Utilization of benzodiazepines and related drugs: a Canadian population-based study, 1997 - 2012

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Abstract

Background: Despite their favourable toxicology profile, benzodiazepines (BZDs) and Z-drugs, (i.e., zopiclone, zaleplon) have been associated with tolerance, dependence, and addiction. Evidence of harm has been widely reported particularly in elderly populations. This study reports incidence and prevalence of BZD and Z-drug use in the entire population of Manitoba over a 16-year period.

Methods: Prescriptions data were obtained from the Drug Product Information Network (DPIN) database (April 1,1996 - March 31, 2012). Sociodemographic information on patients receiving BZDs or Z-drugs was obtained from the Population Registry of Manitoba. Generalized Estimating Equations (GEE) were used to determine change of rates over time and the influence of users' sociodemographic characteristics.

Results: Overall BZD prevalence decreased from 174.7 in 1996/97 to 120.6 per 1,000 in 2011/12; however, the prevalence of Z-drug use increased steadily from 25.2 in 1996/97 to 93.9 per 1,000 in 2011/12. In the elderly, incidence rate of BZD use decreased from 55.5 in 1996/97 to 30.3 users per 1,000 in 2011/2012, while the incidence of Z-drugs increased from 7.3 to 20.3 users per 1,000. The 18 – 64 population showed a decrease in BZD incident use but the increase in Z-drug use was higher than 2-fold. The youngest population showed the lowest rates. Prevalent and incident use of BZDs and Z-drugs were higher in women of older age. Higher use of BZDs was observed in the low-income population.

Conclusion: BZDs are prescribed less frequently to elderly patients in Manitoba; however, zopiclone prescribing has continued to rise for all age groups.

Introduction

Benzodiazepines (BZDs) are one of the oldest classes of medications and they have been used for decades as effective agents in a variety of diagnoses including anxiety disorders, insomnia and seizures. While their toxicology profile is indubitably favourable when compared to other hypnotic/sedatives (i.e., barbiturates), their long-term use has been associated with tolerance, dependence, and addiction [1 - 3]. Evidence of harm, particularly in older people, has been widely reported and includes higher risk for falls and fractures [4-5], motor vehicle collisions [7], as well as cognitive disturbances [8]. The newer non-benzodiazepine agents, zopiclone, zolpidem and zaleplon, commonly called Z-drugs, have a defined indication for sleep disorders and appear to have a lower potential for dependence [9], nevertheless their use can also be problematic for their effects on human performance and driving [10, 11]. As a consequence, clinical practice guidelines have advised against long-term use of these medications and health agencies worldwide have undertaken anti-BZDs and Z-drugs campaigns, not without controversy [12 - 18]. However, the dearth of literature in this area suggests that such recommendations do not seem to have impacted significantly on the utilization of BZDs and Z-drugs in various countries including Canada [19 – 22]. The findings from other countries may not be generalizable to Canada. The only population-based study conducted in Canada used data from the province of BC and examined a period of 10 years between 1996 and 2006 [20]. Since there are long delays between scientific knowledge and clinical practice, it is possible that there may have been changes in prescribing patterns over the recent seven years. This study describes the prescribing of BZDs and Z-drugs to the entire population of a Canadian province over a period of 16 years and investigates characteristics of users and prescribers.

Methods

Study population

All Manitoba residents registered with the provincial health care system who were prescribed a BZD or a Z-drug over the study period were included. No age restrictions were applied but stratifications by age (0-17; 18-64; ≥65 years) and sex were applied. Region of residence (urban vs. rural) and socioeconomic status (SES) were also assessed. According to validated definitions [23], incident (new) users were defined as individuals who had not received a prescription for any of the medications of interest in the year prior to receiving their first prescription, while prevalent users were defined as individuals who had received at least one prescription for a medication of interest in each index year.

Ethical Approval

Ethical consent was obtained from the Health Research Ethics Board of the Faculty of Medicine, University of Manitoba (#H2009-024). The study was conducted in full compliance with the Personal Health Information Act of Manitoba and privacy/confidentiality consent was obtained from the Health Information Privacy Committee of the Government of Manitoba (#2008/2009-48).

