Patterns of benzodiazepine use in a Canadian population sample

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SUMMARY. **Aim** – The objective of this study was to identify clinical and demographic factors that may be associated with benzodiazepine treatment, to describe the reported reasons for use of these medications and to appraise the pattern of use in relation to standard guidelines in a general population sample. **Methods** – Telephone survey methods were employed to select a sample of 3345 people between the ages of 18 and 64. A computer assisted telephone interview, including the Mini Neuropsychiatric Diagnostic Interview (MINI), was administered. Estimates were weighted for design features and population demographics. **Results** – The overall prevalence of benzodiazepines use was 3.3% (95% confidence interval [CI] 2.6 to 4.1%). There was a higher frequency of medication use in women than men, among respondents who were widowed, separated or divorced, and those with lower levels of education. In relation to MINI diagnosis, diagnoses of Panic Disorder and Major Depression increased the probability of taking benzodiazepines. The reported main reason for use was "Sleep disorders" (68.9%), "Anxiety" (35.8%), "Depression" (27.8%) and "Pain management" (21.2%). More than 80% of subjects were taking benzodiazepines for more than one year. **Conclusions** – When compared to previous estimates, the lower frequency of benzodiazepines use suggests that there has been improvement in their evidence-based use at a population level. However our results once more confirm the difficulty stopping the use of these medications once they have been started. Further randomized control studies may help clinicians in having a better practical approach to rational benzodiazepine use.

Declaration of Interest: None.

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Mental illnesses, such as Major Depression as well as Anxiety Disorders, are often treated with combinations of different kinds of medications. BDZ, for example, since their introduction in the 1960s, became one of the most prescribed drugs used to reduce symptoms like anxiety, agitation and sleeplessness in the whole world (Brunette *et al*., 2003; Clark *et al*., 2004). At first, they were widely prescribed because of their safety, efficacy and tolerability (Haw & Stubbs, 2007) but later they have been associated with several negative health consequences, including increased risk of falls, hip fractures (Ray *et al*., 1989; Wagner *et al*., 2004), motor vehicle accidents (Hemmelgarn *et al*., 1997), self care limitations (Hogan *et al*., 2003), daytime sleepiness, blunted reflex and cognitive decline. BDZ can contribute to overdose fatalities (Kassam & Patten, 2006; Vicens *et al*., 2006) and can lead to abuse and dependence (O'Connor *et al*., 1999; Koski *et al*., 2002). Previous studies have also shown how self reported depression and somatization are strongly associated with benzodiazepine craving (Gray *et al*., 2002; Mol *et al*., 2005). "Strong desire or compulsion" is one of the diagnostic criteria for dependence as defined in the International Classification of Diseases, 10th Revision (World Health Organization, 2002). Their possible side effects together with the reports of psychological and physiologic dependence and abuse have made their use increasingly scrutinized by clinicians and regulatory authorities. In the UK, the Commission on Human Medicines published firm guidance limiting BDZ use to 2 to 4 weeks only for the treatment of severe and disabling anxiety or insomnia. Similar restrictions have been introduced in the USA and in Australia (American Psychiatric Association Task force

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on Benzodiazepine Dependency (1990); Royal Australian College of General Practitioners (2000), 2008; Department of Health and Children (2002), 2008; American Psychiatric Association Task force on Benzodiazepine Dependency (1990)) while, in countries like Sweden or China BDZ have been classified as dangerous drugs or narcotics (Haw & Stubbs, 2007). Despite these limitations BDZ remain among the most used and prescribed medications in general practice to treat anxiety and sleep disorders (Petitjean *et al*., 2007). Previous studies reported a positive association between BDZ use and increasing age, female sex, low social economic status and unmarried status (Lagnaoui *et al*., 2004; Magrini *et al*., 1996; Rawson & D'Arcy, 1991). A previous study reported that the association of BDZ use with these variables persisted after adjustment for mood and/or anxiety disorder status (Kassam & Patten, 2006) so that the associations could not be accounted for by confounding with these disorders.

The objective of this study was to identify clinical and demographic factors that may be associated with benzodiazepines treatment, to describe the reported reasons for use of these medications and to appraise the adequacy of treatment in a general population sample.

