diseases-conditions-maladies-affections/mental-illness-2015-maladies-mentales/index-eng.php.

27. Manitoba Centre for Health Policy, Department of Community Health Sciences U of M. Concept: Mood and Anxiety Disorders - Measuring Prevalence. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1391#a_references. Published 2015. Accessed February 21, 2017.

28. MCHP. University of Manitoba - Manitoba Centre for Health Policy - Glossary: Anxiety /Anxiety States. http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102267. Published 2010. Accessed July 11, 2018.

29. Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, Kwok C-W. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med*. 2015;16(4):477-482. doi:10.1016/j.sleep.2014.10.018.

30. Lader M. Benzodiazepine harm: How can it be reduced? *Br J Clin Pharmacol*. 2014;77(2):295-301. doi:10.1111/j.1365-2125.2012.04418.x.

31. Palmaro A, Boucherie Q, Dupouy J, Micallef J, Lapeyre-Mestre M. Immeasurable time bias due to hospitalization in medico-administrative databases: which impact for pharmacoepidemiological studies? *Pharmacoepidemiol Drug Saf*. 2017;26(5):544-553. doi:10.1002/pds.4193.

32. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain. *J Clin Epidemiol*. 2001;54(10):979-985. doi:10.1016/S0895-4356(01)00372-9.

33. Rasouliyan L, Miller DP. The Logic and Logistics of Logistic Regression. In: *Western Users of SAS Software 2006*. Irvine, CA; 2006:1-14. https://www.lexjansen.com/wuss/2006/analytics/ANL-Rasouliyan.pdf.

34. Schreiber-Gregory DN. *Multicollinearity : What Is It , Why Should We Care , and How Can It Be Controlled ?*; 2017. https://analytics.ncsu.edu/sesug/2017/SESUG2017_Paper-160_Final_PDF.pdf.

35. Bennett D. How can I deal with missing data in my study? *Aust New Zeal J public ….* 2001;25(5):464-469. http://onlinelibrary.wiley.com/doi/10.1111/j.1467-842X.2001.tb00294.x/abstract.

36. Lash TL, Fox MP, Maclehose RF, Maldonado G, Mccandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969-1985. doi:10.1093/ije/dyu149.

37. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia

disorder in adults: A clinical practice guideline from the American college of physicians. *Ann Intern Med*. 2016;165(2):125-133. doi:10.7326/M15-2175.

38. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(2):307-349

39. National Institute for Clinical Excellence. *Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia*.; 2004. https://www.nice.org.uk/guidance/ta77/resources/guidance-on-the-use-of-zaleplon-zolpidem-and-zopiclone-for-the-shortterm-management-of-insomnia-2294763557317.

40. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive–compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77-84. doi:10.3109/13651501.2012.667114.

41. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol*. 2014;28(5):403-439. doi:10.1177/0269881114525674.

42. Katzman et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*. 2014;14((Suppl 1)):1-83. doi:10.1186/1471-244X-14-S1-S1.

43. Islam MM. Pattern and probability of dispensing of prescription opioids and benzodiazepines among the new users in Australia: a retrospective cohort study. BMJ Open 2019;9:e030803.

44. Sirdifield C, Chipchase SY, Owen S, Siriwardena AN. A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. *Patient*. 2016:1-15. doi:10.1007/s40271-016-0182-z.

45. Simon GE, VonKorff M, Barlow W, Pabiniak C, Wagner E. Predictors of chronic benzodiazepine use in a health maintenance organization sample. *J Clin Epidemiol*. 1996;49(9):1067-1073. doi:10.1016/0895-4356(96)00139-4.

46. Alessi-Severini S, Bolton JM, Enns MW, et al. Sustained use of benzodiazepines and escalation to high doses in a Canadian population. *Psychiatr Serv*. 2016;67(9):1012-8.

47. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: Examining the impact of increasing research and guideline cautions against long-term use. *Health Policy (New York)*. 2010;97(2-3):122-129.

doi:10.1016/j.healthpol.2010.03.008.

48. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv*. 2003;54(7):1006-1011. doi:http://dx.doi.org/10.1176/appi.ps.54.7.1006.

49. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: A longitudinal study. *Br J Clin Pharmacol*. 2008;65(4):593-599. doi:10.1111/j.1365-2125.2007.03060.x.

50. Jorm AF, Grayson DA, Creasey H, Waite L, Broe GA. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health*. 2000;24(1):7-10. doi:10.1111/j.1467-842X.2000.tb00715.x.

51. Kurko T, Saastamoinen LK, Tuulio-Henriksson A, et al. Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: A national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf*. 2018;(October 2017):3-6. doi:10.1002/pds.4551.

52. Fride Tvete I, Bjørner T, Skomedal T. Risk factors for excessive benzodiazepine use in a working age population: a nationwide 5-year survey in Norway. *Scand J Prim Health Care*. 2015;33(4):252-259. doi:10.3109/02813432.2015.1117282.

53. Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol*. 2012;68(3):311-319. doi:10.1007/s00228-011-1124-2.

54. Fang SY, Chen CY, Chang IS, Wu ECH, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: A population-based study. *Drug Alcohol Depend*. 2009;104(1-2):140-146. doi:10.1016/j.drugalcdep.2009.04.017.

55. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136-142. doi:10.1001/jamapsychiatry.2014.1763.

56. Anderson ABT et al. Long-term use of zopiclone, zolpidem and zaleplon among Danish elderly and the association with sociodemographic factors and use of other drugs. *Pharmacoepidemiol Drug Saf*. 2011;20:378-385. doi:10.1002/pds.

