CANADIAN TRENDS IN BENZODIAZEPINE & ZOPICLONE USE

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ABSTRACT

Background
Benzodiazepines (BDZs) and related sedative-hypnotic drugs can be used as symptomatic treatments for anxiety, insomnia, and agitation. Often, they are used as adjunctive treatments for mood or anxiety disorders. The frequency of use of antidepressant medications has been increasing in Canada, suggesting that effective management of mood and anxiety disorders may be occurring more often in the population. Potential adverse effects of BDZs have also been more clearly defined. It seems reasonable to hypothesize that the frequency of use of these medications may be decreasing over time, but existing published reports are dated.

Objective
To describe the frequency of sedative-hypnotic medication use in a general population sample. The longitudinal National Population Health Survey (NPHS) cohort between 1994 and 2000 was the data source for this study.

Methods
The frequency of use of BDZs and zopiclone in the NPHS was evaluated at four survey iterations: 1994/1995, 1996/1997, 1998/1999, and 2000/2001.

Results
No decline in the frequency of use over time was evident. The pattern of use resembled that previously described in Canada: there is a higher frequency in women, and the frequency of use increases with age.

Conclusion
Survey data of the type reported here cannot differentiate appropriate from inappropriate use. However, these results do indicate that the frequency of use of these medications is not declining, as might have been expected.

Key Words: *Epidemiology, cross-sectional surveys, sedative-hypnotic medications, mood disorders, anxiety disorders, population studies*

In the past 15 years, there have only been three studies that have examined sedative-hypnotic use in Canada. The most extensive analysis was reported by Rawson and D'Arcy in 1991.[1]

These authors used data from four surveys carried out in the preceding two decades: the International Collaborative study of Medical Care Utilization (ICS-MCU), the Canada Health Survey (CHS), the Health Promotion Survey (HPS), and the National Alcohol and Other Drugs Survey (NADS). None of these data sources identified specific drugs, each study relied on omnibus questions inquiring about the use of "sleeping pills", "sedatives", and "tranquilizers" currently, or over various time intervals.

These analyses indicated an overall frequency of use during the two days preceding the interview was 4.9% in the ICS-MCU and 6.1% in the CHS. The proportion reporting sedative-hypnotic use in the last 12 months was

11.9% in the HPS and the proportion reporting sedative-hypnotic use in the preceding 30 days in the NADS was 5.7%. Rawson and D'Arcy reported a higher frequency of use in women and an increasing frequency with increasing age.

Another Canadian study that investigated sedative-hypnotic use, specifically benzodiazepines, was reported by Busto and colleagues in 1989.[2] This study used figures on total sales of drugs in Canada collected by IMS Health. The sales figures were expressed as defined daily dosages (DDD) per 1000 inhabitants per day, providing an approximation of the frequency of use. Patterns of benzodiazepine use were analysed from 1978 to 1987.

This study found that the overall frequency of benzodiazepine use in Canada was approximately constant from 1978 to 1982, at 33 DDD/1000 inhabitants per day. However, from 1983 onwards this increased to 48 DDD/1000 inhabitants per day by 1987. Busto and colleagues found that long half-life benzodiazepine use decreased from 91% of total benzodiazepine use in 1978 to 39% in 1987 whereas short half-life benzodiazepines increased from 9% to 61% during this time period.

A more recent prospective study conducted in Canada by Neutel and colleagues[3] examined characteristics of continuing benzodiazepine (and zopiclone) use. The first two cycles (1994/1995 and 1996/1997) of the National Population Health Survey (NPHS) were used as data sources. In the Neutel et al. analysis, 3.2% of eligible subjects reported taking benzodiazepines in the preceding two days in 1994/1995, and 53.4% of these, also reported use in 1996/1997. The highest proportion of apparently continued use was seen in subjects between the ages of 60 and 79 (62.3%).

The objective of the current analysis was to evaluate the frequency of use of benzodiazepines (BDZs) and zopiclone over a longer period of follow-up in the NPHS cohort. The frequency of use of antidepressant medications has doubled in the NPHS cohort over the interval studied, suggesting that effective management of depressive disorders may be occurring with increasing frequency.[4]

Another non-BDZ sedative-hypnotic drug used in Canada is zaleplon, which could not be included in this analysis, since it was not represented in the drug-classification system used by Statistics Canada for the NPHS at the time of the study. Depending upon the frequency of use of zaleplon in Canada, the overall use of sedative-hypnotic medications may be higher than the estimates reported here.