METHODS

Sample selection

In order to obtain a representative sample from the Alberta population, the sample for the study was collected by telephone survey methods (Esposito *et al*., 2007). Edmonton and Calgary are the two main cities where almost the 2/3 of the Alberta population resides. The sampling procedure was therefore stratified so that approximately 1/3 of the sample would come from each of these cities, with the remaining 1/3 of the sample coming from more rural areas. The survey targeted a population of household residents who have access to a telephone and who were between 18 and 64 years old when they were interviewed.

Data collection

Data collection was carried out between the end of 2005 and March 2006 by the Population Survey Unit of the Quality Improvement and Health Information (QIHI) portfolio within the Calgary Health Region (www.calgaryhealthregion.ca). This unit maintains a constantly updated listing of provincial residential telephone numbers. A random sample of these numbers was selected and their last digit was randomly substituted to broaden coverage in order to avoid bias that might be introduced if households with unlisted numbers were to differ from those with listed numbers.

To select a single subject from the household reached, a pseudo-random procedure, the "last birthday method" was used. Rather than collecting data from the household resident who happened to answer the phone, the household resident who had most recently had a birthday was interviewed. In an effort to complete the data collection nine call-backs were made to telephones that were not answered and these calls were distributed over working hours, evening and weekends.

Measures

The Mini Neuropsychiatric Interview (MINI), a brief structured diagnostic interview (Lecubier *et al*.,1997; Sheehan *et al*., 1997), developed jointly at the University of South Florida and the National Institute for Mental Health in Paris in the 1990s and constantly evolved since then, was used as a diagnostic indicator for Major Depression and a set of common anxiety disorders. This instrument was developed as a case-finding tool for primary care, so that the development process emphasized sensitivity over specificity. Since it has been shown that the instrument tends to overestimate population prevalence and that differences between the performances of survey instruments often relate to the role of "clinical significance" probes in the scoring algorithms (Narrow *et al*., 2002), we incorporated an interference item into the interview. We asked subjects whether their psychiatric symptoms interfered or not with their life and episodes were considered clinically significant if subjects reported "a lot" of interference.

The MINI produces period prevalence estimates covering variable periods of time; past 14 day prevalence for Major Depressive Episodes; past 2 years for Dysthymia; past 1 month for Agoraphobia and Social Phobia and 6-month s for Generalized Anxiety disorder and lifetime prevalence for Panic Disorder.

The interview also included a pharmacoepidemiology module that operated with a cyclical interview structure, initially asking about medications taken for the treatment of broadly defined relevant symptoms ("Do you currently take any prescription medications for anxiety, depression, stress, energy levels, sleeping, pain management, fibromyalgia or migraine headaches?"), and then looping through each disclosed medication with a series of items inquiring about the number and size of tablets, reasons for use of the medication and duration of use. Dosage, recorded in milligrams per day, was determined by combining

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information about the size(s) and number of relevant tablets or capsules taken, including pro re nata (prn) schedules. This report focuses on the use of BDZ and related non-benzodiazepine hypnotics (zaleplon, zopiclone, zolpidem). Even though these drugs are chemically distinct from benzodiazepines, the clinical issues and concerns arising from their use are similar so that for ease of language, the use of these medications is subsequently referred to as BDZ use.

Finally, items evaluating demographic variables and health care utilization were included. Subjects with a mood or anxiety disorder according to the MINI were identified, and the proportion of these taking BDZ drugs was stratified by age, sex, marital status, education level and disability level. A logistic regression model was used to integrate the various frequencies into the simplest possible description of the BDZ use frequencies.

Interviewers working on the project were experienced telephone interviewers, and data collection was preceded by a series of training sessions incorporating both didactic instruction and practice.

