Benzodiazepine use and abuse in Canada

Usoa Busto, PharmD
Krista L. Lanctôt, BSc
Pearl Isaac, BScPhm
Manuella Adrian, MSc(Hyg)

Benzodiazepines are frequently prescribed, yet the extent of their use in Canada has not been described. Such data would be valuable in assessing patient exposure to benzodiazepines and would provide a context to estimate the risk–benefit ratio of these drugs. Analysis of benzodiazepine sales in 1978–87 in Canada, expressed as the defined daily dose (DDD) per 1000 inhabitants per day, showed that the use of these drugs was stable during the first half of the decade, at 33 DDD/1000 inhabitants per day, then steadily increased from 1983 to 1987, reaching 48 DDD/1000 inhabitants per day in 1987. The total use of slowly eliminated benzodiazepines declined, whereas the overall use of rapidly eliminated benzodiazepines increased linearly. In 1978–83 Canada had the second-lowest total benzodiazepine use among several Western countries. The patterns of use and abuse of rapidly eliminated benzodiazepines in 1978–84 showed a close correlation. Our findings indicate that data on drug use can be monitored and linked to clinical data, providing a mechanism for monitoring the relation between use and related illness.

S'il se prescrit beaucoup de benzodiazépines, on n'a pas jusqu'ici, sur leur usage au Canada, réuni les faits qui permettraient de mesurer le contact des individus avec ces médicaments et d'estimer le rapport entre leurs risques et leurs avantages. À partir des chiffres de leur vente de 1978 à 1987 inclusivement, on calcule une dose quotidienne supposée par 1000 personnes. Cette dose, d'abord stable à 33, ce qui plaçait le Canada à l'avant-dernier rang parmi plusieurs pays occidentaux, augmente de façon soutenue à partir de 1983 pour atteindre 48 en 1987. On assiste au déclin de la prise de benzodiazépines à élimination lente mais à l'augmentation linéaire de celle de benzodiazépines à élimination rapide. Pour ces dernières, de 1978 à 1984 on note un parallélisme étroit entre leur usage normal et leur abus. Le tout laisse entrevoir la démonstration de liens entre la prise de médicaments et certains faits cliniques, notamment les effets pathologiques qu'on peut y rapporter.

From the Pharmacy Department, Clinical Pharmacology Programs and Statistical Research, Addiction Research Foundation, Toronto, and the Faculty of Pharmacy and the Department of Pharmacology, University of Toronto

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Reprint requests to: Dr. Usoa Busto, Pharmacy Department, Addiction Research Foundation, 33 Russell St., Toronto, Ont. M5S 2S1

Widespread benzodiazepine use is of much concern to the medical profession and to the general public.[1-3] Benzodiazepines account for two-thirds of the prescriptions for psychotropic drugs.[4] Approximately 1 of every 10 Canadians reports using a benzodiazepine at least once per year, and typically 10% of these users continue their use for more than 1 year.[2] Benzodiazepine use is higher among females and adults aged 50 years or over.[2,5] Therefore, as the proportion of the aged population in Canada increases, parallel changes in benzodiazepine use are expected.

There are no data on the overall Canadian patterns of benzodiazepine use. Such data would

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provide national estimates of benzodiazepine exposure, permit changes in use to be monitored and allow comparison of Canadian data with those from other countries. We carried out a study to examine benzodiazepine use in Canada over a 10-year period. In addition, to investigate whether patterns of benzodiazepine-related illness reflect changing patterns of use of these drugs, we linked data on benzodiazepine use to specific clinical data on patterns of benzodiazepine abuse.