METHODS

The National Population Health Survey (NPHS) is a longitudinal study conducted by Statistics Canada. The initial NPHS cohort consisted of 17,276 household residents sampled from the general population, with certain exceptions (armed forces personnel, native reserves, institutions, and certain remote areas), in 1994/1995.[5] The sample was selected using the Labour Force Survey sampling frame, except in Quebec where households already selected by the Enquête sociale et de santé comprised the sampling frame. In British Columbia, random digit dialling was used to select some subjects. Additional sampling has not refreshed the longitudinal sample. As such, the size of the cohort has diminished over time because of mortality, failure to trace, and refusal. (For a tabulation of NPHS attrition over the study interval please see reference 4) The cohort has also been aging over time and does not include anyone who immigrated to the country since 1994. The proportion of subjects lost to follow-up was approximately 2% per cycle, and less than 0.5% per cycle has been removed from the cohort because of institutionalisation.[4]

The NPHS data are useful because they are derived from a longitudinal cohort and the same items have been used to assess medication use at each cycle. The participants from the 1994/1995 NPHS were re-interviewed in subsequent data collection cycles using many of the same questions and modules. At each iteration subjects were asked to retrieve all of their pill bottles and other medication containers for any medication they had taken in the preceding two days. The specific drugs were then recorded using the Anatomic Therapeutic Classification (ATC) system, Canadian version, consistent with that used in Health Canada's Drug Products Database (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/dpd_terminology_e.html).

In keeping with Ray[6], short half-life benzodiazepines were defined as those with a half-life of less than 24 hours and long half-life benzodiazepines with a half-life of 24 hours or more.

The NPHS interview also included some omnibus questions referring to the use of "sleeping pills" and "tranquilizers" during the preceding month. Data from these questions were not used in this analysis as their extent of agreement with ATC coded data is poor.[7] The NPHS did assign codes for herbal preparations, but these data were also not included in this analysis. Finally, over the counter drugs that are sometimes marketed as sedative-hypnotics (e.g., diphenhydramine) were not included in this analysis. While the drug-use data in the NPHS covered any drug taken in the 2 days preceding the interview, no distinction could be made between "as needed" or "PRN" use and more regular use of the medications.

During the time of this study, there were four cycles of NPHS data available: 1994/1995, 1996/1997, 1998/1999, and 2000/2001. In these cycles, data were collected every 2 years using repeated interviews with members of the NPHS cohort. In the 1994/1995 cycle, a minority of interviews were conducted by telephone (between 20 and 30%), but in more recent cycles almost all NPHS interviews were conducted by telephone. The exact proportion of interviews carried out in person in 1994/1995 cannot be reported because the survey documentation files indicate that "many" interviews were started in person and then completed by telephone.[8] In the current analysis, the baseline NPHS sample of 17,276 was restricted initially to 12,575 (72.8%) subjects who had complete data collection for each cycle. The cycle 4 longitudinal files were used in this analysis, but all estimates were also restricted to those over the age of 18, such that the number of subjects contributing to the estimates made in successive cycles increased as subjects aged 12-17 in 1994/1995 became eligible for inclusion.

The NPHS also contains the World Health Organization's Composite International Diagnostic Interview - Short Form (CIDI-SF) for major depression.[9] The CIDI-SF is an instrument that serves as a screen for common psychiatric disorders; however, only the part diagnosing major depression was consistently used in the NPHS. The University of Calgary Conjoint Medical Ethics Review Board approved the study. All analyses were conducted at the Prairie Regional Data Centre on the University of Calgary campus, using SAS software, Version 8.2. A recommended bootstrap procedure was used, along with sampling weights, in estimation and calculation of 95% confidence intervals for estimates considered *a priori* to be central to the study's objectives. Bootstrap variance estimation is the preferred method of variance estimation because the complexity of the NPHS sampling procedures precludes adequate representation of design effects (multi-stage sampling, clustering and unequal selection probabilities) using conventional survey data analysis procedures.

Statistics Canada has requirements concerning the release of imprecise estimates. These requirements are based on the coefficients of variation associated with those estimates. Values with coefficients of variation exceeding 33.3 cannot be reported.[10]

RESULTS

In the first cycle of the NPHS there were a total of 17,276 respondents, 8,045 men (46.6%) and 9,231 women (53.4%). The mean age of the entire sample was 39.1 years (*SD* =21.8). After restricting the sample to only those who had complete longitudinal data, and who were over the age of 18, there were 9,949 individuals eligible for inclusion in 1994/1995, 10,238 individuals in 1996/1997, 10,532 individuals in 1998/1999, and 10,828 individuals in 2000/2001.