Data Source

Administrative data regarding use of BZDs and related medications (Z-drugs) between April 1,1996 and March 31, 2012 were obtained by accessing the Manitoba Population Health Research Data Repository, housed at the Manitoba Centre for Health Policy. The Repository contains health data for all residents of the province and holds records for virtually all contacts with the Manitoba Health Services Insurance Plan (including physicians, hospitals, personal care homes, home care, and pharmaceutical prescriptions) of all registered individuals. Patient records within the Repository are de-identified using an encrypted personal health information number as a quasi-identifier to protect privacy. Databases accessed for this study included the Population Registry that contains demographic information of all residents of Manitoba and the

Drug Product Information Network (DPIN) that contains prescription data. DPIN captures prescriptions dispensed in Manitoba regardless of the type of coverage (government-sponsored, private or out-of-pocket), therefore providing a comprehensive description of outpatient drug use. Medications administered in hospital and physician samples are not captured. Prescriptions dispensed to First Nation patients served by northern nursing stations may by underestimated because of incomplete data entry in the DPIN system in early years. However, it has been determined that the database is over 90% accurate in capturing prescriptions dispensed in the community [24].

Measures

All BZDs available on the Canadian market at the time of study were included. All DINs (Drug Identification Numbers) were retrieved from Health Canada drug product database using the respective codes of the ATC (Anatomical Therapeutical Chemical) classification system as follows: alprazolam (N05BA12), bromazepam (N05BA08), chlordiazepoxide (N05BA02), clobazam (N05BA09), clonazepam (N03AE01), diazepam (N05BA01), flurazepam (N05BA17), lorazepam (N05BA06), oxazepam (N05BA04), temazepam (N05CD07), triazolam (N05CD05). Zopiclone (N05CF01) and zaleplon (N05CF03) utilization was analysed separately. Zolpidem has never been approved for sale in Canada.

Stratification by age was conducted and three age groups were identified: 0-17; 18-64; ≥65 years. Users' region of residence (rural vs. urban) was determined by postal codes registered with Manitoba Health. SES was determined on the basis of the median neighbourhood income quintiles from Statistics Canada based on the dissemination area in which they resided: low income included the lowest and second lowest quintiles, high income included the three highest quintiles. Individuals for whom a neighbourhood income could not be assigned (i.e., residents of personal care homes, psychiatric facilities, prisons or wards of the Public Trustee and Child and

Family services) were grouped into a “not found” category (NF). Prescriber specialties were derived from the “scrambled” physician identification number reported on the prescription and classified as general practitioner (GP), psychiatrist or “other” medical specialty.

Analyses

Separate analyses were conducted to evaluate prevalent and incident utilization of BZDs and Z-drugs. Generalized Estimating Equations (GEE), which addressed the correlated structure of the data, were used to analyse the incident and prevalent utilization over time as number of users per 1,000, and to determine the influence of sociodemographic characteristics (i.e., age, sex, region of residence and SES) on prescribing over the entire study period as described above. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Incidence

Overall incidence rates of utilization are presented in Figure 1. BZD use decreased from 26.3 new users per 1,000 in 1996/97 to 22.5 per 1,000 persons in 2011/12 fiscal year, while utilization of Z-drugs increased from 3.9 to 9.9 per 1,000 during the same time period. Incidence rate of BZD use decreased significantly in the older adults (≥65 years of age) from 55.5 per 1,000 in 1996/97 to 30.3 per 1,000 in 2011/2012, but use of Z-drugs consistently increased in this population from 7.3 per 1,000 to 20.3 per 1,000 over the same time period (Figure 2). There were a total 37,691 new elderly users of zopiclone (or zaleplon) between 1996/97 and 2011/2012.

The adult population between 18 and 64 years of age showed a slight decrease in BZD incident

use from 30.1 per 1,000 to 27.6, but the increase in Z-drug use was higher than 2-fold from 4.7 per 1,000 in 1996/97 to 11.1 per 1,000 in 2011/12 (Figure 2). Total new users of zopiclone/zaleplon in the 18-64 years of age group between 1996/97 and 2011/12 were 99,361.

The youngest segment of the population (up to 17 years of age) showed the lowest overall rates of incident use of BZDs and Z-drugs with only 1,589 new users of Z-drugs over the time period of the study; however, in this population both classes of drugs showed a significant increase in utilization from 2.20 per 1,000 in 1996/97 to 3.95 per 1,000 in 2011/12 for BZDs and from 0.19 per 1,000 to 0.39 per 1,000 for Z-drugs over the same time period (Figure 2).