57. Scott KM, Wells JE, Angermeyer M, et al. Gender and the relationship between marital status and first onset of mood, anxiety and substance use disorders. *Psychol Med*. 2010;40(9):1495-1505. doi:10.1017/S0033291709991942.

58. Patten SB, Williams JVA, Lavorato DH, Kassam A, Sabapathy CD. Sedative – Hypnotic Use in a Canadian General Population Cohort During 12 Years of Follow-up. *Can J Psychiatry*. 2010;55(12):792-799.

59. Mattos MK, Sereika SM, Naples JG, Albert SM. Differences in Benzodiazepine Receptor Agonist Use in Rural and Urban Older Adults. *Drugs - Real World Outcomes*. 2016;3(3):289-296. doi:10.1007/s40801-016-0080-7.

60. Manthey L, Van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: The Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol*. 2011;71(2):263-272. doi:10.1111/j.1365-2125.2010.03818.x.

61. Sakshaug S, Handal M, Hjellvik V, et al. Long-term Use of Z-Hypnotics and Co-Medication with Benzodiazepines and Opioids. *Basic Clin Pharmacol Toxicol*. 2016. doi:10.1111/bcpt.12684.

Availability of Data and Materials

Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at MCHP. The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository.

Author Statement

Jaden Brandt contributed to the conception, design, acquisition of data, analysis, and writing of the manuscript. Donica Janzen contributed to the analysis, interpretation, and writing of the manuscript. Silvia Alessi-Severini contributed to the interpretation and writing of the manuscript. Dan Chateau contributed to the interpretation and analysis of the study. Murray Enns contributed to the interpretation and writing of the study. Alexander Singer contributed to the interpretation and writing of the study. Christine Leong contributed to the conception, design, interpretation, and writing of the manuscript.

Conflict of Interest Disclosure

The authors declare no conflicts of interest related to any aspects of this work.

Funding

This work was supported by the College of Pharmacy at the University of Manitoba. Additional student funding for JB was granted by the Provincial Government of Manitoba in the form of a Manitoba Graduate Scholarship stipend. Funding sources had no role in the conduct of research and/or preparation of the article.

Patient and Public Involvement

We have a patient advisory group who provided feedback on the dissemination of research findings.

Table 1. **Characteristics of BZRA Users by First Use Episode Duration**

		Short-term	Long-term	Total
Number of Users		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
*Sex Distribution**	*Male*	74,487 (37.7%)	4,295 (46.1%)	78,782 (38.1%)
	Female	123,057 (62.3%)	5,029 (53.9%)	128,086 (61.9%)
Age Category	*18-44*	101,709 (51.5%)	2,776 (29.8%)	104,487 (50.5%)
	45-64	66,752 (33.8%)	3,320 (35.6%)	70,072 (33.9%)
	65+	29,143 (14.7%)	3,231 (34.6%)	32,374 (15.6%)
SEFI-2 Score	*<-1*	24,955 (12.6%)	1,089 (11.7%)	26,044 (12.6%)
	-1 to 0	81,718 (41.4%)	3,835 (41.1%)	85,553 (41.3%)
	0 to 1	64,967 (32.9%)	3,274 (35.1%)	68,241 (33.0%)
	>1	25,966 (13.1%)	1,129 (12.1%)	27,095 (13.1%)
Residence Distribution	*Urban*	125,950 (63.7%)	5,802 (62.2%)	131,752 (63.7%)
	Rural	71,656 (36.3%)	3,525 (37.8%)	75,181 (36.3%)
High Residential Mobility		36,392 (18.4%)	2,385 (25.6%)	38,777 (18.7%)

Receipt of Income Assistance		18,530 (9.4%)	1,222 (13.1%)	19,752 (9.5%)
Marriage Record		102,461 (51.9%)	4,618 (49.5%)	107,079 (51.8%)
*Johns Hopkins Healthcare Resource Utilization Band***	*0* *(no utilization)*	3,001 (1.5%)	349 (3.7%)	3,350 (1.6%)
	1	5,798 (2.9%)	182 (2.0%)	5,980 (2.9%)
	2	33,974 (17.2%)	1,192 (12.8%)	35,166 (17.0)
	3	127,824 (64.7%)	5,151 (55.2%)	132,975 (64.3%)
	4	20,065 (10.2%)	1,486 (15.9%)	21,551 (10.4%)
	5 *(high-utilization)*	6,882 (3.5%)	964 (10.3%)	7,846 (3.8%)
		Short-term	**Long-term**	**Total**
Number of Users		**197,606 (100%)**	**9,327 (100%)**	**206,933 (100%)**
Charlson Comorbidity index Score	*0*	148,257 (75.0%)	5,783 (62.0%)	154,040 (74.4%)
	1	36,261 (18.4%)	2,031 (21.8%)	38,292 (18.5%)
	2+	13,088 (6.6%)	1,513 (16.2%)	14,601 (7.1%)
Non-BZRA Psychotropic Prescription Dispensations	*0*	111,216 (56.3%)	3,862 (41.4%)	115,078 (55.6%)
	1	17,661 (8.9%)	518 (5.6%)	18,179 (8.8%)
	2+	68,729 (34.8%)	4,947 (53.0%)	73,676 (35.6%)
Opioid Prescription Dispensations	*0*	132,027 (66.8%)	5,855 (62.8%)	137,882 (66.6%)

