Health Canada Santé Canada

Drug Utilization Review of Benzodiazepine Use in First Nations and Inuit Populations

Drug Use Evaluation (DUE) Bulletin September 2005

Non-Insured Health Benefits

The Non-Insured Health Benefits (NIHB) Program provides supplementary health benefits, including prescription and non-prescription drugs, for registered First Nations and recognized Inuit throughout Canada.
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Recommendations

In December 2003, the NIHB Program created a Drug Use Evaluation Advisory Committee (DUEAC)[1] to provide recommendations to the Program to promote improvement in the health outcomes of First Nations and Inuit clients through effective use of pharmaceuticals.

This DUE Bulletin reviews the Committee's findings from its drug use evaluation of benzodiazepine claims submitted to the NIHB Program. Based on those findings the Committee recommends that:

1. Prescribers and pharmacists be vigilant about the risks involved with the long-term use of benzodiazepines.
2. In order to promote the optimal use of benzodiazepines in anxiety and insomnia and to avoid dependence, new prescriptions be carefully monitored and be of limited duration (one to four weeks for anxiety disorders and up to 14 days for insomnia).

The DUEAC[1] of the NIHB Program recommended that a review of benzodiazepine use be undertaken because of the potential for overuse and abuse. This topic meets predefined criteria as an issue the Committee would consider because benzodiazepines are widely prescribed. In Western societies it is estimated that 10%-20% of adults regularly take benzodiazepines, despite a paucity of evidence suggesting benefit, but clear evidence of harm (including dependence).[2]

Although benzodiazepines possess other effects (for example, anticonvulsant and muscle relaxant properties), their predominant clinical use is in the treatment of anxiety and sleep disorders. Benzodiazepines are also used in the acute management of symptom control associated with serious psychiatric illnesses. When used appropriately and for short periods of time, they are relatively safe. However with chronic use, benzodiazepines are associated with tolerance and addiction and in the elderly, cognitive impairment and falls.[3]

The efficacy of benzodiazepines for long term treatment of anxiety or insomnia is controversial. Evidence of continued efficacy beyond a few months is not well documented. Brief, interrupted courses of treatment should be proposed at the start of therapy, perhaps of one to four weeks' duration, with a tapered withdrawal of the drug. As well, there is little or no rationale to using more than one benzodiazepine at a time.[2,3]

Generally the manufacturers of benzodiazepines recommend the duration of treatment should be as short as possible with regular assessment of the patient. The need for continued treatment should be evaluated, especially if the patient is symptom free. In the management of anxiety disorders, therapy with a benzodiazepine should be considered as an adjuvant and not exceed two months, including the tapering-off period. In the management of insomnia, therapy should be limited to 7 to 14 days.[4,5]

[1]For further information on the DUEAC, please see the November 2004 NIHB Drug Bulletin.

[2]Holbrook AM et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000; 162: 225-33.

[3]Lader MH. Benzodiazepines: a risk-benefit profile. *CNS Drugs* 1994; 1: 377-387.

[4]Compendium of Pharmaceutical and Specialties 2005

[5]Product Monographs

Clinical efficacy of the various benzodiazepines is similar, but pharmacokinetic properties can vary considerably. Duration of action depends in part on the half-life of the drug and the presence or absence of active metabolites. Drugs with long elimination half-lives usually have long durations of action and are associated with prolonged sedation.[4,6]

One area of concern with benzodiazepines is the use in elderly patients. Elderly patients are especially vulnerable to the effects of benzodiazepines; aging increases the half-life.[3,7] "Beers Criteria" lists long-acting benzodiazepines ($t_{1/2}$ > 100 hours) as inappropriate for elderly patients, while short and intermediate acting agents should only be used at reduced doses and for limited periods of time.[7]

Purpose of the Drug Use Evaluation (DUE)

The objective of this DUE was to identify patterns of benzodiazepine prescribing and utilization among First Nations and Inuit populations and to quantify clients at risk.

Methods

This was a retrospective analysis of an encrypted data set protecting patient privacy. Clients of the NIHB Program who had been dispensed a benzodiazepine from April 1, 2002 until March 31, 2004 (24 months) comprised the study population. Benzodiazepines, covered under the NIHB Program, were included in the study (Table).

