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

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ABSTRACT

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

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

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

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

INTRODUCTION

The use of benzodiazepine receptor agonists (BZRAs), benzodiazepines (BZD) and Z-Drugs, in the treatment of anxiety and insomnia has shifted based on the evolving data on safety risks and limited efficacy on long-term use in the literature.1-4 On their initial introduction into clinical practice in the late 1960s, BZD were considered to be a safer alternative to barbiturates.3 However, safety concerns such as psychomotor impaired accidents (ie, falls and motor-vehicle accidents), dependency and misuse/abuse are now well known.6-8 Recent studies have also raised concerns proposing possible links to dementia, recurrence of mood episode, respiratory disease exacerbation and suicide with long-term BZRA use.9-13 However, the association of BZRA use for these newer harms is uncertain given conflicting evidence and confounding in previous studies.14

In spite of ongoing adverse effect concerns, justification for less restrictive BZRA use have stemmed from their clinical utility as rapidly effective anxiolytic sedatives.15 Some view that limiting BZRA use is at times impractical.16 Moreover, the use of alternative pharmacotherapy, including trazodone, atypical...
antipsychotics, barbiturates, and tricyclic antidepressants are not without adverse effects. It should also be noted that the difficulties with de-prescribing BZRA s reported in the literature have added caution to the initiation of these agents in practice.4 17

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

METHODS

Study design and data sources

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

Cohort inclusion/exclusion criteria

Eligible patients were adults age 18 years and older who initiated a new benzodiazepine or Z-drug prescription (defined as no use in the 1-year prior to the first prescription20 21 between 1 April 2001 and 31 March 2015, with no preceding dispensations from 1 April 2000 to 31 March 2001 (first year of the dataset) to avoid prevalent user bias (figure 1). All individuals with at least 1 year of registry coverage prior to and after the first prescription was required for cohort inclusion. As such, individuals who received a benzodiazepine in the distant past could be included in the cohort as a new user, provided that the benzodiazepine was not used in the past 1 year. A sensitivity analysis was also performed in which incident use was defined as no prescription for a BZRA was received in the 3 years prior to the first prescription.23

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

To reduce confounding, we established cohort exclusion criteria that otherwise may have justified long-term use of BZDs in clinical scenarios beyond the scope of general guideline recommendations for anxiety and insomnia. Namely, patients were excluded if they had ≥1 ICD code for cancer, a seizure disorder or if there was placement in the Manitoba palliative care drug programme at any point in the 5 years preceding their first prescription for a BZRA (online supplemental table A3). Where patients became palliative ≥1 year after the initial BZRA dispensation, their ongoing use of BZRA was
To assess the robustness of the primary outcome, six sensitivity analyses (online supplemental tables A8 and A9) were conducted to determine how the proportion of long-term use changed under differing parameter assumptions. The threshold duration for long-term use was adjusted to values ranging from 60 days to 365 days. Additionally, the episode lapse criteria (ie, prescription gap rule) was changed. While the analysis was not exhaustive for every conceivable combination of these key parameters, the selected values were chosen because...
they were judged to be representative of how peers in the international clinical community may have defined or measured ‘long-term use’ of BZRA. All data were cleaned and analysed using SAS V 9.4.

RESULTS
Episodic BZD/Z-drug use
Study population demographics are presented in table 1. There were 206933 patients in our cohort representing 931771 unique BZRA dispensations over the 15-year study duration. Over the study period, cohort individuals had a median of three and average of 4.5 BZRA use episodes, respectively. First episodes of use were of a median duration of 20 days (IQR=10–30 days). For all use episodes, the median average use duration was 30 days (IQR=15–111 days). Evaluation of long-term use revealed that 4.51% of patients used a BZRA for ≥180-days in their ‘first’ episode of use. At most, this proportion increased to 9.64% when a sensitivity analysis of 60 days or greater was used for the definition of ‘long-term use’ for the first episode of use. However, the proportion of long-term users increased considerably after averaging for all episodes for each user (sensitivity analysis range: 15.6%–35.1%) (online supplemental table A7).

To evaluate treatment duration for insomnia, a sensitivity analysis was performed on only Z-drugs (n=110663), which found similar results (online supplemental tables A9–A12).

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

Both the crude and adjusted ORs are presented for the full cohort in table 2.

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

DISCUSSION
This study found approximately 4.5% of the full cohort and 7.4% of the Z-drug cohort were ‘long-term’ first-episode users according to the best available evidence-based consensus definition of 180 days. 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) compared with BZD for anxiety disorder (up to ≤12 weeks depending on indication). Therefore, these results suggest greater disparity from practice guidelines in the case of Z-drug use for insomnia. Of note, more recent insomnia guidelines have recognised that while non-drug alternatives have a favourable safety profile, these interventions may be difficult to achieve for certain populations, which could explain the deviation between practice recommendations and real-world use of these agents.

