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NOVEL MEASURES OF BENZODIAZEPINE & Z-DRUG UTILISATION TRENDS IN A CANADIAN PROVINCIAL ADULT POPULATION (2001-2016)

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ABSTRACT

Purpose

(1) To evaluate trends for benzodiazepines (BZD) and Z-Drugs over 15-years in a general Canadian adult population measured by: (a) consumption (b) pharmacologic exposure (c) dose intensity, and (d) prevalence of use. (2) To demonstrate the utility of Diazepam Milligram Equivalents (DME) based measurements when used in conjunction with traditional standard measurements of drug utilization.

Methods

Administrative data covering all prescriptions from April 2001-March 2016 for BZD and Z-Drugs for patients ≥18 years was used. Consumption was calculated as DDD/1000-person days. Dose intensity (DI) was determined by conversion of individual daily doses to DME. Pharma-cologic exposure (PE) was calculated as DME-DDD/1000-person days. Prevalence was determined as the proportion of the adult population with receipt of ≥1 prescription in a given year. Changes were assessed using either Poisson or simple linear regression at an alpha of 0.05.

Results

Z-Drug usage (~99% zopiclone) statistically increased on every measure over the course of the study period; consumption (8.2 to 28.6 DDD/1000-person days), PE (4.1 to 14.3 DME-DDD/1000-person days), DI (5.0 to 5.43 DME/day) and prevalence (2.0% to 4.8%). For BZD the only statistically significant changes were in DI (17.1 to 20.1 DME/day) and prevalence (9.3% to 8.1%). Consumption and PE gradually increased from 2001 to 2011 for BZD before declining thus producing a non-significant trend for BZD.

Conclusion

(1) Z-Drug usage increased markedly from 2001 to 2016 whereas BZD use only increased in terms of DI. (2) DME-based measurements enable further interpretation of BZD utilization compared to sole reliance on DDD.

Key Words: Benzodiazepines, Z-Drugs, Drug Utilization, Population Use, Diazepam Milligram Equivalence, Defined Daily Dose

Benzodiazepines (BZD) and Z-Drugs (i.e., zopiclone, eszopiclone, zolpidem, zaleplon) persist as commonly used central nervous system depressant medications for the treatment of anxiety disorders and insomnia, respectively.[1] Their popularity among patients and clinicians is primarily owed to their effectiveness and rapid onset in producing anxiolysis compared to other agents such as antidepressants which typically require weeks to months before perceived benefit. Unfortunately, this rapid effectiveness is often limited by tolerance and dependence with repeated dosing, risk of psychomotor impaired accidents (motor-vehicle accidents, falls) and potential misuse (use other than as prescribed or diversion).[2–4] For these reasons, clinical practice guidelines universally recommend short-term use (4–12 weeks) or as needed use as an adjunct to other agents such as antidepressants as a means to optimally balance the benefit-risk ratio.[5–10] Furthermore, use of psychosocial interventions or alternative pharmacotherapy is widely advocated as first-line treatment options over BZD and Z-Drug use, especially for older adults.[11]

Beyond this well-established body of evidence, emerging literature has raised additional concerns that BZD and Z-Drugs may be causal contributors to increased rates of infection, dementia, pancreatitis and respiratory disease exacerbations.[12–16] Currently, the total body of evidence is either insufficient and/or too conflicting to substantiate any of these associations.[17] Nonetheless, this research adds to the existent and long-standing controversies and concerns regarding usage of this medication class. For these reasons, observational studies evaluating utilisation patterns over time remain highly relevant for informing health policy or professional practice. Furthermore, as morbidity and mortality risk is substantially increased with combination BZD-opioid use, benzodiazepine utilisation studies can provide additional information for public health use in nations experiencing opioid epidemics.[18,19]

Observational studies in the past decade on BZD, both in North America and abroad, have found that concerning or questionable patterns of use persist in different patient populations despite the long-standing conservative approach advocated by practice guidelines.[20–25] This drug utilisation study (part of a larger project) sought to update past utilisation work on benzodiazepines and Z-Drugs in the province of Manitoba, Canada as well as to examine utilisation patterns by different indicators that went unexplored by the previous study.[26] As Manitoba is the province located most geographically central within Canada and has a stable, yet diverse population, the results of this study may be partially generalizable to other provinces.

The primary study objectives were to determine and evaluate trends, measured annually, from 2001 to 2016 for the following outcome measures (defined in methods):

1. *Consumption* by drug class, individual agent and age-sex category
2. *Pharmacologic exposure (PE)* by drug class and age-sex category
3. *Dose intensity (DI)* by drug class, individual agent and age-sex category
4. *Prevalence* of 'any' use by drug class and age-sex category

METHODS

Study Design, Data Source and Data Validity

This drug utilisation study used routinely collected administrative prescription drug dispensation data, entered by community pharmacy personnel into the Drug Program Information Network (DPIN) from April 1st 2001 to March 31st 2016. DPIN is

maintained and operated by the Provincial Drug Programs department of Manitoba Health. Patient level data elements are de-identified by a confidential algorithmic process which scrambles patients' Personal Health Information Number (PHIN) prior to transmission and further data cleaning by the Manitoba Centre for Health Policy (MCHP) at the University of Manitoba.[27] The DPIN database has been previously validated.[28]

The Manitoba Population Health Insurance Registry was also used for this study. This registry was used to determine the number of all adult individuals registered by Manitoba Health in the province for each fiscal year as well as to ascertain their date of birth and biological sex. The registry does not comprehensively account for the indigenous population in remote areas, federal employees or very new residents. However, it has been shown repeatedly to closely approximate alternative population data sources such as the Canadian government census.[29]

Data Description, Exclusion and Analytic Preparation

All outpatient prescription claims for adults (≥18 years) from April 1st 2001 to March 31st 2016 for benzodiazepines and Z-Drugs were extracted for the study. DPIN prescription drug claims (i.e., individual line-level observations) include information on de-identified PHIN, date of drug dispensed, drug product, strength, dosage form, metric quantity dispensed and day supply. The date variable for each dispensation was categorized by fiscal year (April 1 – March 31st) for the purposes of aggregate annual calculations. The DPIN and registry datasets were linked by scrambled PHIN and fiscal year. New variables were generated on each line-level observation for total dispensed milligrams (equation 1), daily dose (equation 2) and Diazepam Milligram Equivalent (DME) daily dose (equation 3).