Data analysis

The analysis consisted of the estimation of weighted proportions. Sampling weights were calculated to account for design effects (number of "voice" phone lines to the household, number of eligible household residents, differential probability of selection depending on residence in one of the three sampling regions). A post-stratification adjustment was made to the weights in order to standardize estimates to the age and sex distribution of the Alberta population. A logistic regression analysis was carried out to investigate factors associated with BDZ treatment. The following independent variables were inserted into the model: gender (male=0, female=1), age (<45 years old=0, >45 years old=1), marital status (married=0; unmarried=1), education (not post secondary school degree=0, degree=1), antidepressant use (no=0, yes=1), diagnosis (no disorder=0, Major depression disorder current, Dysthymia, Panic disorder lifetime, agoraphobia, Social Phobia, Generalized anxiety disorder=1). All the analyses were made using STATA version 9.

RESULTS

Sample characteristics

IIn total, 18113 telephone numbers were called. The majority of these reached non-working or unanswered phones, businesses or fax machines. Of 4054 that reached households from which eligible subjects could be selected, there were 635 individual refusals (15.7%). 3419 subjects consented to participate in the interview and finally 3394 interviews were completed. After checks for data completeness and accuracy, 45 records were removed from the data set because of concerns about data quality. The final analysis included data collected from the remaining 3345 subjects.

The unweighted sample included 1345 (40.2%) men and 2000 (59.8%) women. Weighted proportions of men and women were 50.2% and 49.8%, respectively. The unweighted mean age was 42.3 years (weighted mean age 39.6 years). In the remainder of this report, estimates are weighted unless specified otherwise. With respect to marital status, 66.4% of subjects were married or living in common-law, 13.4% were divorced, widowed or separated and 20.2% were single. Most (56.5%) of the subjects had some education beyond grade twelve (i.e. beyond high school graduation), 22.0% reported that their highest level of education was grade twelve, 13.7% had attended some high school, but did not graduate and 7.8% reported that all of their education was below the high school level.

Benzodiazepine treatment

The overall prevalence of BDZ use was 3.3% (95% CI 2.6 to 4.1%). Zoplicone, which strictly speaking, is not a BDZ but, which has similar effects, was the drug with the highest proportion of use 39.7% (95% CI 28.6 to 50.9%), followed by lorazepam 33.8% (95% CI 22.7 to 45.0%), clonazepam 14.4% (95% CI 4.6 to 24.1%), temazepam 8.8% (95% CI 0.5 to 17.0%), triazolam 3.2% (95% CI 0 to 7.6%) and others (bromazepam, oxazepam and diazepam) 15.1% (95% CI 5.4 to 24.8%).

As shown in Table I there was a higher frequency of medication use in women than men, among widowed, separated or divorced, and the less educated respondents. BDZ use increased with age; it almost tripled from the 18-25 year age group to the 45-65 year group.

In relation to MINI diagnosis, Panic Disorder was the diagnosis associated with the highest frequency of benzodiazepine use. 28.2% (95% CI 13.3 to 64.3%) of subjects with current Panic Disorder reported taking at least one benzodiazepine. Other MINI diagnoses were associated with a lower probability of benzodiazepine use. Finally, there were seventy-two (2.7%) (95% CI 1.3 to 2.4%) subjects who didn't have any MINI diagnoses but who were using BDZ at the moment of the interview.

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Table I – *Prevalence of benzodiazepine use by sociodemographic variables and diagnosis.*

		N 3345	Percent % unweighted	Percent % weighted	95% Confidence Interval
Sex					
	Male	34/1345	2.5	1.6	0.9-2.4
	Female	117/2000	5.8	5.0	3.7-6.4
Marital status					
	Never married	23/674	3.4	2.9	1.1-4.7
	Married or living common-law	84/2219	3.8	3.1	2.2-4.0
	Widowed separated divorced	44/448	9.8	6.7	4.0-9.4
Education					
	Less than secondary school graduation	18/259	6.9	4.5	1.6-7.5
	Secondary school graduation, No post-secondary education	37/735	5.0	4.1	2.0-6.2
	Some post-secondary education	22/459	4.8	3.9	1.6-6.2
	Post secondary degree/diploma	73/1885	3.9	2.7	1.9-3.6
Age					
	18-25 years	4/373	1.1	1.4	0.4-3.1
	26-44 years	42/1447	2.9	2.3	1.3-3.4
	45-65 years	105/1525	6.9	5.4	4.0-6.8
Benzodiazepine's use / disorder					
	Major Depressive Episode, current	36/157	22.9	22.2	12.1-32.4
	Dysthymia	1/20	5.0	1.0	1.0-2.1
	Panic Disorder, Current	11/39	28.2	38.8	13.3-64.3
	Agoraphobia	31/175	17.7	17.1	8.0-26.1
	Social Phobia	13/77	16.9	18.0	2.1-3.4
	Generalized Anxiety Disorder	30/145	20.7	16.2	6.8-25.6
	No Diagnosis	72/2694	2.7	1.8	1.3-2.4