The proportion of patients who met criteria for ‘long-term’ use after accounting for all of their use-episodes (ie, rather than just the first episode of use) was approximately 3.5 times higher than the proportion of patients meeting criteria after only their first episode of use. These results may indicate that repeated episodes of BZRA use may be associated with a higher risk of being exposed to a BZRA for a duration of ≥180 days in one episode. An area of future research is to examine whether repeated episodes of BZRA use is associated with progression to long-term use as demonstrated in a previous study that observed the number of episodes of dispensing in the first month was a significant predictor of the total duration of dispensing in the later period. Of note, the majority of people with repeated use still only take BZRAs for intermittent, short-term periods. Furthermore, confounding variables such as age and accrued comorbidity over time may influence the risk of future long-term use in some patients. Nonetheless, these results support the observed difficulty in deprescribing once BZRA use has become chronic, which has also been reported in previous literature. Lastly, other clinical considerations such as risk of protracted withdrawal symptoms, risk of rebound insomnia and/or anxiety, severity of indication, patient dissatisfaction, limited alternate drug and non-drug interventions, or
Table 1  Characteristics of BZRA users by first use episode duration

| No of users              | Short term | Long term | Total     |
|-------------------------|------------|-----------|-----------|
|                         | 197,606 (100%) | 9327 (100%) | 206,933 (100%) |
| **Sex distribution**   |            |           |           |
| Male                    | 74,487 (37.7%)  | 4295 (41.6%)  | 78,782 (38.1%)  |
| Female                  | 123,057 (62.3%)  | 5029 (58.4%)  | 128,086 (61.9%)  |
| **Age category**        |            |           |           |
| 18–44                   | 101,709 (51.5%)  | 2776 (29.8%)  | 104,487 (50.5%)  |
| 45–64                   | 66,752 (33.8%)  | 3320 (35.6%)  | 70,072 (33.9%)  |
| 65+                     | 29,143 (14.7%)  | 3231 (34.6%)  | 32,374 (15.6%)  |
| **SEFI-2 score**        |            |           |           |
| ≤1                      | 24,955 (12.6%)  | 1089 (11.7%)  | 26,044 (12.6%)  |
| −1 to 0                 | 81,718 (41.4%)  | 3835 (41.1%)  | 85,553 (41.3%)  |
| 0 to 1                  | 64,967 (32.9%)  | 3274 (35.1%)  | 68,241 (33.0%)  |
| >1                      | 25,866 (13.1%)  | 1129 (12.1%)  | 27,095 (13.1%)  |
| **Residence distribution** |         |           |           |
| Urban                   | 125,950 (63.7%)  | 5802 (62.2%)  | 131,752 (63.7%)  |
| Rural                   | 71,656 (36.3%)  | 3525 (37.8%)  | 75,181 (36.3%)  |
| **High residential mobility** |         |           |           |
| 36,392 (18.4%)          | 2385 (25.6%)  | 38,777 (18.7%)  |
| **Receipt of income assistance** |       |           |           |
| 18,530 (9.4%)           | 1222 (13.1%)  | 19,752 (9.5%)  |
| **Marriage record**     |            |           |           |
| 102,461 (51.9%)         | 4618 (49.5%)  | 107,079 (51.8%)  |
| Johns Hopkins Healthcare Resource Utilisation Band†† | 0 (no utilisation) | 3001 (1.5%)  | 3350 (1.6%) |
|                        | 1          | 148,257 (75.0%)  | 154,040 (74.4%)  |
|                        | 2          | 36,261 (18.4%)  | 38,292 (18.5%)  |
|                        | 3+         | 13,088 (6.6%)  | 14,601 (7.1%)  |
| **Charlson Comorbidity Index Score** |       |           |           |
| 0                      | 148,257 (75.0%)  | 5783 (62.0%)  | 154,040 (74.4%)  |
| 1                      | 36,261 (18.4%)  | 2031 (21.8%)  | 38,292 (18.5%)  |
| 2+                     | 13,088 (6.6%)  | 1513 (16.2%)  | 14,601 (7.1%)  |
| **Non-BZRA psychotropic prescription dispensations** | 0 (no utilisation) | 111,216 (56.3%)  | 115,078 (55.6%)  |
|                        | 1          | 38,62 (41.4%)  | 41,578 (18.8%)  |
|                        | 2+         | 17,661 (9.9%)  | 19,179 (8.8%)  |
| **Opioid prescription dispensations** |       |           |           |
| 0                      | 132,027 (66.8%)  | 5855 (62.8%)  | 137,882 (66.6%)  |
| 1                      | 30,530 (15.5%)  | 1011 (10.8%)  | 169,423 (15.2%)  |
| 2+                     | 34,405 (17.7%)  | 2461 (26.4%)  | 37,510 (18.2%)  |
| **Sex of prescriber issuing first prescription††** |       |           |           |
| Male                   | 143,619 (75.3%)  | 6928 (76.5%)  | 150,547 (75.3%)  |
| Female                 | 47,128 (24.7%)  | 2126 (23.5%)  | 49,254 (24.7%)  |
| **Age of prescriber issuing first prescription‡‡** |       |           |           |
| 50+ years              | 95,629 (52.1%)  | 4775 (53.9%)  | 100,404 (52.2%)  |
| <50 years              | 87,833 (47.9%)  | 4074 (46.1%)  | 92,908 (47.8%)  |
| **Type of prescriber issuing first prescription§§** |       |           |           |
| General practitioner   | 146,823 (91.6%)  | 7013 (87.5%)  | 153,836 (91.4%)  |
| Psychiatry             | 6338 (4.1%)  | 624 (7.8%)  | 6962 (4.1%)  |
| Other                  | 7183 (4.5%)  | 375 (4.7%)  | 7558 (4.5%)  |
| **Period of first prescription** |       |           |           |
| 2001–2006              | 90,008 (45.5%)  | 2608 (28.0%)  | 92,616 (44.8%)  |
| 2006–2011              | 65,750 (33.3%)  | 3170 (34.0%)  | 68,920 (33.3%)  |
| 2011–2016              | 41,848 (21.2%)  | 3549 (38.1%)  | 45,397 (21.9%)  |

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

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

BZRA, benzodiazepine receptor agonist; GP, general practitioner; SEFI-2, Socio-Economic Factor Index-2.
interference with another prescriber’s decisions likely undermine potential deprescribing efforts.

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

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

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

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

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

BZD, benzodiazepines; COPD, chronic obstructive pulmonary disease.

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

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

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

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