1. $Quantity \times Dosage\ Strength = Total\ Prescription\ Milligrams$
2. $\frac{Total\ Prescription\ Milligrams}{Day\ Supply} = Daily\ Dose$
3. $Daily\ Dose \times Conversion\ Factor = DME\ Daily\ Dose$

Observations were excluded if any of the data fields mentioned above were missing. Exclusions also occurred if either the days supply or quantity dispensed was '0'. This was because it was questionable that a true dispensation took place and because it would result in errors in the calculation of other generated variables. Furthermore, observations were excluded where the quantity dispensed exceeded 1000 oral units (i.e., tablets) with a corresponding day supply of 30 days or less. This was because these claims were not only incredulous but more likely also attributed to pharmacy data entry error. Removal of observations using these criteria would be expected to make the results more conservative in their estimates and so were deemed to be acceptable to exclude these claims.

Health registry data provided dates of birth and biological sex for the majority of the Manitoba adult population (>98%). Using the registry, the total adult population as well as the populations for male and females in the distinct age ranges 18-65 and 65+ were calculated for each fiscal year to serve as the denominator for outcome measures.

Outcome Measures

Consumption was calculated for each drug on the basis of their assigned Anatomical Therapeutic Chemical (ATC) classification codes and Defined Daily Dose (DDD) values as per the World Health Organizations Collaborating Centre for Drug Statistics Methodology (Table 1).[30] Consumption was measured and reported as the number of DDD/1000 persons/day. The DME conversions were derived from work conducted by Dr. Ashton (Table 1).[31,32] These equivalency sources appeared to us as the most prominent in the literature to date (though this is debatable).[23,33] *DI*, measured as mean daily dose per year, was calculated in original milligrams and then converted to DME for each drug and by class (DME/day on a weighted basis by proportional use of each drug per year). Estimated annual PE, measured by number of DME-DDD/1000 inhabitants per day, while similar to our calculation of consumption, accounts for relative differences in potency of agents to aid in interpretation and standardized comparison of utilisation to other nations or geographic regions.[33] This measure is more interpretable because it represents the

TABLE 1 ATC, DDD and DME conversion ratios for Benzodiazepines and Z-Drugs used in Manitoba, Canada (2001-2016)[32]

Drug	ATC code	DDD	Equivalence to 10 mg Diazepam (mg)
Alprazolam	N05BA12	1 mg	0.5 mg
Bromazepam	N05BA08	10 mg	5 mg
Chlordiazepoxide	N05BA02	30 mg	25 mg
Clobazam	N05BA09	20 mg	20 mg
Clonazepam	N03AE1	8 mg	0.5 mg
Potassium Clorazepate	N05BA05	20 mg	15 mg
Diazepam	N05BA01	10 mg	10 mg
Flurazepam	N05CD01	30 mg	30 mg
Lorazepam	N05BA06	2.5 mg	1 mg
Oxazepam	N05BA04	50 mg	20 mg
Nitrazepam	N05CD02	5 mg	10 mg
Temazepam	N05CD07	20 mg	20 mg
Triazolam	N05CD05	0.25 mg	0.5 mg
Zaleplon	N05CF03	10 mg	20 mg
Zolpidem	N05CF02	10 mg	20 mg
Zopiclone	N04CF01	7.5 mg	15 mg

approximate number of daily doses equal to 10 mg of diazepam rather than the distinct DDD values of all agents pooled together into a class estimate.[33] Lastly, *prevalence* was measured as the percent proportion of the total registry population in a given year who received at least one dispensation of a benzodiazepine or Z-Drug, regardless of dose or duration.

Statistical Techniques

Trends for consumption, PE and prevalence (all being dependent on population count data) were statistically evaluated using Poisson regression in a generalized linear model. DI (being independent of population count data) was evaluated using bivariate linear regression. Regression sub-analyses were conducted by age-sex stratification (18–64, 65+). Statistical rates of change were determined and reported at 95% confidence intervals. Model goodness of fit was assessed by data visualization and review of statistics such as the R-square (linear regression), dispersion index and log-likelihood (Poisson). Three sensitivity analyses were undertaken on DI and PE by applying different DME conversion values from alternative sources,[34,35] or by modification of the original source given an 'outlier' BZD (clonazepam)[32] (Supplemental Appendix 1). All programming, data manipulation and analysis was conducted using Base SAS v9.4©.

RESULTS

There were 12,407,898 dispensations (73.8% BZD, 26.2% Z-Drug) available for 394,151 patients from April 1st 2001 to March 31st 2016. 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) thus bringing the final analyzable dataset to 12,406,330 dispensations for 394,126 patients over the 15-year period.

Utilisation by Drug Class

Table 2 displays the statistical results on the primary outcome measures for the overall study population unstratified by age or sex grouping and according to drug class. Figure 1 visually depicts the trends for these measures.