Prevalence

Overall prevalence of BZD use in the entire population increased slightly from 66.7 users per 1,000 in 1996/97 to 72.4 users per 1,000 in 2011/12, but prevalence of Z-drug use increased significantly from 10.9 per 1,000 in 1996/97 to 37.0 per 1,000 in 2011/12 (Figure 3). Stratification by age group (Figure 4) showed that since 2005/06 the elderly population had the highest prevalence of use for both BZDs and Z-drugs. BZD prevalence decreased from 174.7 per 1,000 in 1996/97 to 120.6 in 2011/12; however, the prevalence of Z-drug use increased steadily from 25.2 per 1,000 in 1996/97 to 93.9 per 1,000 in 2011/12. In the two other age groups prevalence of BZD use increased from 62.1 to 67.9 per 1,000 and from 2.7 to 5.6 per 1,000 in the 18 - 64 age group and in the 0-17 group, respectively. For the Z-drugs, prevalence increased from 12.2 to 37.8 per 1,000 and from 0.29 to 0.62 per 1,000 in the 18 - 64 age group and in the 0-17 group, respectively (Figure 4).

Denominators for the three age groups ranged from 296,658 in 1996/97 to 291,782 in 2011/12 for the 0-17 years of age, from 692,539 to 793,093 for the 18-64 years of age, and from 154,890 to 176,498 for the 65 years of age and older.

Effects of age, sex, place of residence and SES

Stratification by sex was also conducted. Incidence rates in females were higher than in males across the 16-year observation period for both BZD and Z-drug use. BZD use decreased slightly in females from 33.2 to 28.3 per 1,000, compared to a decrease from 19.2 to 17.3 per 1,000 in males. Incidence rates for Z-drug use increased in females from 4.6 to 11.8 per 1,000, while in males the increase was from 3.2 to 8.0 per 1,000. Prevalence of BZD use in males was 42.7 per 1,000 in 1996/97 and 44.4 per 1,000 in 2011/12. In females prevalence was 80.1 per 1,000 in 1996/97 and 77.0 in 2011/12. Prevalence of Z-drug use increased from 13.4 to 47.4 per 1,000 in females and from 8.3 to 26.4 per 1,000 in males. Please refer to Table 1 and Table 2 for details.

Prescribers

In 2011/12, more than 1 million prescriptions for BZDs and Z-drugs were dispensed in Manitoba. In 1996/97 a total of 379,259 prescriptions were for BZDs alone and 44,020 were for Z-drugs. In 2011/12, the number of prescriptions for BZDs and Z-drugs had increased to 726,409 and 277,811, respectively. Lorazepam was the most prescribed BZD accounting for more than 1/3 of all BZD prescriptions across the timeframe of the study. Each year general practitioners wrote more than 80% of all prescriptions and psychiatrists wrote approximately 15 % of all prescriptions, the rest was written by physicians of other medical specialties.

Interpretation

Substantial prescription pattern changes were observed over time in the population of Manitoba. Fewer patients were initiated on a BZD during the study period; however, the prevalence of use was not significantly affected and it remained relatively stable in the adult population between 18

and 64 years of age, which suggests that patients are probably staying on the medications longer than recommended.

Our analyses discriminated between BZDs and zopiclone/zaleplon, which are not chemically related to BZDs but share similar pharmacological activity on the $GABA_A$ receptor. These agents have been marketed as hypnotic medications superior to BZDs mainly because of their favourable pharmacokinetic and safety profiles despite a lack of evidence for substantial clinical improvement [25].

Our findings are similar to those observed in other studies conducted internationally where the utilization of BZDs and Z-drugs was assessed separately [26-29] and confirm that Z-drugs have largely replaced BZDs especially in the elderly population. In Canada, prescribing of BZDs and Z-drugs in the population of British Columbia was described by a report covering a 10-year span from 1996 to 2006 [20]. The results showed a slight decrease in the overall utilization of both BZDs and Z-drugs in the elderly population, but an overall increase in the younger segments of the population, particularly in females and in individuals of low income.