	1	30,530 (15.5%)	1,011 (10.8%)	169,423 (15.2%)
	2+	35,049 (17.7%)	2,461 (26.4%)	37,510 (18.2%)
*Sex of Prescriber Issuing First Prescription****	*Male*	143,619 (75.3%)	6,928 (76.5%)	150,547 (75.3%)
	Female	47,128 (24.7%)	2,126 (23.5%)	49,254 (24.7%)
Age of Prescriber Issuing First Prescription†	*50+ Years*	95,629 (52.1%)	4,775 (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%)	7,013 (87.5%)	153,836 (91.4%)
	Psychiatry	6,338 (4.1%)	624 (7.8%)	6,962 (4.1%)
	Other	7,183 (4.5%)	375 (4.7%)	7,558 (4.5%)
Period of First Prescription	*2001-2006*	90,008 (45.5%)	2,608 (28.0%)	92,616 (44.8%)
	2006-2011	65,750 (33.3%)	3,170 (34.0%)	68,920 (33.3%)
	2011-2016	41,848 (21.2%)	3,549 (38.1%)	45,397 (21.9%)

*N=197,544 (short-term users); N=9,324 (long-term users); N=206,868 (total users)
**N=197,544 (short-term users); N=9,324 (long-term users); N=206,868 (total users)
***N=190,747 (short-term users); N=9,054 (long-term users); N=199,801 (total users)
†N=183,462 (short-term users); N=8,851 (long-term users); N=192,313 (total users)
‡N=160,344 (short-term users); N=8,012 (long-term users); N=168,356 (total users)

Table 2 – Statistical Associations between Predictor Variables and Long-term Use of BZRAs

Independent Variable		Use Duration					
		≥180 Days		≥90 Days		≥60 Days	
		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 (1.35-1.47)	1.33 (1.27-1.39)	1.40 (1.35-1.45)	1.34 (1.29-1.40)	1.30 (1.26-1.34)	1.27 (1.23-1.31)
Age	18-44	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.82 (1.73-1.92)	2.24 (2.11-2.38)	1.77 (1.70-1.85)	2.00 (1.91-2.10)	1.81 (1.77-1.86)	1.89 (1.82-1.97)
	65+	4.06 (3.86-4.28)	5.15 (4.81-5.52)	3.56 (3.41-3.72)	4.11 (3.88-4.36)	3.34 (3.22-3.47)	3.52 (3.36-3.70)
Rural Residence		1.07 (1.02-1.11)	1.10 (1.04-1.15)	0.97 (0.93-1.00)	0.97 (0.94-1.02)	0.90 (0.87-0.92)	0.92 (0.88-0.95)
High Residential Mobility		1.52 (1.45-1.60)	1.14 (1.08-1.21)	1.35 (1.29-1.40)	1.06 (1.01-1.11)	1.14 (1.10-1.18)	1.01 (0.97-1.06)
Income Assistance		1.46 (1.37-1.55)	1.68 (1.55-1.81)	1.14 (1.08-1.21)	1.35 (1.26-1.45)	0.88 (0.83-0.93)	1.12 (1.06-1.20)
Socio-Economic Factor Index-2 (SEFI-2) Score	<-1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.08 (1.00-1.15)	0.99 (0.92-1.07)	0.96 (0.91-1.02)	0.91 (0.86-0.97)	0.90 (0.87-0.95)	0.89 (0.85-0.94)
	0 to 1	1.16 (1.07-1.24)	1.02 (0.94-1.10)	0.98 (0.93-1.04)	0.92 (0.87-0.98)	0.87 (0.83-0.91)	0.89 (0.84-0.94)
	>1	1 (0.92-1.09)	0.93 (0.84-1.03)	0.78 (0.73-0.84)	0.80 (0.74-0.87)	0.63 (0.59-0.67)	0.73 (0.68-0.78)
Married		0.91 (0.87-0.95)	0.79 (0.76-0.83)	1.01 (0.98-1.05)	0.89 (0.85-0.92)	1.13 (1.10-1.16)	0.95 (0.92-0.99)
Opioid Use		1.19 (1.14-1.27)	1.16 (1.11-1.22)	1.08 (1.04-1.12)	1.09 (1.05-1.14)	0.99 (0.96-1.02)	1.05 (1.01-1.09)
Independent Variable		Use Duration					

		≥180 Days		≥90 Days		≥60 Days	
		Crude OR (95% CI)	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*
Psychotropic Rx Use (non-BZRA)		1.82 (1.75-1.90)	1.93 (1.83-2.02)	1.62 (1.56-1.67)	1.75 (1.69-1.83)	1.34 (1.30-1.38)	1.49 (1.44-1.54)
Charlson Comorbidity Index Score	*0*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.44 (1.36-1.51)	1.11 (1.04-1.17)	1.33 (1.27-1.39)	1.08 (1.02-1.13)	1.24 (1.19-1.29)	1.04 (1.00-1.08)
	2+	2.96 (2.79-3.15)	1.43 (1.32-1.55)	2.41 (2.29-2.54)	1.33 (1.24-1.42)	2.01 (1.92-2.11)	1.23 (1.15-1.31)
Resource Utilization Band	*0-3*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4	1.84 (1.73-1.95)	1.15 (1.07-1.23)	1.58 (1.50-1.66)	1.08 (1.01-1.14)	1.37 (1.31-1.43)	1.00 (0.94-1.05)
	5	3.48 (3.24-3.73)	1.46 (1.33-1.60)	2.73 (2.56-2.92)	1.31 (1.20-1.42)	2.21 (2.08-2.35)	1.17 (1.09-1.27)
Male Prescriber of First Prescription		1.07 (1.02-1.12)	1.03 (0.98-1.09)	1.07 (1.02-1.11)	1.04 (0.99-1.09)	1.01 (0.98-1.05)	0.98 (0.94-1.02)
Prescriber Age ≥50 Years		1.08 (1.03-1.12)	0.98 (0.94-1.03)	1.08 (1.04-1.12)	0.99 (0.95-1.03)	1.15 (1.11-1.18)	1.08 (1.04-1.11)
Type of Prescriber of First Prescription	*GP*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	Psychiatrist	2.06 (1.89-2.25)	2.11 (1.93-2.32)	1.85 (1.72-2.00)	1.89 (1.75-2.05)	1.54 (1.44-1.65	1.63 (1.51-1.75)
	Other	1.09 (0.98-1.21)	0.92 (0.82-1.03)	1.07 (0.98-1.17)	0.92 (0.84-1.01)	1.16 (1.07-1.24)	1.03 (0.96-1.11)
Period of First Prescription	*2001-2006*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1	1 (ref)
	2006-2011	1.66 (1.58-1.75)	1.74 (1.64-1.85)	1.58 (1.51-1.65)	1.65 (1.57-1.7)	1.41 (1.36-1.46)	1.48 (1.42-1.54)
	2011-2015	2.93 (2.78-3.08)	2.99 (2.80-3.18)	2.59 (2.48-2.71)	2.71 (2.57-2.8)	1.97 (1.90-2.05)	2.07 (1.98-2.16)