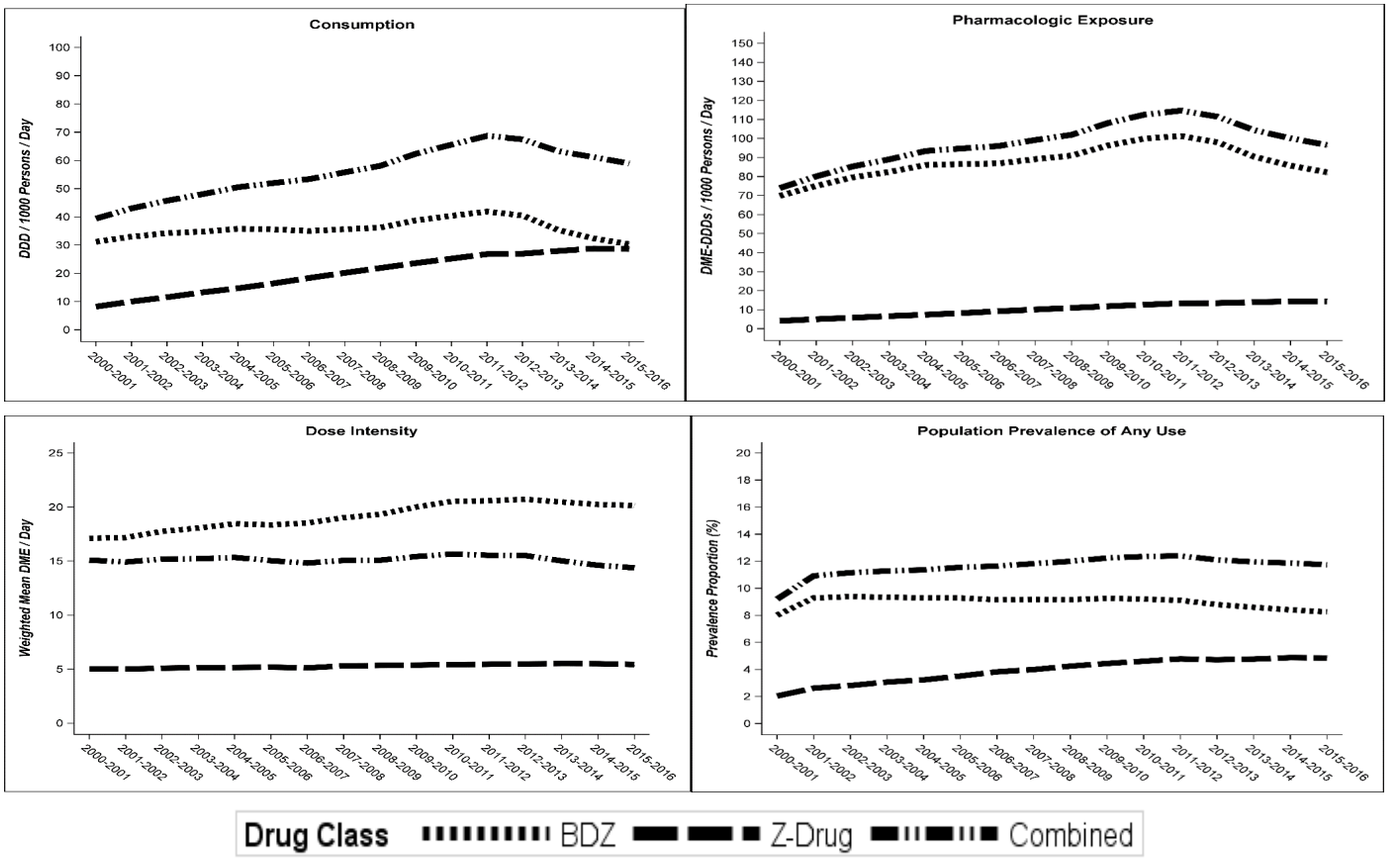
There was a statistically significant increase for Z-Drugs (~99% prescriptions were for zopiclone) on all measures of utilisation. In contrast, in terms of statistical significance for BZD, only DI increased and prevalence dropped. Nevertheless, there was an observed steady rise in consumption and PE for BZD until 2011. The decline that occurred thereafter which nullified any statistical significance in the trend is largely explained by a previous audit-feedback intervention study aimed to reduce inappropriate BZD prescribing in primary care around this time period.[36]

When BZD and Z-Drugs were pooled together only the consumption trend remained significant. This was because the proportional difference in use and the DME dose range between Z-Drugs and BZD resulted in the negation of the other utilisation measures. For example, while the DI increased for both BZD and Z-Drugs separately, the increasing prevalence of Z-Drug use, decreasing prevalence of BZD use and lower DME based dose for Z-Drugs cancelled out any significant trend for combined DI. Interestingly, the average day supply per dispensation decreased

TABLE 2 Main Results - Absolute and Relative Changes in Utilisation Measures for BZD & Z-Drugs (2001-2016)

Parameter	Z-Drug	BZD	Combined (BZD + Z-Drug)
Consumption (DDD/1000 Persons/ Day)	Absolute increase from 8.2 (2001) to 28.6 (2016) *Relative* increase of 6.2% each year (95% CI 3.7%–8.6%)	No statistically significant trend; 31.2 (2001) to 30.3 (2016) Annual rate of change; –0.7% (95% CI –2.5% to 1.0%)	Absolute increase from 39.4 (2001) to 58.9 (2016) *Relative* increase of 1.7% *each* year (95% CI 0.3%–3.1%)
Pharmacologic Exposure (DME-DDD/1000 Persons/ Day)	Absolute increase from 4.1 (2001) to 14.3 (2016) *Relative* increase of 6.2% *each* year (95% CI 2.7%–9.6%)	No statistically significant trend; 69.8 (2001) to 82.2 (2016) Annual rate of change; 0.1% each year (95% CI –1.3% to 1.4%)	No statistically significant trend; 73.9 (2001) to 96.5 (2016) Annual rate of change; 0.7% *each* year (95% CI –0.4%–1.8%)
Dose Intensity (DME/ Day)	Absolute increase from 5.0 (2001) to 5.43 (2016) Increase in average daily dose by 0.036 DME *each* year (95% CI 0.030–0.042)	Absolute increase from 17.1 (2001) to 20.1 (2016) Increase in average daily dose by 0.25 DME *each* year (95% CI 0.20–0.30)	No statistically significant trend; 15.1 (2001) to 14.4 (2016) Rate of annual change; -0.01 DME *each* year (95% CI –0.05 to 0.03)
Prevalence (% Proportion of Manitoban Adults)	Absolute increase from 2.0% in 2001 to 4.8% in 2016. *Relative* increase of 3.4% *each* year (95% CI 2.4–4.5%)	Absolute decrease from 9.3% in 2001 to 8.1% in 2016. *Relative* decrease of 1.8% *each* year (95% CI –2.3 to –1.2%)	No statistically significant trend; 9.2% (2001) to 11.7% (2016) *Relative* annual change of -0.4% *each* year (95% CI –1.0%–0.2%)