Things change if we look at the prevalence of disorders among people who were using benzodiazepines. 23.8% (95% CI 12.1 to 32.4%) of subjects who were taking at least one of these drugs had a diagnosis of Major Depression at the moment of the study. A prevalence around 20% was found for anxiety disorders and a prevalence of 7.3% (95% CI 3.7 to 26.4%) was associated with the diagnosis of Panic Disorder.

A logistic regression analysis adjusting for diagnosis, demographic characteristics and antidepressant use, confirmed that having Panic Disorder or a Major Depression diagnosis increased the probability of taking a benzodiazepine drug, OR=2.4 (95% CI 1.2 to 5.5); OR=2.0 (95% CI 1.0 to 4.1) respectively. Demographic characteristics that show an association with benzodiazepine use are gender and age; female gender and age older than 44 years. Each of these factors is associated with a higher frequency of BDZ use. Moreover the regression shows that the factor that is most strongly associated with BDZ use is contemporary antidepressant use, OR=3.6 (95% CI 2.4 to 5.4). (Table II)

Table III reports the main reasons provided by people when asked to report why they were taking at least one BDZ medication. The main reasons reported were "Sleep disorders" (68.9%), "Anxiety" (35.8%), "Depression" (27.8%) and "Pain management" (21.2%). These percentages add up to more than 100% since respondents could select more than one reason for use.

Information about the consistency of the pattern of use with clinical guidelines should ideally have been estimated by considering both dosage and duration of treatment. The adequacy of dosage was evaluated by comparing what reported by each respondent to the corrispective DDD for each drug (Nosè & Barbui, 2008).

Unluckily since most of the population on BDZ medication were not able to provide exact information about the number or the size of tablets or capsules taken, it was not possible to calculate the dosage they were taking. However, just considering the reported duration of treatment, we were able to collect information from 143 subjects. Unexpectedly, in relation to what was already mentioned regarding guidelines and restrictions for BDZ use, 118 (82.5%) (95% CI 75.3 to 88.3) respondents reported that they were taking BDZ since more than one year, 18 (12.6%) (95% CI 7.6 to 19.2) since a period of time longer than eight weeks but shorter than one year and only 7 (4.9%) (95% CI 2.0 to 9.8) since less than eight weeks.

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Table II – *Logistic regression analysis. Effect of disorder, antidepressant use and demographic characteristics on benzodiazepine use.*

	OR	95% CI	P value
Female	1.7	1.1-2.5	0.012
≥ 45 years	2.8	1.9-4.1	<0.001
Completed degree	0.8	0.6-1.2	0.351
Unmarried status	0.9	0.6-1.5	0.789
Antidepressant use	3.6	2.4-5.4	<0.001
No disorder*	1		
Major Depression	2.0	1.0-4.1	0.063
Dysthymia	0.6	0.1-5.5	0.699
Panic Disorder Lifetime	2.4	1.2-5.1	0.017
Agoraphobia	1.3	0.7-2.2	0.373
Social Phobia	0.7	0.3-1.5	0.408
Generalized Anxiety Disorder	1.9	1.1-3.2	0.026

*Reference group

Table III – *Reported reasons for taking benzodiazepine medications.*

REASON REPORTED	N	%
Depression	42	27.8
Anxiety	54	35.7
Stress	5	3.3
Sleep	104	68.9
Energy Levels	3	2.0
Migraine	10	6.6
Pain Management	32	21.2
Fibromyalgia	5	3.3
Other	0	0