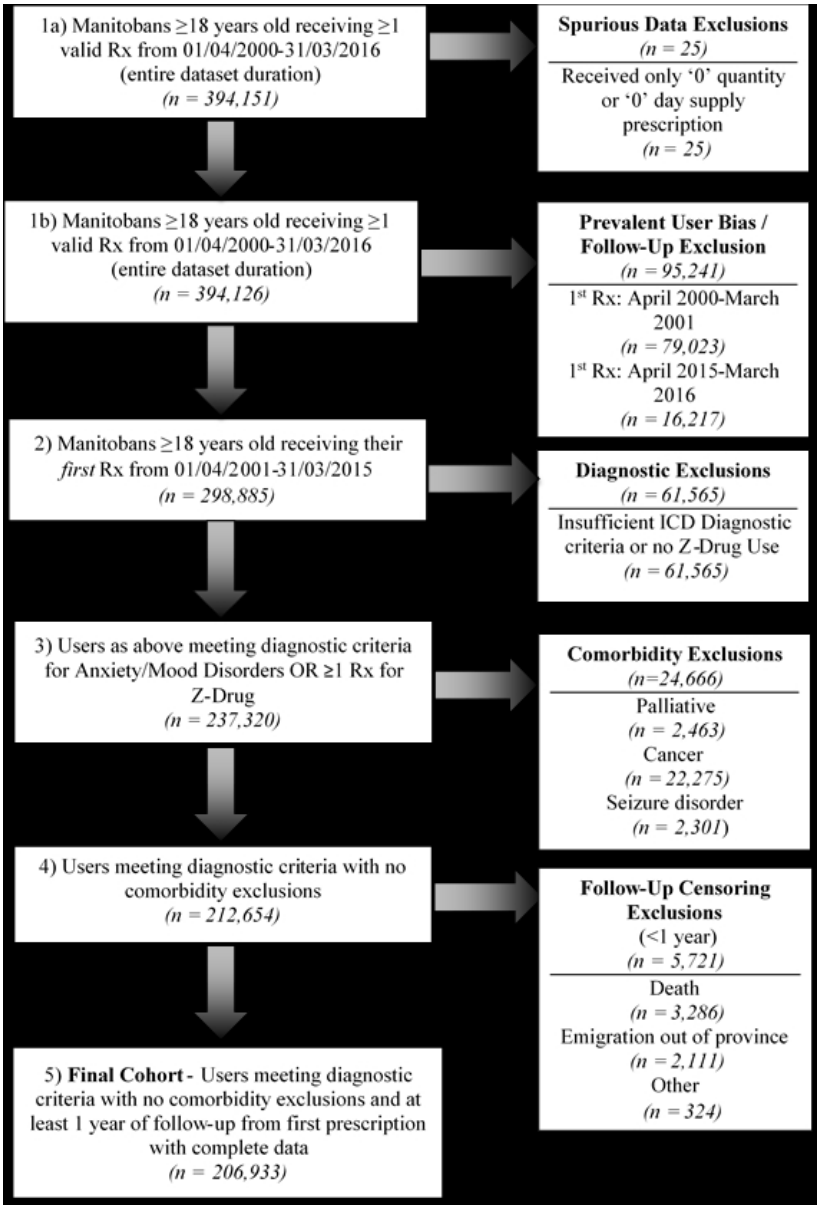
36/bmjopen-2020-046938 on 1 November 2021. Downloaded from

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=9,327)*	Z-Test of Two Proportions
Myocardial Infarction	2,474 (1.3%)	281 (3.0%)	$p < 0.01$
Congestive Heart Failure	3,943 (2.0%)	628 (6.7%)	$p < 0.01$
Peripheral Vascular Disease	2,367 (1.2%)	256 (2.7%)	$p < 0.01$
Cerebrovascular Disease	3,690 (1.9%)	544 (5.8%)	$p < 0.01$
Dementia	2,928 (1.5%)	796 (8.5%)	$p < 0.01$
COPD	23,064 (11.7%)	1,163 (12.5%)	$p = 0.02$
Connective Tissue/Rheumatic Disease	2,793 (1.4%)	222 (2.4%)	$p < 0.01$
Peptic Ulcer Disease	2,140 (1.1%)	114 (1.2%)	$p = 0.20$
Mild Liver Disease	2,406 (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%)	1,099 (11.8%)	$p < 0.01$
Complicated Diabetes	1,611 (0.8%)	252 (2.7%)	$p < 0.01$
Paraplegia and Hemiplegia	794 (0.4%)	136 (1.5%)	$p < 0.01$
Renal Disease	1,858 (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%)	$p < 0.01$