FIG 1. Benzodiazepine/z-drug utilisation trends by drug class.



over time from 2001–2016; 32.4 days to 25 days for BZD-Z-Drugs combined, 32 days to 22 days for BZD and 34 days to 31 days for Z-Drugs.

Utilisation by Age-Sex Category

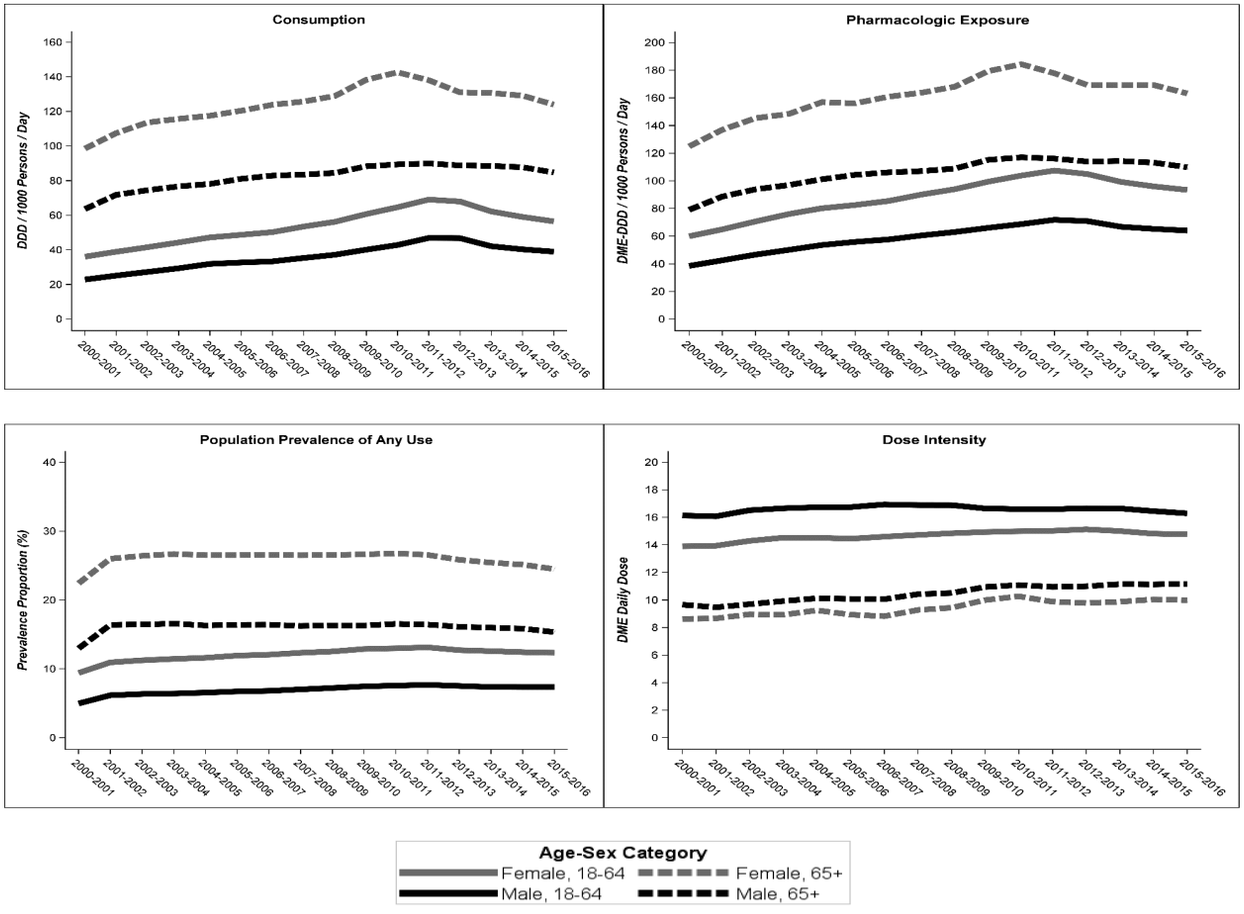
Figure 2 depicts the trends over time for these same outcome measures, stratified by age and sex category. Regression model trend results for the age-sex categories on the main outcome measures are presented in Table 3. Notably, consumption and PE for BZD+Z-Drugs combined increased over the study period for all age groups. DI, measured by DME, increased more for the 65+ population relative to younger adults but remained lower overall, as would be expected based on known physiologic and pharmacokinetic changes that occur with aging, necessitating lower average doses. The reverse pattern was observed for prevalence, wherein the rate of change showed a statistically significant increase in adults under 65 despite that prevalence remained consistently higher each year for older adults, particularly older females.

Utilisation by Agent

Figure 3 compares the proportion of prescriptions each agent represents in the first and last year of the study. This was calculated by dividing the number of prescriptions for a particular drug in that year by the total number of BZD/Z-Drug prescriptions in that same year. The relative percentage change in utilization of each agent is provided at the end of each horizontal bar.