Sex differences have been observed in our study: both prevalent and incident use of BZDs and Z-drugs were consistently higher in women especially of older age. While this finding is not unique to the Canadian context, studies in other countries where insurance coverage of short-acting BZDs and Z-drugs is restricted have reported that male patients were more likely to receive BZDs compared to females [28]. Place of residence did not seem to have a significant effect on incidence rates, while low SES show opposite effects for BZD and Z-drug use, with more pronounced use of BZDs in the low income segment of the population. We speculate that the higher rates of mental disorders in women and lower socioeconomic status groups may explain the higher rates of benzodiazepines [30].

Limitations of our study are seen in the administrative nature of the data used for the analyses, which do not provide information on the clinical benefits of medication use. Our study did not capture medications used in hospitals, or in a limited number of personal care homes (nursing homes) of the province; however, the DPIN database is comprehensive of outpatient use of pharmaceuticals regardless of insurance coverage. Moreover, psychotropic medications such as BZDs and Z-drugs have been historically covered by the government-sponsored drug programs as unrestricted benefits. As a result no segment of the province population could have experienced any limitation in terms of access to their prescriptions.

The DPIN database does not include information on diagnoses, therefore reasons for prescribing cannot be determined; however, Z-drugs are indicated specifically for the treatment of insomnia and are still perceived by general practitioners as more effective and safer than BZDs for this indication [31]. Therefore, it could be inferred that insomnia might be the most prevalent diagnosis affected by a switch in new prescriptions from a BZD to a Z-drug. It is important to note that zaleplon was discontinued in 2007 and the number of users has been generally quite low over the timeframe of the study. Zopiclone is in fact the only agent that demonstrated a rapid increase in utilization rate in the last few years. Finally, it is recognized that prescription databases are only records of dispensations. Data collected are only “proxy” of use as it is unknown if prescriptions filled are actually consumed.

Our study was not designed to assess the impact of specific warnings or interventions aimed at improving prescribing habits; however, it appears that physicians in Manitoba have been concerned about the potential harm of prescribing BZDs to their elderly patients, as it has been the case for other psychotropic medications [32], and have responded by initiating fewer and fewer older individuals on a BZD over the study period. The rise in zopiclone prescribing, however, remains a reason for concern.

Conclusion

While BZDs are prescribed less frequently to elderly patients in Manitoba, zopiclone prescribing has continued to rise in all age groups. It remains to be investigated if the decline of BZD use in the elderly is limited to the diagnosis of insomnia or whether other medications have replaced BZD therapy in conditions such as anxiety. Patients of all ages seem to stay on a BZD or zopiclone for extended periods of time and might experience difficulties in discontinuing treatment. It will be important to explore interventions [33] that can be successful in helping patients discontinue BZD and Z-drug use when no longer necessary.