Figure Legend/Caption

Figure 1. Flowchart of study population



Flowchart of study population

48x70mm (300 x 300 DPI)

Supplemental Appendix Tables

Table A1 –Raw Data Sources and Relevant Corresponding Data Elements

Database	Date Range of Data	Relevant Data Elements
Drug Program Information Network (DPIN)	Apr. 1/2000 – Mar. 31/2016	Prescriptions for benzodiazepines (ATC codes N03AE, N05BA, N05CD), Z-Drugs (N05CF), Antidepressants, Antipsychotics, Mood stabilisers, Lithium and Opioids -Drug, dosage strength, dosage type, metric quantity dispensed, day supply, date of dispensation
Manitoba Health Insurance Registry	Apr. 1/1996 – Mar. 31/2016	Birth date/age of patient; sex; location of residence, marital status, date of Manitoba Health coverage, date of coverage end, reason for coverage end (i.e death, emigration etc.)
Medical Claims (Physician Billings)	Apr. 1/1996 – Mar. 31/2016	Services - type of physician (e.g., psychiatrist); dates of services, specific diagnoses (ICD-9 or ICD-10 equivalent)
Hospital Separations Abstracts	Apr. 1/1996 – Mar. 31/2016	Diagnoses (ICD-9 or ICD-10 equivalent), length of stay, admission dates, discharge dates,
Provider Registry/Physician Master File	Apr. 1/1996 – Mar. 31/2016	Physician Age, Sex, Specialty
Social Allowances Management Information Network (SAMIN)	Apr. 1/2001– Mar. 31/2013	Receipt of income assistance

Table A2 – International Classification for Disease Coding for Mood/Anxiety/Sleep Disorders (Cohort Inclusion)

	Source 1 - CPHA	Source 2 - MCHP	Study Algorithm

ICD Codes	All Mental Health Disorders: 9-CM: 290-319 10-CA: F00-F99	Mood Disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety Disorders: 300 (ICD-9-CM) or F40-F42	Mood disorders: 296 and 311 (ICD-9-CM) or F30-F34, F39 (ICD 10-CA) Anxiety disorders: 300 (ICD-9-CM) or F40-F43 (ICD-10-CA) Sleep disorders: 307, 780 or F51, G47 ICD-10-CA)
Case Definition	≥1 hospitalization or outpatient medical claim within 1 year	≥1 hospitalization or ≥1-3 outpatient medical claims within 3-5 years*	≥1 hospitalization or ≥3 outpatient medical claims within 5 years**

**Range of similar definitions between studies from 2000 to 2016*

***The decision to use a 5-year pre-exposure window was based on the fact that all patients received a BZRA, which itself increases specificity for anxiety/sleep disorder diagnoses.*

Table A3 – International Classification for Disease Coding Algorithms for Seizure, Cancer and Palliation (Cohort Exclusion)

	Seizure	**Cancer and other Neoplasms**	**Palliation**
ICD Codes	9-CM: 345 10-CA: G40	9-CM: 140-165, 170-176,179-195, 200-208 10-CA: C00-C99	N/A*
Case Definition	≥1 hospitalization or ≥3 outpatient medical claim within 5 years before index date	≥1 hospitalization or ≥3 outpatient medical claims within 5 years before index date	Carrier code indicating palliative drug program enrollment in DPIN

**While ICD codes do exist for palliation, the DPIN carrier code '04' is expected to be a reliable indicator of when patients become ill enough that community use of medication is required for symptom management.*

Table A4 – Independent 'Patient' Variables for Prediction of Long-Term BZRA Use

Baseline Patient Characteristics	Definition (Variable Type)	Measurement Period
Age	*3 age groups; 18-44, 45-64, 65+ (Ordinal)*	*Index Date*
Sex	*Male or Female (Dichotomous Categorical)*	*Index Date*
Region	*Urban; Winnipeg or Brandon postal-codes* *Rural; Any other Manitoba postal-code* *(Dichotomous Categorical)*	*Census Period closest in time to the index date*
Socioeconomic Status	*Socio-Economic Factor Index – Version 2 (SEFI-2) score composite of four variables based on geography;* *i) unemployment rate* *ii) average household income* *iii) proportion of single-parent households* *iv) proportion of population without high school education.* *Scores <0 indicate more favourable socioeconomic conditions* *Scores >0 indicate less ideal socioeconomic conditions* *(Ordinal Scale)*	*Census Period closest in time to the index date*
Income Assistance	*Record of income assistance (Dichotomous Categorical)*	*Up to 1-year before the Index Date*
Marriage Record	*Record of Marriage (Dichotomous Categorical)*	*Entire available registry period up to the Index Date*
Residential Mobility (i.e frequent mover)	*Average of 1 move every 3 years from beginning of registry coverage to index date (Dichotomous)*	*Entire available registry period up to the Index Date*
Comorbidity Burden	*Charlson Comorbidity Index (CCI) Score; 0, 1, 2+ (Ordinal Scale)*	*Up to 1-year before the Index Date*
Healthcare Resource Use	*Johns Hopkins Adjusted Clinical Groups Resource Utilization Band (Ordinal*	*Up to 1-year before the Index Date*

	Scale); placement into a band (0 to 5) based on grouping of ICD	
Prescription Psychotropic Use (non-BZRA)	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*
Prescription Opioid Use	*Receipt of Prescription (Dichotomous Categorical)*	*Up to 1-year before the Index Date and 6 months after the Index Date*

Table A5 - Independent 'First-Prescription' Variables for Prediction of Long-Term BZRA Use