Analysis of DI trends by individual agent, in their respective milligram potencies, revealed statistically significant increases in daily doses for zopiclone, temazepam, triazolam, alprazolam, oxazepam and diazepam over the study period. Chlordiazepoxide, clobazam and clonazepam saw statistically significant decreases in daily dose. All other agents had

FIG 2 Combined Benzodiazepine/Z-Drug Utilisation Trends by Age-Sex Categories.



non-significant changes in DI at an alpha of 0.05. The agent that saw the greatest change in average dose over time was alprazolam, rising 34.7% from 0.98 mg/day (2001) to 1.32 mg/day (2016).

Consumption trends (DDD/1000-person days) by individual agent revealed statistically significant increases (% increase per year) for zopiclone (7.4%), alprazolam (4.4%), temazepam (3.4%), clonazepam (2.9%) and clobazam (1.1%). Statistically significant decreases (% reduction per year) were observed for flurazepam (13.2%), chlordiazepoxide (12.5%) triazolam (12.5%), potassium clorazepate (9.0%), oxazepam (7.5%), bromazepam (5.8%), nitrazepam (4.4%), diazepam (2.1%) and lorazepam (0.3%). Zolpidem and zaleplon were not analyzed individually due to their limited representation and incomplete market availability over the study duration.

Sensitivity Analysis for DME-Based Utilisation Measures

Detailed results for sensitivity analyses are provided in Supplemental Appendix 1. Substitution of DME conversion values from 3 differing sources did not result in significant change in trends for DI or PE for Z-Drugs or BZD when assessed separately. However, when they were combined, discrepant trends emerged. For individual agents, some equivalency values differed by two-fold or more and this would dramatically impact class-based DME estimates if such agents constituted a large portion of the annual prescription share.

Notably, average daily dose in DME remained significantly higher for clonazepam compared to other agents, thus prompting an additional post-hoc sensitivity analysis wherein its conversion value

TABLE 3 Absolute and Relative Changes in Utilisation Measures for BZD + Z-Drugs (2001-2016) by Age-Sex Category

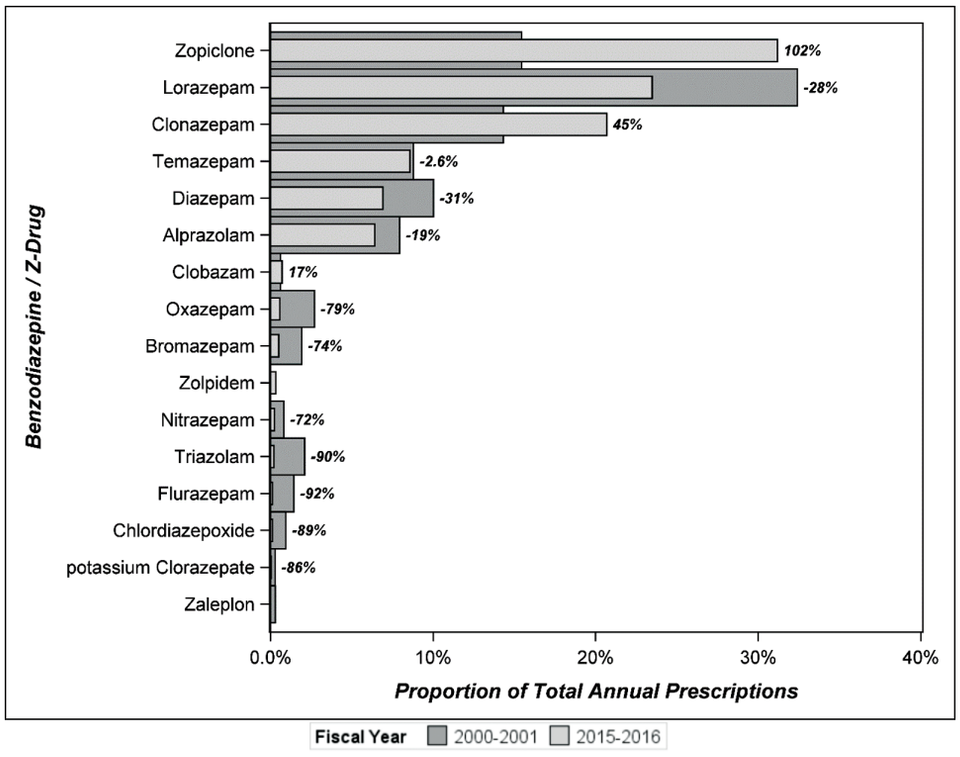
Parameter (combined BZD + Z-Drug)	Male, 18–64	Female, 18–64	Male, 65+	Female, 65+
Consumption (DDD/1000 Persons/ Day)	Absolute increase from 22.8 (2001) to 39.0 (2016) Relative increase of 3.8% *each* year (95% CI 3.79%–3.80%)	Absolute increase from 36.0 (2001) to 56.4 (2016) Relative increase of 3.4% *each* year (95% CI 3.44% to 3.45%)	Absolute increase from 63.6 (2001) to 84.7 (2016) Relative increase of 1.6% *each* year (95% CI 1.59%–1.60%)	Absolute increase from 98.5 (2001) to 123.9 (2016) Relative increase of 1.5% *each* year (95% CI 1.46%–1.47%)
Pharmacologic Exposure (DME-DDD/1000 Persons/ Day)	Absolute increase from 38.5 (2001) to 64.0 (2016) Relative increase of 3.2% *each* year (95% CI 3.2%–3.21%)	Absolute increase from 59.9 (2001) to 93.4 (2016) Relative increase of 3.0 % each year (95% CI 2.98% to 2.99%)	Absolute increase from 79.0 (2001) to 109.8 (2016) Relative increase of 1.8% each year (95% CI 1.80%–1.82%)	Absolute increase from 124.8 (2001) to 163.2 (2016) Relative increase of 1.6% *each* year (95% CI 1.58% to 1.58%)
Dose Intensity (DME/Day)	No statistically significant trend; 16.1 (2001) to 16.3 (2016) Rate of annual change; 0.01 *each* year (95% CI –0.02–0.04)	Absolute increase from 13.9 (2001) to 14.8 (2016) Increase in average daily dose by 0.07 DME *each* year (95% CI 0.04–0.09)	Absolute increase from 9.7 (2001) to 11.2 (2016) Increase in average daily dose by 0.12 DME *each* year (95% CI 0.10 to 0.14)	Absolute increase from 8.62 (2001) to 10.0 (2016) Increase in average daily dose by 0.10 DME *each* year (95% CI 0.07–0.13)
Prevalence (% Proportion of Manitoban Adults)	Absolute increase from 5.0% (2001) to 7.4% (2016) *Relative* increase of 1.8% *each* year (95% CI 1.7%–1.9%)	Absolute increase from 9.4% (2001) to 12.3% (2016) *Relative* increase of 1.3% *each* year (95% CI 1.2% to 1.3%)	No statistically significant trend; 13.0% (2001) to 15.3% (2016) *Relative* change of 0.1% *each* year (95% CI 0.04% – 0.2%)	No statistically significant trend; 22.4% (2001) to 24.5% (2016) *Relative* change of –0.02% *each* year (95% CI –0.08%–0.05%)