Methods

Data on use

Figures on total sales of drugs in Canada, as collected by Intercontinental Medical Statistics of Canada Ltd. (an international market survey firm with Canadian headquarters in Montreal), were used as the database. Figures on cumulative year-end sales are based on invoices of drug deliveries to a sample panel of community and hospital pharmacies. These data are then projected nationally to represent total sales to community pharmacies and hospitals.[6]

We used the method for drug use studies recommended by the World Health Organization,[7] which describes drug consumption in a defined daily dose (DDD) per 1000 inhabitants per day, where the DDD is "the assumed average dose per day for the drug used on its main indication in adults".[8] The DDD is a technical unit of measurement that permits comparison of drug use despite variations in drug prices or the active substance content of pharmaceutical preparations.[8] Under ideal circumstances — continual use of a drug for one indication — the DDD/1000 inhabitants per day should give a rough estimate of the proportion of the population using the drug.[8]

One of the advantages of the DDD method is the easy and inexpensive use of data on drugs available in most countries. Also, this method provides important information on continuous overall therapeutic profiles over time that can be used to formulate health policy, measure effects of educational and regulatory efforts and define areas for further investigation. Limitations include the assumption that all drugs that are sold are consumed and the fact that the DDD may not accurately represent prescribed daily doses, which may change with different indications, and does not take into account the frequency of combination therapy.[9,10]

Primary data entry and conversion to DDD/1000 inhabitants per day were done on a microcomputer. Patterns of benzodiazepine use were examined for 1978–87 and compared with those for other countries[11-13] from 1978 to 1983. Table I shows the DDD for 12 benzodiazepines marketed in Canada as sedative–hypnotics and anxiolytics, their kinetic classification and their range of therapeutic dosages.[14,15]

Data on abuse

Information is systematically collected on demographic characteristics of patients (e.g., age and sex) as well as on drug(s) abused (e.g., name, dose, frequency, duration and source) for all patients coming to the Clinical Institute of the Addiction Research Foundation in Toronto and meeting the American Psychiatric Association's diagnostic criteria for benzodiazepine abuse and dependence.[16] Data on the types of benzodiazepine used by 284 such patients between 1978 and 1984[17] were obtained and linked to data on overall benzodiazepine use over the same period.

Results

Overall benzodiazepine use in Canada was stable from 1978 to 1982, at 33 DDD/1000 inhabitants per day. It began to increase in 1983, reaching 48 DDD/1000 inhabitants per day in 1987 (Fig. 1). Closer analysis showed a shift in the patterns of use within this group of drugs: the overall use of slowly eliminated benzodiazepines (elimination half-life [$t_{1/2\beta}$] 15 hours or more) decreased from 91% of total benzodiazepine use in 1978 to 39% in 1987, whereas the use of rapidly eliminated benzodiazepines ($t_{1/2\beta}$ less than 15 hours) increased linearly ($r = 0.995$, slope = 3.2) from 9% to 61% (Fig. 1).

The relation between patterns of benzodiazepine use in Canada and patterns of abuse of and dependence on these drugs is shown by comparing the proportion of benzodiazepine users using rapidly eliminated benzodiazepines with the proportion of patients admitted to the Clinical Institute of

Table I — Defined daily dose (DDD) and kinetic classification of benzodiazepines*

Classification and drug	Usual daily dose, mg[15]	DDD, mg[12]
Rapidly eliminated		
Alprazolam	0.125–3	1.0
Bromazepam	3–30	10
Ketazolam	15–60	30
Lorazepam	0.5–4	2.5
Oxazepam	5–120	50
Temazepam	15–30	20
Triazolam	0.125–0.5	0.5
Slowly eliminated		
Chlordiazepoxide		
Oral	5–40	30
Parenteral	25–100	50
Clorazepate	3.75–60	20
Diazepam	2–40	10
Flurazepam hydrochloride	15–30	30
Nitrazepam	2.5–30	5

*Clonazepam, although available in Canada, has not been included, because its primary indication is as an anticonvulsant. The lower dose corresponds to the initial recommended dose for elderly people.

the Addiction Research Foundation with the diagnosis of benzodiazepine abuse or dependence who were using rapidly eliminated drugs (Fig. 2). Patterns of use and those of abuse or dependence were found to be closely related (correlation coefficient 0.94).

Between 1978 and 1983 there were wide variations in the overall use of benzodiazepines in Canada, Denmark, Finland, Iceland, Norway, Sweden and the United States, Canada having the second-lowest rate of use (Fig. 3). Three countries showed a moderate increase: Canada (33.1 to 38.6 DDD/1000 inhabitants per day), Denmark (75 to 89.3) and Sweden (46 to 50). Use in Finland and Norway was stable (33 v. 32 and 54 v. 53 respectively). Iceland showed a moderate decrease (71 v. 62). However, in Canada and the Nordic countries overall, use increased from 312 to 324 DDD/1000 inhabitants per day.