Characteristics of First Consultation and Subsequent Prescription	**Definition**	**Measurement Period**
Fiscal Year Period	*Fiscal year of first prescription Assigned to 3 five-year intervals; 2001-2005, 2006-2010, 2011-2015 (Ordinal)*	*Index Date*
Prescriber	*10 Years or More (Dichotomous)*	*Index Date*
Sex of Prescriber	*Male or Female (Dichotomous)*	*Index Date*
Prescriber Specialty	*General Practitioner, Psychiatry or Other (Categorical)*	*Index Date*

Table A6 – Logistic Regression Methodology

Criteria	Approach
Variable Selection	-Informal selection via published literature -Simple logistic regression; β values ($p < 0.25$)
Variable Coding	-Dichotomous Categorical; 0 or 1 -Ordinal; discrete number scale starting at 1 -Polychotomous Categorical; 0 or 1 with auto-generated dummy variables -No continuous variables retained
Events-per-Variable	-Minimum 10 events per independent variable rule
Conformity of Linear Gradient	-Ordered categorical variables assessed for conformity of linear gradient; nonconformity handled by variable transformation or separation into additional (design) variables (i.e fiscal year was shown to be linear with respect to outcome so condensed variable into 5-year increments)
Interaction effects	-Assessed at $p < 0.01$. Suspected interactions included; age*sex, residential mobility*SEFI*income assistance, psychotropic use*opioid use, RUB*CCI
Collinearity	-Analysis of variance inflation factor, correlation coefficients, eigenvalues -Significant collinearity; combine variables or removal of inferior explanatory variable
Statistical Significance	-Wald 95% CI for β and OR's
Goodness-of-Fit Measures	-C-statistic, Log-Likelihood Ratio, Hosmer-Lemeshow Statistic
Fitting Procedure	-Stepwise addition/subtraction of variables -Assessment of clinical significance

Table A7 – Goodness of Fit for Final Logistic Regression Models Predicting Long-Term Use of BZRA

Model	Model Type	Independent Variables	Likelihood Ratio (higher is better)	C statistic	Hosmer-Lemeshow Chi-Square Statistic
1	Main-Effects	9 Variables; Age-Sex Category, Period of First Rx, Psychotropic Use, Opioid Use, Income Assistance, Marriage, RUB CCI Score, Residential Mobility	6932 ($p < 0.001$)	0.739	10.78 ($p = 0.215$)
2	Main-Effects + Interaction Effects	10 Variables: All from Model 1 + Residential Mobility*Income Assistance	6945 ($p < 0.001$)	0.739	11.02 ($p = 0.20$)

Table A8 – Proportion of Long-Term BZRA Use by Differing Parameters and Duration Thresholds

Scenario*	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Cohort
A1**	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	9,327	4.51%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	13,745	6.64%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	19,948	9.64%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	13,050	6.31%
A5	First-Use Episode ≥ 180 days	90 Days	16,831	8.13%
A6	First-Use Episode ≥ 270 days	90 Days	15,214	7.35%
A7	First-Use Episode ≥ 365 days	90 Days	14,219	6.87%
B1	Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	38,853	18.78%
B2	Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	58,442	28.24%
B3	Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	72,639	35.10%
B4	Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	44,593	21.55%
B5	Mean Episode Duration ≥ 180 days	90 Days	50,142	24.23%
B6	User Mean Episode Duration ≥ 270 days	90 Days	39,395	19.04%
B7	User Mean Episode Duration ≥ 365 days	90 Days	32,200	15.56%

*A=First Episode Scenario; B=Mean Episode Duration Scenario
**Primary Scenario Used for Logistic Regression

Table A9 - Proportion of Long-Term Z-Drug Use by Differing Parameters and Duration Thresholds

Scenario	Long-Term Use Parameter	Prescription Lapse Criteria	Patients (n)	Proportion of Sub-Cohort
A1	First-Use Episode ≥ 180 days	30 days or 50% of previous Day Supply	8,206	7.41%
A2	First-Use Episode ≥ 90 days	30 days or 50% of previous Day Supply	12,155	11.0%
A3	First-Use Episode ≥ 60 days	30 days or 50% of previous Day Supply	17,126	15.5%
A4	First-Use Episode ≥ 180 days	60 Days or 50% of previous Day Supply	10,437	9.43%
A5	First-Use Episode ≥ 180 days	90 Days	12,719	11.49%
A6	First-Use Episode ≥ 270 days	90 Days	11,117	10.04%
A7	First-Use Episode ≥ 365 days	90 Days	10,045	9.07%
B1	User Mean Episode Duration ≥ 180 days	30 days or 50% of previous Day Supply	21,859	19.75%
B2	User Mean Episode Duration ≥ 90 days	30 days or 50% of previous Day Supply	32,020	28.92%
B3	User Mean Episode Duration ≥ 60 days	30 days or 50% of previous Day Supply	39,690	35.85%
B4	User Mean Episode Duration ≥ 180 days	60 Days or 50% of previous Day Supply	24,098	21.77%
B5	User Mean Episode Duration ≥ 180 days	90 Days	26,477	23.92%
B6	User Mean Episode Duration ≥ 270 days	90 Days	21,040	19.01%
B7	User Mean Episode Duration ≥ 365 days	90 Days	17,358	15.68%

Table A10 – Patient Characteristics of Z-Drug Users by First Use Episode Duration