was changed from 1 mg = 20 DME to 1 mg = 10 DME. This 'modified' Ashton scale, with all other BZD conversions being held constant, constituted the third sensitivity analysis. However, while the statistical significance of the trends did not change, the daily DI dropped by a range of 1-3 DME for each year of the study for both BZD and combined BZD with Z-Drugs.

DISCUSSION

This study provides updated information on utilisation of BZD and Z-Drugs in a large Canadian population. The presented data and trends provide valuable information that may be of use to prescribers, pharmacists and healthcare authorities in Manitoba to guide efforts to improve usage of BZD and Z-Drugs. This remains an important ongoing

FIG 3 Proportion of annual prescriptions in first and last year by BZD



endeavor because of the delicately complex balance between benefits and risks inherent to use of these medications, as well as the differing opinions expressed among health professionals on their place in therapy.[37–39]

Overall, the annual prevalence of combined BZD+Z-Drug use amongst adults (ranging between 9–12%) was similar to the various national estimates for prevalence of use.[40,41] However, comparison of average consumption estimates for all of Canada, taken from the 2017 technical report of the International Narcotics Control Board (INCB) for the years 2014-2016, revealed that average Manitoba consumption of BZD (not including Z-Drugs) over this 3-year period was lower than the total Canadian estimate at 32.7 and 55.3 DDD/1000 person days, respectively.[42] However, this comparison should be viewed cautiously given the relative differences and underlying assumptions between these data sources. Namely that one uses pharmacy dispensing records and the other uses international manufacture and import/export reporting records.

The higher prevalence, consumption and PE in the 65+ population and particularly females, is a finding that has been repeatedly encountered in pharmacoepidemiologic studies.[43] While this was not surprising, the vulnerability of this population to the cognitive and psychomotor impairing effects of these drugs is an ongoing concern. Furthermore, the increase in DI over the study period in this population was unexpected and, while the magnitude of absolute increase in DME/day is debatable in terms of its clinical significance, the fact that the DI increased as opposed to remaining stable or decreasing is problematic in and of itself.

The increased utilisation of Z-Drugs (almost completely zopiclone) and decline of BZD use is in accordance with past observations in Manitoba[26] and elsewhere.[44–47] However, widespread substitution of BZD use with Z-Drug use, while often considered the 'lesser of 2 evils' in terms of safety, is neither devoid of substantial risk nor clearly superior in effectiveness.[48–50] Additionally, the increase in all measures of Z-Drug usage may indicate a rise in the burden of

insomnia and related sleep disorders in the Manitoba population over the 15-year study period. Observed increases in DI or consumption of common hypnotic benzodiazepines such as temazepam and triazolam lend further support to this hypothesis. These trends may be explained, but not definitively confirmed, by factors such as pharmacologic tolerance with longer use, population aging[51] and increased widespread use of various sleep-disrupting, mobile technologies.[52] As newer, seemingly safer pharmacotherapies for insomnia, such as orexin-1 antagonists (i.e., suvorexant) and melatonin receptor agonists (i.e ramelteon), continue to become available and gain evidence-based recognition as potential alternative first-line treatments, the use of BZD and Z-Drugs may decline in the years that follow.[53] Until then, a focus on non-pharmacologic treatment modalities combined with deprescribing intervention knowledge would be expected to be useful to improve quality of life and prevent harm in at-risk users.[54]

The usage of particular BZDs merit discussion. First, the use of alprazolam is higher now than in the early 2000s (though it peaked in the period from 2011-2013) despite its reputation for overdose and misuse potential relative to other BZDs.[55,56] The slight reduction in its use after 2013 is likely not coincidental with the timing of the IMPRxOVE study in Manitoba, which aimed to reduce potentially inappropriate BZD use.[36] Nevertheless, return to the level of alprazolam utilisation predating the 2010s could be viewed as a continued goal worth pursuing.