Discussion

We found an overall increase in the use of benzodiazepines in Canada from 1983 to 1987. Since benzodiazepines are prescribed drugs, these findings reflect patterns of benzodiazepine prescription in Canada. The overall increase is the result of a linear increase in the use of rapidly eliminated benzodiazepines. This increase closely parallels the increase in problems of abuse and dependence with these drugs.

Overall, total benzodiazepine use increased in Canada. However, geographic variations in use within provinces are to be expected. For example, whereas the overall use in Canada was relatively stable from 1978 to 1982, th use in Saskatchewan decreased slightly.[18] Also, variations in use of individual compounds are likely.

Appropriate benzodiazepine use should be viewed in the context of symptoms for which these drugs are appropriately prescribed (i.e., anxiety and insomnia). Our findings certainly do not answer the question of whether the prescription of benzodiazepines in Canada (e.g., dose, frequency and duration of use) is appropriate for the prevalence of anxiety and insomnia in this country. However, comparative data from various countries suggest that such large variations in benzodiazepine use cannot be accounted for by differences in the prevalence of anxiety and insomnia,[19] even though geographic, demographic and cultural differences may account for some of the variation.[20] Such wide geographic discrepancies in the use of benzodiazepines suggest that their use (and hence prescription) may not always be in accordance with the usual recommendations for rational therapy.[19]

Benzodiazepines are effective for the short-term treatment of anxiety and sleep disorders. However, there is little evidence that they are useful for longer therapy. Nevertheless, between 1% and 3% of the population in the Western world use these drugs daily for more than 1 year.[2,19] In one Canadian study 3.3% of prescriptions for

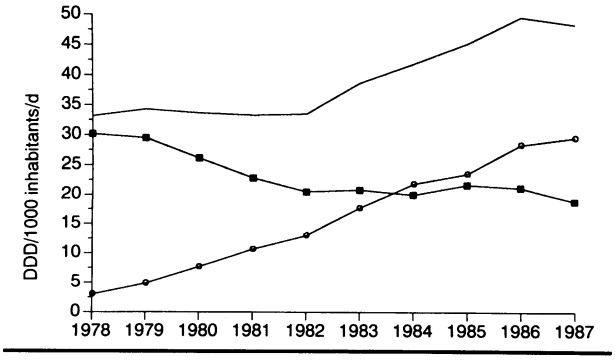

Fig. 1 — Use of benzodiazepines in Canada, 1978–87. Solid line = total use of benzodiazepines; squares = use of slowly eliminated benzodiazepines; circles = use of rapidly eliminated benzodiazepines; DDD = defined daily dose (see Methods section).

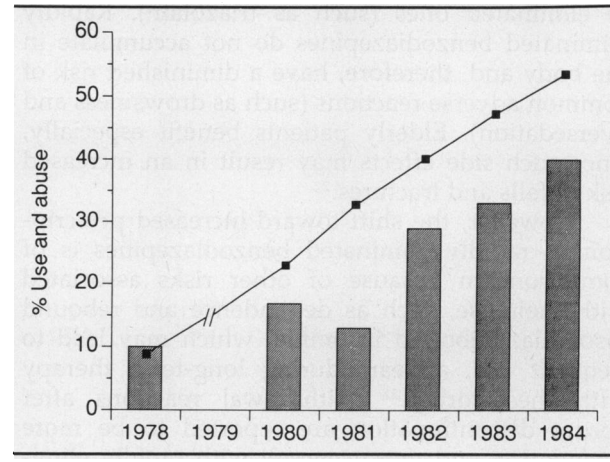

Fig. 2 — Relation between use and abuse of rapidly eliminated benzodiazepines in Canada, 1978–84. Bars = proportion of benzodiazepine users using rapidly eliminated drugs; solid line = proportion of patients with diagnosis of benzodiazepine abuse or dependence using rapidly eliminated drugs.