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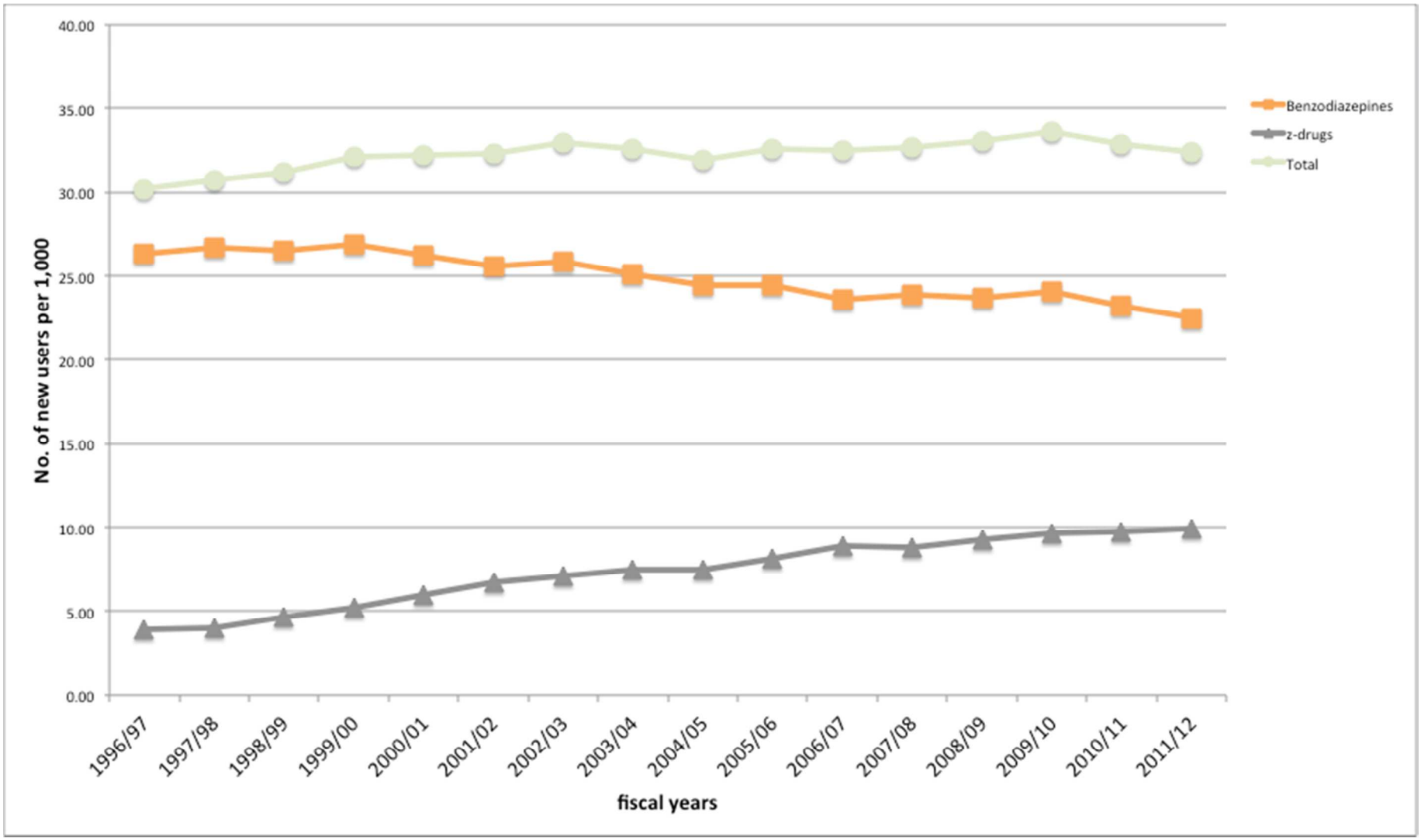