While lorazepam has easily maintained its position as the most frequently used BZD, it was gradually supplanted by zopiclone (when the drug classes were combined) with respect to the overall annual prescription share. Clonazepam use continued to rise over the study period, albeit not in terms of DI. Similar observations of rising clonazepam use were made in 2 recent studies.[47,57] In the neighbouring Canadian province of Ontario, Davies et al. reported a gradual increase in prevalence of clonazepam use by ~70% from 1998 to 2013 in the 65+ population.[57] These authors speculate that the perception of superiority of clonazepam over other BZD amongst prescribers, resulting in its increase in use, is owed to its favorable pharmacokinetic profile (long half-life with no active metabolites) and clinical trial evidence supporting its use as a monotherapy or adjunctive treatment for certain anxiety disorders, even with long-term use.[58,59] Kurko et al., in a Finnish population register study, observed that, contrary to the other BZD, long-term use of clonazepam increased in the elderly population.[47]

By contrast, other long-acting BZD such as diazepam, chlordiazepoxide and flurazepam saw sustained decreases in their utilisation. Furthermore, this pattern of reduction in use was not limited to the long-acting agents, as any agent that was infrequently used in 2000 became even less so by 2016. If this trend continues, it appears that total BZD use will essentially be consolidated in the use of only 7 agents; zopiclone, lorazepam, clonazepam, temazepam, diazepam, alprazolam and clobazam. Indeed, these 7 agents are already representative of the various indications and pharmacokinetic properties needed to individualize therapy for patients in clinical practice, thus arguably limiting the need for other BZDs. This shift towards the simplification of BZD use in Manitoba via elimination of older BZD could be perceived as an improvement indicative of progressive practice change over time.

This study was unique insofar as it explored BZD and Z-Drug utilisation trends by DME based indicators; DI and PE. While the sensitivity analysis demonstrated the volatility of these indicators in terms of their annual point estimates, the overall trends remained stable in terms of which measures statistically increased or decreased. Importantly, the calculated values for PE (DME-DDD) were consistently and markedly higher than the WHO standard consumption method (DDD). This suggests that the traditional reliance on the latter method may underestimate meaningful population use of BZD and Z-Drugs. This distinction would be important in understanding how the magnitude of population exposure could be correlated with population harm outcomes such as overdoses or motor-vehicle accidents. While prone to ecological fallacy and confounding, in the absence of linkage of individual level data and longitudinal follow-up, this method may be of some practical use for adoption in ongoing pharmacovigilance monitoring (especially when used in tandem with prescription opioid data) if it is shown to positively correlate with important harm outcomes.

STRENGTHS AND LIMITATIONS

This study had some important strengths and limitations which should be recognized when interpreting the results. In terms of strengths, the DPIN database provides an almost complete and highly accurate account of dispensed prescriptions in the province of Manitoba. The use of multiple indicators and sub-analyses offered a nearly complete interpretation of aggregated BZD and Z-Drug use in Manitoba over the past 15 years. Lastly, a sensitivity analysis, using various DME conversion sources, ensured the validity of the utilisation trends by confirmation of their consistency and directionality, in spite of differences between sources in the determination of annual point estimates.

In terms of limitations, duration of use and individual patient characteristics beyond age and sex were not assessed and so this limits the ability to make more targeted inferences relevant to clinical practice decision-making. Furthermore, as these medications are frequently taken on an as needed ('prn') basis, it was impossible to know which dispensing observations were characterized by as needed use and which ones were dosed on a regular basis. Therefore, misclassification, especially in the determination of DI is possible. However, it would be expected that this misclassification would be non-differential over time and therefore less likely to produce false positive trends. Though, this too is under the assumption that the proportion of 'prn' to 'regular' dosed prescriptions remained stable over time. Lastly, as with any drug utilisation study relying on administrative prescription claims, dispensation data ultimately represents an overestimate of medication consumption. Given these important limitations, the rigor of this study was aimed towards the determination of trends and less the absolute precision of annual point estimates.

CONCLUSION

This study has important conclusions both provincially within Manitoba in terms of clinical practice and beyond its borders in terms of drug utilisation research. In regards to the former, utilization of BZD gradually increased until the 2011–2013 period before declining. This recent decline may be attributable to both the provincial wide audit and feedback study during this period as well as the clinical culture of recent years emphasizing deprescribing. To this point, the continued reduction in use of older, long-acting BZD, witnessed in this study, may be perceived as an improvement in prescribing practice. Though, further improvement may be sought by focusing on reducing the use of the 'problem' BZD alprazolam and ensuring the increasing reliance on clonazepam as a BZD of choice is appropriate and justified. Also concerning is the fact that Z-Drug use in the Manitoba population remains high. Although, utilization may be stabilizing given data from the most recent years. Non-pharmacologic treatment modalities or safer pharmacologic options should continue to be emphasized in the treatment of sleep disorders. In terms of drug utilisation research for BZD and Z-Drugs, DME based measurements, while somewhat unstable, may aid in the interpretation of the extent and intensity of PE in patient populations. However, DME based sources and values for particular agents (i.e clonazepam) should be further refined and validated to improve future measurement of population benzodiazepine exposure.

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COMPLIANCE WITH ETHICAL STANDARDS SECTION

Access to the data for this project was approved by the University's Health Research Ethics Board (HREB) and the Health Information Privacy Committee (HIPC) of the provincial government.

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(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.

The authors report no conflicts of interest related to this study.

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SUPPLEMENTAL APPENDIX – SENSITIVITY ANALYSIS ON DME BASED INDICATORS

Table – Conversion Sources and Values Used

Drug	Ashton[1]	Ashton (modified)	Shader & Greenblatt[3]	Alessi-Severini[2]
Alprazolam	0.5 mg	0.5 mg	1 mg	1 mg
Bromazepam	5 mg	5 mg	N/A	10 mg
Chlordiazepoxide	25 mg	25 mg	50 mg	20 mg
Clobazam	20 mg	20 mg	N/A*	20 mg
Clonazepam	0.5 mg	**1 mg**	0.5 mg	0.5 mg
Potassium Clorazepate	15 mg	15 mg	15 mg	NA*
Diazepam	10 mg	10 mg	10 mg	10 mg
Flurazepam	30 mg	30 mg	30 mg	30 mg
Lorazepam	1 mg	1 mg	2 mg	2 mg
Oxazepam	20 mg	20 mg	30 mg	20 mg
Nitrazepam	10 mg	10 mg	10 mg	10 mg
Temazepam	20 mg	20 mg	30 mg	30 mg
Triazolam	0.5 mg	0.5 mg	0.25 mg	0.25 mg
Zaleplon	20 mg	20 mg	N/A*	20 mg
Zolpidem	20 mg	20 mg	10 mg	NA*
Zopiclone	15 mg	15 mg	N/A*	7.5 mg

*In absence of available value, Ashton value was used.