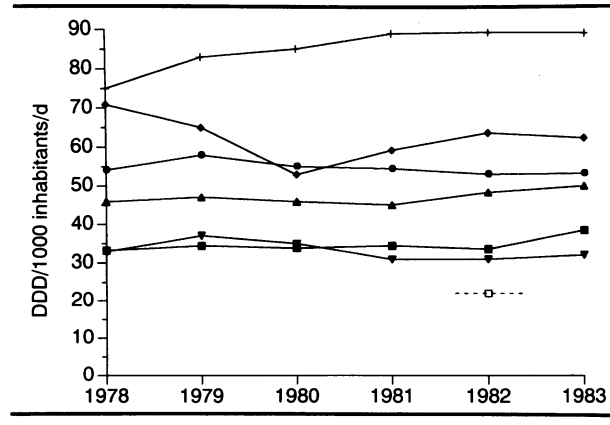

Fig. 3 — Benzodiazepine use in seven countries, including Canada, 1978–83.[11–13] Plus signs = Denmark; diamonds = Iceland; circles = Norway; triangles pointing up = Sweden; triangles pointing down = Canada; black squares = Finland; white square = United States (1 year only).

benzodiazepines were judged to be excessive.[21] Furthermore, available evidence indicates that only 23% of patients with anxiety actually receive treatment,[22] and although the vast majority of people with severe insomnia receive no medication,[23] elderly patients receive a disproportionately large percentage of the prescriptions for sedative-hypnotics.[24,25] Although benzodiazepines are remarkably safe, dependence on high and long-term therapeutic dosages has been clearly documented.[26] Unnecessary use of these drugs, especially in the elderly, may lead to needless problems associated with their use.

There has been a shift in Canada toward increased use of the more recently marketed rapidly eliminated benzodiazepines. Since overall benzodiazepine use has increased only slightly, this shift probably means that physicians have transferred patients using slowly eliminated compounds (such as diazepam and chlordiazepoxide) to rapidly eliminated ones (such as triazolam). Rapidly eliminated benzodiazepines do not accumulate in the body and, therefore, have a diminished risk of common adverse reactions (such as drowsiness and oversedation). Elderly patients benefit especially, since such side effects may result in an increased risk of falls and fractures.[27]

However, the shift toward increased prescription of rapidly eliminated benzodiazepines is of some concern because of other risks associated with their use, such as dependence and rebound insomnia. Rebound insomnia, which may lead to frequent use, appears during long-term therapy with these drugs.[28] Withdrawal reactions after abrupt discontinuation are reported to be more frequent[29,30] and more severe[31] with rapidly eliminated benzodiazepines than with slowly eliminated ones. Accordingly, more clinical problems associated with rapidly eliminated benzodiazepines would be expected. This expectation is confirmed by the changes in the patterns of benzodiazepine abuse and dependence observed in our institution. As benzodiazepine use changes, patterns of abuse and dependence also change.

The shift in use from slowly eliminated benzodiazepines to rapidly eliminated ones has also been noted by other investigators. Using a different method (analysing prescriptions of the Saskatchewan Prescription Drug Plan), the Joint Committee on Drug Utilization concluded that the 73% increase in sedative-hypnotic prescriptions from 1977 to 1983 in Saskatchewan did not reflect an increase in the population of the province but, rather, a true increase in benzodiazepine use.[18] The use of triazolam, a very rapidly eliminated benzodiazepine ($t_{½\beta}$ approximately 2 hours), increased from 17% of the total benzodiazepine use in 1979 to 60% in 1983 in Saskatchewan.[32]

Our findings must be interpreted with caution since methods of analysing drug use and drug-related illness have limitations.[33,34] To overcome these limitations we carefully cross-validated our results by comparing them with results obtained in other parts of Canada and in other countries. Consistent patterns emerged both nationally and internationally.

The usefulness of studies on drug use has been widely demonstrated.[1,9] So far, such studies have not been a priority in research in spite of the fact that they have been shown to be inexpensive indicators of the trends in drug use and of the effects of educational programs for health professionals. There is a need for continued monitoring of drug use to allow studies that provide insights into the public health consequences of drug use.

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