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Sex Distribution	*Male*	40,516 (39.5%)	3,473 (42.3%)	43,989 (39.8%)
	Female	61,943 (60.5%)	4,731 (57.7%)	66,674 (60.2%)
Age Category	*18-44*	42,663 (41.6%)	1,795 (21.9%)	44,458 (40.2%)
	45-64	39,817 (38.9%)	3,184 (38.8%)	43,001 (38.9%)
	65+	20,011 (19.5%)	3,227 (39.3%)	23,238 (21.0%)
SEFI-2 Score	*<-1*	13,678 (13.3%)	981 (12.0%)	14,659 (13.2%)
	-1 to 0	45,136 (44.1%)	3,674 (44.8%)	48,810 (44.1%)
	0 to 1	33,719 (32.9%)	2,885 (35.2%)	36,604 (33.1%)
	>1	9,958 (9.7%)	666 (8.1%)	10,624 (9.6%)
Residence Distribution	*Urban*	63,207 (61.7%)	3,313 (40.4%)	66,520 (60.1%)
	Rural	39,284 (38.3%)	4,893 (59.6%)	44,177 (39.9%)
High Residential Mobility		22,408 (21.9%)	2,523 (30.8%)	24,931 (22.5%)
Receipt of Income Assistance		8,351 (8.2%)	758 (9.2%)	9,109 (8.2%)
Marriage Record		57,308 (55.9%)	4,595 (56.0%)	61,903 (55.9%)
Johns Hopkins Healthcare Resource Utilization Band	*0 (no utilization)*	1,771 (1.7%)	234 (2.9%)	2,005 (1.8%)
	1	3,205 (3.1%)	175 (2.1%)	3,380 (3.1%)
	2	17,523 (17.1%)	1,012 (12.3%)	18,535 (16.7%)
	3	65,067 (63.5%)	4,699 (57.3%)	69,766 (63.0%)
	4	10,810 (10.6%)	1,259 (15.3%)	12,069 (10.9%)
	5 (high-utilization)	4,083 (4.0%)	825 (10.1%)	4,908 (4.4%)

		Short-term	Long-term	Total
Number of Users		**102,459 (100%)**	**8,204 (100%)**	**110,663 (100%)**
Charlson Comorbidity index Score	*0*	72,490 (70.8%)	4,528 (55.2%)	77,018 (69.6%)
	1	19,495 (19.0%)	1,905 (23.2%)	21,400 (19.3%)
	2+	10,506 (10.3%)	1,773 (21.6%)	12,279 (11.1%)
Non-BZRA Psychotropic Prescription Dispensations	*0*	27,797 (27.1%)	1,784 (21.7%)	29,581 (26.7%)
	1	36,939 (36.1%)	2,156 (26.3%)	39,095 (35.3%)
	2+	37,755 (36.8%)	4,266 (52.0%)	42,021 (38.0%)
Opioid Prescription Dispensations	*0*	47,427 (46.3%)	3,298 (40.2%)	50,725 (45.8%)
	1	34,505 (33.7%)	2,772 (33.8%)	37,277 (33.7%)
	2+	20,559 (20.1%)	2,136 (26.0%)	22,695 (20.5%)
Sex of Prescriber Issuing First Prescription	*Male*	71,485 (69.8%)	5,627 (68.6%)	77,112 (69.7%)
	Female	28,485 (27.8%)	2,273 (27.7%)	30,758 (27.8%)
Age of Prescriber Issuing First Prescription	*50+ Years*	47,871 (46.7%)	4,014 (48.9%)	51,885 (46.9%)
	<50 Years	49,257 (48.1%)	3,758 (45.8%)	53,015 (47.9%)
Type of Prescriber Issuing First Prescription	*General Practitioner*	78,610 (76.7%)	6,366 (77.6%)	84,976 (76.8%)
	Psychiatry	3,912 (3.8%)	475 (5.8%)	4,387 (4.0%)
	Other	3,881 (3.8%)	381 (4.6%)	4,262 (3.9%)
Period of First Prescription	*2001-2006*	34,360 (33.5%)	1,526 (18.6%)	35,886 (32.4%)
	2006-2011	37,752 (36.8%)	2,808 (34.2%)	40,560 (36.7%)
	2011-2016	30,379 (29.6%)	3,872 (47.2%)	34,251 (31.0%)

Table A11 – Frequency of Charlson Comorbidity Group Diagnoses by First Use Episode Duration for Z-Drug Cohort

Charlson Diagnosis	Short-Term 'First-Episode' Users *(n=102,459)*	Long-Term 'First-Episode' Users *(n=8,204)*	Z-Test of Two Proportions
Myocardial Infarction	1,836 (1.8%)	306 (3.7%)	$p < 0.01$
Congestive Heart Failure	3,174 (3.1%)	700 (8.5%)	$p < 0.01$
Peripheral Vascular Disease	1,772 (1.7%)	284 (3.5%)	$p < 0.01$
Cerebrovascular Disease	2,321 (2.3%)	550 (6.7%)	$p < 0.01$
Dementia	1,925 (1.9%)	865 (10.5%)	$p < 0.01$
COPD	12,357 (12.1%)	1,171 (14.3%)	$p < 0.01$
Connective Tissue/Rheumatic Disease	1,906 (1.9%)	243 (3.0%)	$p < 0.01$
Peptic Ulcer Disease	1,111 (1.1%)	123 (1.5%)	$p < 0.01$
Mild Liver Disease	1,672 (1.6%)	139 (1.7%)	$p = 0.33$
Moderate/Severe Liver Disease	275 (0.2%)	38 (0.4%)	$p < 0.01$
Uncomplicated Diabetes	9,317 (9.1%)	1,150 (14.0%)	$p < 0.01$
Complicated Diabetes	1,639 (1.6%)	328 (4.0%)	$p < 0.01$
Paraplegia and Hemiplegia	508 (0.5%)	136 (1.7%)	$p < 0.01$
Renal Disease	1,543 (1.5%)	293 (3.6%)	$p < 0.01$
Cancer	2,109 (2.1%)	247 (3.0%)	$p < 0.01$
Metastatic Carcinoma	429 (0.4%)	45 (0.5%)	$p = 0.04$
HIV/AIDS	118 (0.1%)	16 (0.2%)	$p = 0.02$