[1]Ashton H. benzo.org.uk : Benzodiazepine Equivalence Table. http://www.benzo.org.uk/bzequiv.htm. Published 2007. Accessed February 3, 2017.
[2]Alessi-Severini S, Bolton JM, Enns MW. Sustained Use of benzodiazepines and escalation to high doses in a Canadian Population Psychiatr Serv 2016;67(9):1012–18. doi:10.1176/appi.ps.201500380.
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Sensitivity Analysis of DME Conversion Values on Overall Pharmacologic Exposure and Dose Intensity Trend Estimates

Source	Parameter	Z-Drug	BDZ	Combined (BDZ + Z-Drug)
Ashton (main results)[1]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	Absolute increase from 4.1 (2001) to 14.3 (2016) *Relative* increase of 6.2% *each* year (95% CI 2.7% –9.6%)	No statistically significant trend; 69.8 (2001) to 82.2 (2016) Annual rate of change; 0.1% each year (95% CI –1.3% to 1.4%)	No statistically significant trend; 73.9 (2001) to 96.5 (2016) Annual rate of change; 0.7% *each* year (95% CI –0.4%–1.8%)
	Dose Intensity (DME/Day)	Absolute increase from 5.0 (2001) to 5.43 (2016) Increase in average daily dose by 0.036 DME *each* year (95% CI 0.030–0.042)	Absolute increase from 17.1 (2001) to 20.1 (2016) Increase in average daily dose by 0.25 DME *each* year (95% CI 0.20–0.30)	No statistically significant trend; 15.1 (2001) to 14.4 (2016) Rate of annual change; –0.01 DME *each* year (95% CI –0.05 to 0.03)
Clonazepam conversion change (Modified Ashton)	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	Absolute increase from 4.1 (2001) to 14.3 (2016) *Relative* increase of 6.2% *each* year (95% CI 2.7%–9.6%)	No statistically significant trend; 60.0 (2001) to 65.4 (2016) Annual rate of change; –0.3% (95% CI –1.5%–0.9%)	No statistically significant trend; 64.1 (2001) to 79.7 (2016) Annual rate of change; 0.4% (95% CI –0.7%–1.7%)
	Dose Intensity (DME/Day)	Absolute increase from 5.0 (2001) to 5.43 (2016) Increase in average daily dose by 0.036 DME *each* year (95% CI 0.030-0.042)	Absolute increase from 14.7 (2001) to 16.0 (2016) Increase in average daily dose by 0.147 DME each year (95% CI 0.095-0.199)	No statistically significant change; 13.1 (2001) to 11.9 (2016) Annual rate of change; –0.037 (95% CI –0.077–0.002)

Alessi-Severini et al.[2]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	Absolute increase from 8.13 (2001) to 28.4 (2016) *Relative* increase of 6.4% *each* year (95% CI 3.8%–9.0%)	No statistically significant trend; 51.4 (2001) to 61.9 (2016) Annual rate of change; 0.01% (95% CI –1.3% to 1.4%)	Absolute increase from 59.5 (2001) to 90.3 (2016) *Relative* increase of 1.5% *each* year (95% CI 0.3%–2.7%)
	Dose Intensity (DME/Day)	Absolute increase from 9.9 (2001) to 10.8 (2016) Increase in average daily dose by 0.08 DME *each* year (95% CI 0.06–0.09)	Absolute increase from 12.6 (2001) to 15.2 (2016) Increase in average daily dose by 0.19 DME *each* year (95% CI 0.16–0.22)	Absolute increase from 12.4 (2001) to 13.4 (2016) Increase in average daily dose by 0.10 DME *each* year (95% CI 0.08–0.13)
Shader et al.[3]	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	Absolute increase from 8.2 (2001) to 28.6 (2016) *Relative* increase of 6.2% *each* year (95% CI 3.7%–8.6%)	No statistically significant trend; 51.1 (2001) to 62.0 (2016) Annual rate of change; 0.1% (95% CI –1.2% to 1.4%)	Absolute increase from 59.3 (2001) to 90.5 (2016) *Relative* increase of 1.5% *each* year (95% CI 0.3%–2.7%)
	Dose Intensity (DME/Day)	Absolute increase from 10.0 (2001) to 10.9 (2016) Increase in average daily dose by 0.07 DME *each* year (95% CI 0.06 –0.08)	Absolute increase from 12.5 (2001) to 15.2 (2016) Increase in average daily dose by 0.19 DME *each* year (95% CI 0.16–0.22)	Absolute increase from 12.1 (2001) to 13.5 (2016) Increase in average daily dose by 0.11 DME *each* year (95% CI 0.08–0.13)
Clonazepam conversion change (Modified Ashton)	*Pharmacologic Exposure (DME-DDD/1000 Persons/Day)*	Absolute increase from 4.1 (2001) to 14.3 (2016) *Relative* increase of 6.2% *each* year (95% CI 2.7%–9.6%)	No statistically significant trend; 60.0 (2001) to 65.4 (2016) Annual rate of change; –0.3% (95% CI –1.5%–0.9%)	No statistically significant trend; 64.1 (2001) to 79.7 (2016) Annual rate of change; 0.4% (95% CI –0.7% – 1.7%)
	Dose Intensity (DME/Day)	Absolute increase from 5.0 (2001) to 5.43 (2016) Increase in average daily dose by 0.036 DME *each* year (95% CI 0.030–0.042)	Absolute increase from 14.7 (2001) to 16.0 (2016) Increase in average daily dose by 0.147 DME each year (95% CI 0.095–0.199)	No statistically significant change; 13.1 (2001) to 11.9 (2016) Annual rate of change; –0.037 (95% CI –0.077–0.002)