Figure 1- Crude incidence rates of use of benzodiazepines and Z-drugs

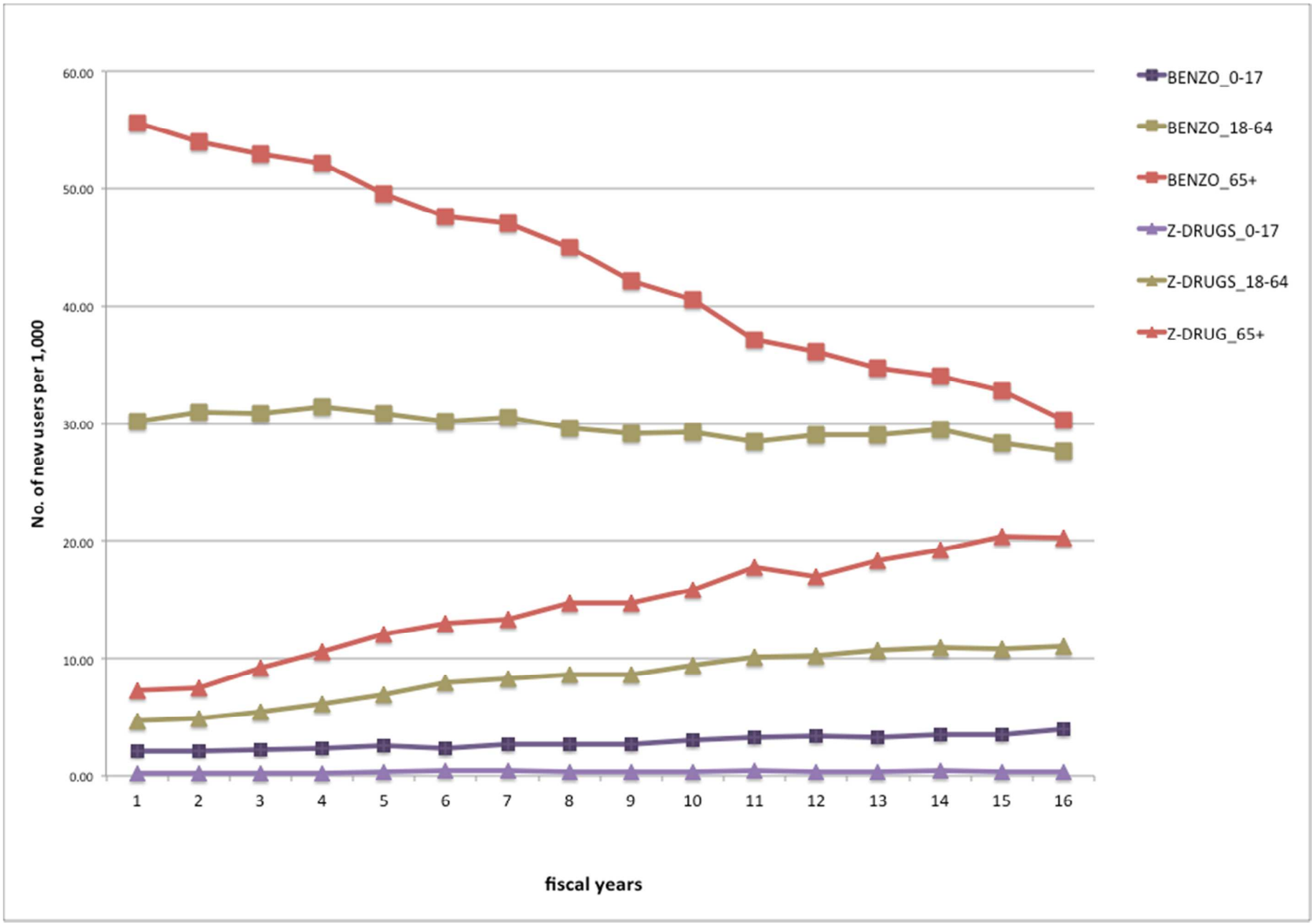

Figure 2- Crude incidence rates of use of benzodiazepines and Z-drugs by age group