Table A12 – Statistical Associations between Predictor Variables and Long-term Use of Z-Drugs

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		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		1.12 (1.07-1.18)	1.04 (0.99-1.09)	1.13 (1.08-1.17)	1.05 (1.01-1.10)	1.08 (1.03-1.12)	1.04 (1.00-1.08)
Age	*18-44*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	45-64	1.90 (1.79-2.02)	2.02 (1.89-2.17)	1.74 (1.66-1.82)	1.78 (1.68-1.88)	1.71 (1.64-1.78)	1.68 (1.60-1.76)
	65+	3.83 (3.61-4.07)	3.71 (3.44-4.00)	3.24 (3.08-3.40)	3.08 (2.90-3.28)	2.99 (2.87-3.12)	2.78 (2.64-2.93)
Rural Residence		0.92 (0.88-0.96)	1.13 (1.07-1.19)	0.99 (0.96-1.03)	1.02 (0.98-1.07)	1.08 (1.04-1.11)	0.95 (0.91-0.99)
High Residential Mobility		1.59 (1.51-1.67)	1.26 (1.19-1.33)	1.53 (1.46-1.59)	1.21 (1.15-1.27)	1.30 (1.26-1.35)	1.12 (1.07-1.17)
Income Assistance		1.15 (1.06-1.24)	1.47 (1.34-1.61)	1.02 (0.95-1.09)	1.29 (1.19-1.40)	0.82 (0.77-0.87)	1.08 (1.00-1.17)
SEFI-2 Score	*<-1*	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	-1 to 0	1.14 (1.06-1.22)	1.07 (0.99-1.16)	1.03 (0.97-1.09)	0.98 (0.92-1.04)	0.95 (0.91-1.00)	0.94 (0.89-0.99)
	0 to 1	1.19 (1.11-1.29)	1.08 (0.99-1.17)	1.04 (0.98-1.11)	0.99 (0.93-1.06)	0.92 (0.87-0.97)	0.93 (0.88-0.99)
	>1	0.93 (0.84-1.03)	0.84 (0.75-0.94)	0.80 (0.73-0.87)	0.77 (0.70-0.85)	0.68 (0.63-0.73)	0.72 (0.66-0.78)
Married		1.00 (0.96-1.05)	0.86 (0.82-0.91)	1.07 (1.03-1.10)	0.93 (0.89-0.98)	1.13 (1.09-1.17)	0.98 (0.94-1.01)
Opioid Use		1.28 (1.22-1.34)	1.15 (1.09-1.21)	1.26 (1.21-1.31)	1.15 (1.11-1.20)	1.18 (1.14-1.21)	1.11 (1.07-1.15)

Independent Variable		Use Duration					
		≥180 days		≥90 days		≥60 days	
		Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Psychotropic Rx Use (Non-BZRA)		1.34 (1.27-1.41)	1.24 (1.17-1.32)	1.35 (1.29-1.41)	1.27 (1.20-1.33)	1.22 (1.17-1.27)	1.19 (1.14-1.24)
Charlson Comorbidity Index Score	0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1	1.56 (1.48-1.65)	1.25 (1.18-1.33)	1.45 (1.39-1.52)	1.21 (1.15-1.27)	1.33 (1.28-1.38)	1.13 (1.08-1.19)
	2+	2.70 (2.55-2.87)	1.46 (1.36-1.58)	2.34 (2.22-2.46)	1.38 (1.29-1.47)	2.02 (1.93-2.12)	1.30 (1.22-1.37)
Resource Utilization Band	0-3 (≤Moderate)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	4 (High)	1.67 (1.56-1.78)	1.16 (1.08-1.25)	1.47 (1.39-1.56)	1.09 (1.01-1.16)	1.30 (1.24-1.37)	1.00 (0.95-1.07)
	5 (Very High)	2.89 (2.67-3.13)	1.55 (1.41-1.70)	2.43 (2.26-2.61)	1.42 (1.30-1.55)	1.97 (1.85-2.11)	1.22 (1.12-1.32)
Male Prescriber of First Prescription		0.99 (0.94-1.04)	0.97 (0.92-1.03)	0.98 (0.94-1.02)	0.98 (0.93-1.02)	0.94 (0.90-0.97)	0.93 (0.90-0.97)
Prescriber Age ≥50 Years		1.10 (1.05-1.15)	0.98 (0.93-1.03)	1.10 (1.06-1.15)	0.98 (0.94-1.02)	1.15 (1.11-1.19)	1.05 (1.01-1.09)
Prescriber of First Prescription	GP	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Psychiatrist	1.50 (1.36-1.66)	1.96 (1.76-2.17)	1.36 (1.25-1.49)	1.72 (1.57-1.89)	1.11 (1.02-1.20)	1.38 (1.27-1.51)
	Other	1.21 (1.09-1.35)	0.92 (0.82-1.03)	1.18 (1.07-1.29)	0.91 (0.83-1.00)	1.19 (1.10-1.29)	0.98 (0.91-1.07)
Period of First Prescription	2001-2006	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	2006-2011	1.68 (1.57-1.79)	1.57 (1.46-1.68)	1.67 (1.59-1.76)	1.56 (1.47-1.66)	1.53 (1.46-1.60)	1.46 (1.39-1.54)
	2011-2015	2.87 (2.70-3.05)	2.45 (2.28-2.65)	2.83 (2.69-2.97)	2.44 (2.30-2.59)	2.20 (2.10-2.29)	1.96 (1.86-2.07)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10-11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7, fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	Fig 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*12-13*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*n/a*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 2-3
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.