DISCUSSION

The present pharmacoepidemiological survey described the prevalence and correlates of BDZ use in a large Canadian population sample. The prevalence of BDZ use of 3.3% reveals a lower consumption in comparison with other countries. For example, higher consumption rates of anxiolytic drugs, especially benzodiazepines, have been reported in France (7.5%) (Lagnaoui et al., 2004) and Italy (8.6%) (Magrini *et al*., 1996). Our estimates were instead consistent with those reported by previous Canadian studies (Neutel *et al*., 2003; Neutel, 2005; Kassam & Patten, 2006) as well as with those from other Western countries where clinical guidelines limit use to short term treatments and only for some specific anxiety disorders (Pelissolo *et al*., 2002; 2007). European studies evaluating BDZ use over longer period of time reported higher frequency of use, for example 9.8% over the past12-months in the ESEMeD survey (ESEMeD Investigators, 2004). The exclusion of older people from the study's population could therefore be a possible cause of these differences in the frequency reported. The finding that increasing age, low social economic status, low education, low income and unmarried status were factors associated with BDZ use is consistent with the data reported in previous European studies (Lagnaoui *et al*., 2004; Magrini *et al*., 1996). These factors were significantly associated with BDZ use even after adjustment for the presence of mood or anxiety disorders, thus suggesting that BDZ use may be consider as an indicator of psychosocial difficulties more than a proxy of the presence of a specific mental disorder. The diagnosis with the highest rate of BDZ use is Panic disorders. However, among people using BDZ, the more common diagnosis was Major Depression. A reasonable cause of this could be that Major Depressive Disorder, as well as Panic disorder, are strongly associated with BDZ use, but Major Depressive Disorder has a higher prevalence in the population. The most important variable predicting BDZ use was found to be the contemporary use of antidepressant drug. These associations underline the complexity of the relevant issues and highlight the necessity of cooperation between mental health workers (psychiatrist, nurses, social workers, educators) in order to lead to an improvement of the quality of life of these patients.

The present study has limitations. Telephone surveys are subject to selection bias if factors related to telephone access or willingness to participate in such surveys are also related to the variables under investigation. If factors influencing the household or individual response rates were also related to depression and its treatment, then bias might have resulted. Similarly, selection bias could result from the trend toward cell phone or internet phone use if exclusive users of cell phones (or Internet phones) differ in ways that are related to depression and its treatment (Esposito *et al*., 2007). Homeless as well as institutionalized people were excluded so that the results cannot be generalized to these populations. Moreover, the exclusion of individuals aged above 65 years did not allow to describe the epidemiology of BDZ use in this age group. This probably represents the main limitation of our study considering the high prevalence of use of BDZ in elderly individuals with risks of adverse reactions and dependence. As the frequency increased with age, exclusion of those >65 would lead to a lower frequency of use.

Insomnia was the main reason reported by subjects for BDZ use, and sleep difficulties are frequently reported symptoms recognized by people taking BDZs. An important clinical concern is that BDZ may be used as a symptomatic treatment of insomnia because potentially treatable underlying causes of insomnia (e.g. a mood or anxiety disorder) have not been detected. "Pain management" was the reason

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reported by 21.2% of subjects. This is a fascinating result as we included the issue of pain management since antidepressants are sometimes used for this reason. BDZ are muscle relaxants so they could be used for pain related to muscle spasms but that could not account for 20% of their use. In this way our result is rather strange and notable.

Although it is not possible to draw any firm conclusion about the adequacy of BDZ treatment, we found that 82.5% of people using BDZ were using them from more than one year. The issue of length of treatment is particularly relevant because these drugs are considered to have a low benefit/risk ratio in most anxiety disorders (limited efficacy, cognitive side effects, withdrawal and dependence problems). By contrast, BDZ are often helpful in Mood as well as in Psychotic Disorder in order to control some symptoms like agitation so that their long term use could be helpful in the maintaining a good health state. Moreover it's important to underline that previous studies showed that the main factor associated with length of BDZ use was use in the past (Mol *et al*., 2006). It seems that once BDZ use has started, other factors associated with BDZ use become less important in long-term use than they are in the earlier phases BDZ use. Our study once more confirms the difficulty to stop the use these medications once it has been started. Further randomized control studies may help clinicians in having a better practical approach in BDZ use.

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