The overall frequencies of BDZs or zopiclone in the four successive cycles were: 2.6% (95% CI 2.2-3.0), 2.8% (95% CI 2.4-3.2%), 2.8% (95% CI 2.4-3.2), and 3.2% (95% CI 2.9-3.4). The frequency of reported use in at least one of the four cycles was 6.6%. Of NPHS respondents, 0.7% took a BDZ/SSH in all four cycles of the NPHS.

The frequency of use was consistently higher in women than in men, with no evidence of change in this pattern over time. In 1994/1995 the frequency of use in women was 3.6% (95% CI 3.0-4.2) and in men was 1.6% (95% CI 1.1-2.0). In the 2000/2001 cycle the frequency in women was 3.9% (95% CI 3.2-4.6) and in men was 2.4% (95% CI 1.8 – 2.9). Age was categorized in a

variety of ways in the analysis, and the frequency of use consistently increased with age irrespective of the categorization employed. In subjects aged 18 to 44, estimates of the frequency of use were associated with coefficients of variation that were not reportable according to the NPHS data release guidelines. In the 45-64 age group the frequencies of use were approximately 2% at all cycles (e.g. 2.2% (95% CI 1.8 – 2.6) in 1998/1999), whereas the 65 and over age group had consistently higher frequencies of use (e.g., 7.4% (95% CI 5.8-8.9) in 1994/1995 and 8.2% (95% CI 6.6-9.7) in 2000/2001).

TABLE 1 Frequency (%) of benzodiazepine and zopiclone use by demographic characteristics

	1994/1995 (95% CI)	**1996/1997 (95% CI)**	**1998/1999 (95% CI)**	**2000/2001 (95% CI)**
Marital Status				
Married or Common-law	2.3(1.9-2.8)	2.8(2.3-3.3)	2.3(1.9-2.7)	2.2(1.6-2.9)
Single, Separated, Divorced, Widowed	3.3(2.6-4.0)	3.0(2.4-3.7)	3.6(2.8-4.4)	3.6(3.0-4.2)
Income				
Low Income	3.7(3.1-4.3)	3.8(3.1-4.5)	4.3(3.6-5.1)	5.3(4.3-6.3)
High Income	1.8(1.4-2.3)	2.2 (1.2-2.8)	1.8(1.3-2.2)	2.2(1.8-2.7)
Education				
High Education	1.8(1.4-2.3)	2.1(1.6-2.6)	2.2(1.7-2.6)	2.5(2.0-2.9)
Low Education	3.8(3.2-4.5)	4.1(3.4-4.9)	3.9 (3.2-4.5)	4.5(3.7-5.3)

Table 1 shows the frequency of BDZ/SSH use in relation to marital status, education and income over the four cycles. Education was categorized at two levels, subjects with less than high school education and subjects having graduated from high school, with or without additional post-secondary schooling. Income was designated as "low" using Statistics Canada formulae that account for total family income adjusted for family size. The "lowest" and "low middle" income categories were aggregated for analysis. The frequency of use was higher in those who were single, separated, divorced or widowed compared to those who were married or in a common-law relationship. This pattern was consistent across all four cycles. The frequency of use in the low-income groups consistently exceeded that of the high-income group across the four cycles. The frequency of use was consistently higher in the low education group.

TABLE 2

Frequency of benzodiazepine and zopiclone use in patients with major depressive episodeand mental health resource use

	Cycle 1 % (95% CI)	Cycle 2 % (95% CI)	Cycle 3 % (95% CI)	Cycle 4 % (95% CI)
Use in patients with major depressive of episode	10.6 (7.3-13.9)	12.3 (8.4-16.3)	10.7 (6.8 – 14.7)	11.2 (7.7-14.7)
Use in patients with self-reported mental health resource use	12.9 (9.5-16.2)	15.2 (11.6-18.7)	11.0 (8.0-14.0)	11.4 (8.5-14.3)

Table 2 shows the overall frequency of benzodiazepine and zopiclone use in relation to major depression and mental health care utilization (in the preceding 12-months). Prevalence data for these clinical characteristics are also provided. The frequency of use was consistently higher in those with MDE and in those using mental health resources. However, the table also indicates that most users of these subjects did not have an episode of major depression in the preceding year and did not report consulting a health professional about their mental health. In the 2000/2001 cycle, the frequency of use in subjects not reporting one or more consultations with health professionals was 2.5% (95% CI 2.1 – 2.9) compared to 11.4% (95% CI 8.5-14.3) in those with at least one such consultation. In this cycle, 11.4% of subjects reported one or more consultations about mental health. The frequency of long half-life benzodiazepine use in the 18-64 year old subjects did not change over time: 33.4%, 32.0%, 31.9%, and 36.6% in the four interview cycles. The 95% confidence interval for cycle 4 (27.0 to 46.0) was calculated to provide an indication of the degree of precision associated with these estimates. The estimates are not highly precise, and are not suggestive of a trend.