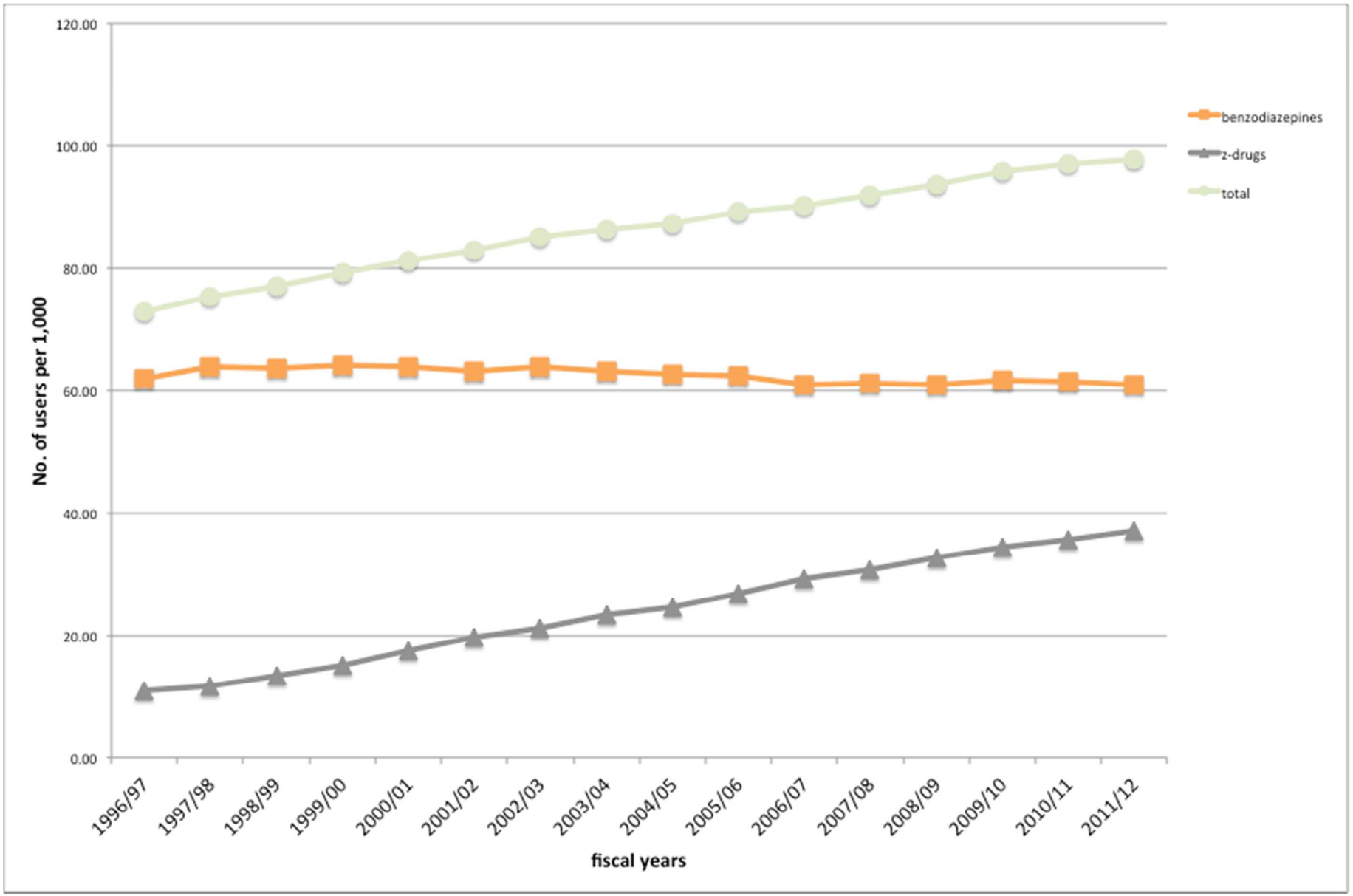

Figure 3 - Prevalence of use of benzodiazepines and Z-drugs

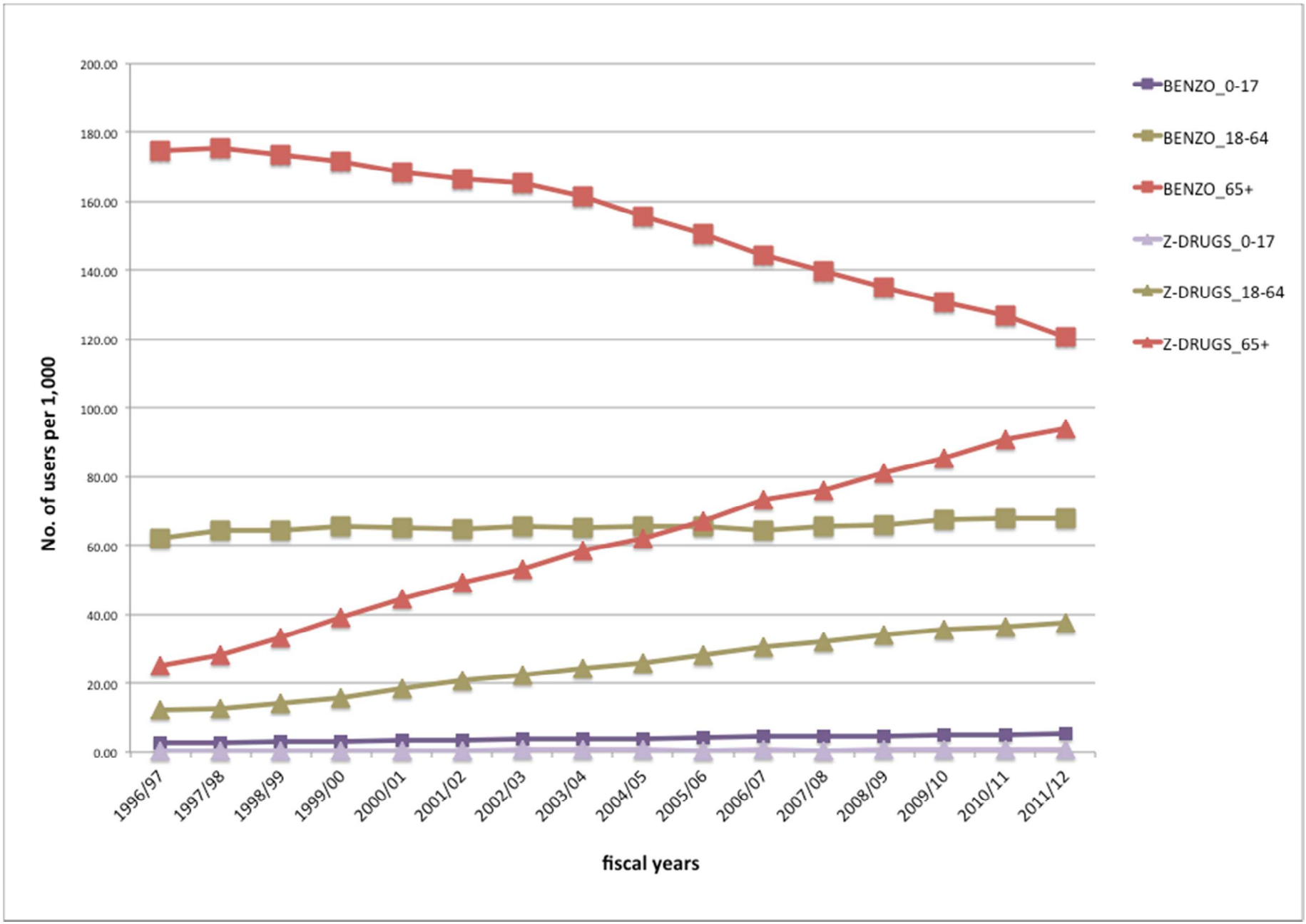

Figure 4- Prevalence of use of benzodiazepines and Z-drugs by age groups

Table 1 - Incidence: effects of age, sex, region of residence and socioeconomic status

Medications		BZDs+z-drugs overall	BZDs alone	Z-drugs alone
Users/1,000 year 1996/97		30.2	26.3	3.9
Users/1,000 year 2011/12		32.4	22.5	9.9
Change in rate per year		1.00 NS	0.99*	1.06*
Age effect	18-64 vs. 65+	0.65*	0.70*	0.56*
	0 -17 vs.65+	0.06*	0.07*	0.02*
Sex effect	male vs. female	0.70*	0.69*	0.72*
Region effect	rural vs. urban	1.07 NS	0.91 NS	0.93 NS
SES effect	high vs. low	0.97 NS	0.93 NS	1.10*
	NF vs. low	1.21*	1.32*	0.85 NS

* indicates a statistically significant effect ($p<0.05$)

Note: results for change in yearly rate, age, sex, SES and region of residence effects are presented as relative rates (adjusted for age, SES, region and sex).

BZDs= Benzodiazepines, Z-drugs=zopiclone, zaleplon, NS = not significant, SES = socioeconomic status, NF = income unknown (includes individuals to whom a neighbourhood income cannot be assigned: residents of personal care homes, psychiatric facilities, prisons or wards of the Public Trustee and Child and Family services)

Table 2 – Prevalence: effects of age, sex, region of residence and SES

Medications		BZDs+Z-drugs overall	BZDs alone	Z-drugs alone
Users/1,000 year 1996/97		72.8	66.7	10.9
Users/1,000 year 2011/12		97.9	72.4	37.0
Change in rate per year		1.02*	1.01 NS	1.08*
Age effect	18-64 vs. 65+	0.50*	0.52*	0.44*
	0 -17 vs. 65+	0.03*	0.03*	0.01*
Sex effect	male vs. female	0.66*	0.65*	0.64*
Region effect	rural vs. urban	0.88*	0.85*	1.04 NS
SES effect	high vs. low	0.91 NS	0.88*	1.02*
	NF vs. low	1.53*	1.56*	1.25*

* indicates a statistically significant effect ($p<0.05$)

Note: results for change in yearly rate, age, sex, SES and region of residence effects are presented as relative rates (adjusted for age, SES, region and sex).

BZDs= Benzodiazepines, Z-drugs=zopiclone, zaleplon, NS = not significant, SES = socioeconomic status, NF = income unknown (includes individuals to whom a neighbourhood income cannot be assigned: residents of personal care homes, psychiatric facilities, prisons or wards of the Public Trustee and Child and Family services)