When investigating the use of long half-life benzodiazepines in those aged 65 and over, the frequencies in cycles 1, 2, 3, and 4 were 28.0%, 24.1%, 24.7%, and 20.0% respectively. The 95% confidence interval for the 2000/2001 estimate (11.4 to 30.0) was calculated in order to provide an indication of the precision of these estimates. The point estimates indicate a diminishing frequency of use of long half-life medications in this age group in the NPHS cohort, imprecision associated with the estimates means that no firm inferences can be made to the general population.

TABLE 3 Frequency (%) of Use of Individual Benzodiazepine and Zopiclone

Benzodiazepine or Similar Sedative-Hypnotic	1994/1995	1996/1997	1998/1999	2000/2001
alprazolam	10.0	12.1	8.1	5.6
bromazepam	4.7	3.5	3.9	4.2
clonazepam	9.9	10.2	13.9	14.8
diazepam	9.1	7.2	5.9	5.9
flurazepam	5.7	3.2	3.7	-
lorazepam	35.1	35.3	39.9	38.3
oxazepam	10.6	-	8.9	8.1
temazepam	9.1	9.0	7.3	7.2
zopiclone	-	7.1	6.8	12.3

Table 3 shows the frequency of use of individual benzodiazepines and zopiclone in all four cycles of the NPHS for those reporting use. The benzodiazepine with the highest frequency of use was lorazepam. The frequencies of use for clonazepam and zopiclone increased across the four cycles whereas the frequency of use for alprazolam and diazepam decreased. The frequency of use of certain long half-life benzodiazepines such as clobazam, chlordiazepoxide, chlorazepate, and nitrazepam were too imprecise to be reported according to Statistics Canada data release guidelines. The estimated frequency of use of the short half-life benzodiazepine triazolam was also too imprecise to be reported.

DISCUSSION

An objective of this project was to update the results of earlier studies by Rawson and D'Arcy[1] and Busto.[11] Because of methodological differences direct comparisons cannot be made. The surveys that were analyzed by Rawson and D'Arcy use general questions about classes of drugs rather than ATC codes. The Busto study was based on pharmaceutical claims data. For these reasons, it is not possible to directly compare the results to those of previous studies. However, the pattern that was observed in the past, increasing use with increasing age and a higher frequency of use in women, is consistent with the earlier results.

The frequency of use of these medications in the over 65 age group may have been underestimated because of the exclusion of subjects without complete data collection at each cycle. Since elderly subjects are more subject to mortality or institutionalization, the excluded group may have had an elevated frequency of use. Similarly, if subjects using benzodiazepines were more likely to be lost to follow-up, then additional underestimation of the frequencies may have resulted.

Our *a priori* expectation was that the frequency of BDZ/SSH use would decline in the NPHS cohort due to increased awareness of conditions that may have caused non-specific symptomatic treatment in the past (e.g., the use of sedative or anxiolytic drugs to treat insomnia or anxiety in the context of unrecognized major depression). However, no evidence of a trend in this direction was found.

The pattern of use of specific BDZ/SSH medications, however, may be changing. This analysis did not use statistical procedures for repeated measures to examine trends over time. Procedures for time-series analyses could be used

for this purpose, but an accompanying set of bootstrap procedures for variance estimation would need to be developed first. With this proviso in mind, the use of some agents appears to be increasing, at least in the NPHS cohort, while the use of other medications is decreasing in frequency. The most notable change is the apparently increasing use of zopiclone.

Several European studies have reported high frequencies of continued use of benzodiazepines. Isacson reported that approximately 10% of subjects in a Swedish prescription registry were taking benzodiazepines in 1976, and that 24% of these were still taking them 13 years later.[12] A study conducted in the Netherlands used prescription records to follow 425 initial users, and reported that 14% of them continued to use benzodiazepines 8 years later.[13] However, these studies used repeated prescriptions to measure continued use, and cannot be directly compared to the NPHS, which employed four separate measures of past 2-day use. All of these reports, however, are consistent with the idea that continued use of benzodiazepines occurs with a considerable frequency in the population.

Survey data such as that analyzed here cannot address issues of appropriateness of use of medications. This is an issue, however, that should be explored further by detailed clinical studies. Such studies may also be able to explain the lack of an expected decline in the use of these medications.

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