Benzodiazepines Listed As Benefits Under NIHB[6-8]

Generic Name (Brand Name)	Half-life (hrs) in healthy adults*	Diazepam Equivalents (# of mg = 10 mg diazepam)
Alprazolam (Xanax®)	12 to 15	1
Bromazepam (Lectopam®)	8 to 30	6
Chlordiazepoxide (Librium®)	100	30
Clobazam (Frisium®)**	10 to 46	20
Clonazepam (Rivotril®)***	20 to 80	1
Clorazapate (Tranxene®)	100	15
Diazepam (Valium®)	100	10
Flurazepam (Dalmane®)	100	22
Lorazapam (Ativan®)	10 to 20	2
Nitrazepam (Mogadon®)	16 to 55	10
Oxazepam (Serax®)	5 to 15	30
Temazepam (Restoril®)	10 to 20	20
Triazolam (Halcion®)	1.5 to 5	0.5

*Half-lives vary from patient to patient and will be influenced by age, hepatic and renal function.
**Clobazam is used mainly as an anticonvulsant
***Clonazepam is also used as an anticonvulsant and other conditions such as restless legs syndrome

Doses of benzodiazepines vary from agent to agent and from indication to indication. However the literature provides methods to compare equivalent doses of benzodiazepines. Comparisons can be done using diazepam equivalents[6] or defined daily dose (DDD). The usual daily dose of diazepam is 10 mg or 1 DDD. The maximum daily dose of diazepam recommended in the Compendium of Pharmaceutical Specialties is 40 mg.[4]

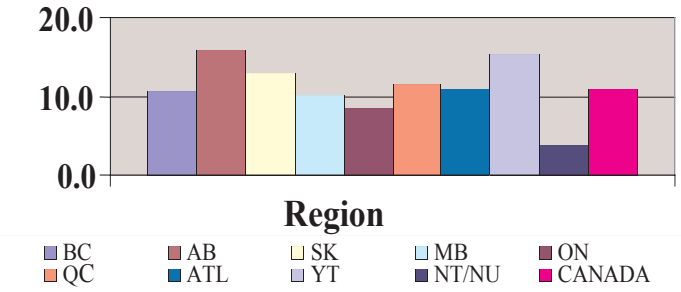
The system of Defined Daily Doses (DDDs) developed and maintained by the World Health Organization (WHO) standardizes the measurement of drug prescribing. Drugs are given a value representing the average maintenance dose per day in its main indication in adults. It must be emphasized the DDD is simply a unit of measure. For more information on the DDD system, please refer to the WHO Web site at: www.whocc.no/atcddd

The primary outcome measure was to determine the overall utilization of benzodiazepines among NIHB clients; secondary outcomes included identifying clients at risk for benzodiazepine abuse and patterns of benzodiazepine use among the elderly. The benchmark for abuse was set at the equivalent of 40 mg of diazepam per day, along with parameters around numbers of prescribers, providers and early refills.[2, 4]

Key Findings

1. For the period of analysis (April 2002 to March 2004) 80,495 individuals had at least one claim for a benzodiazepine in the NIHB Program. There were over 900,000 individual claims for benzodiazepines. Claimants were predominantly female (63%), between the ages of 18 and 64 years (87%) and residing in western regions (Figure I).

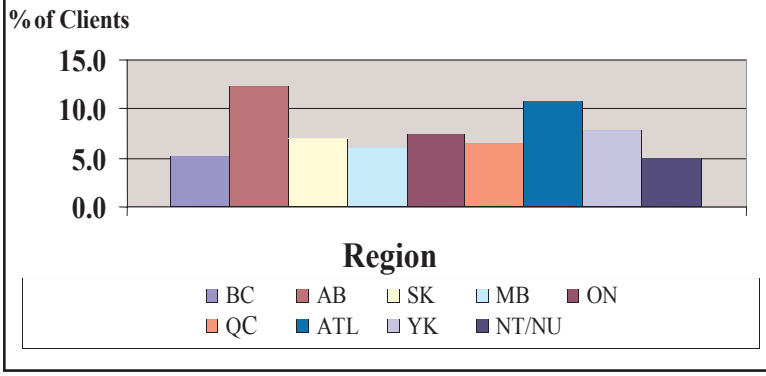
Figure I. Percent of Total NIHB Eligible Population with at Least 1 Benzodiazepine Claim (by Region)



[6]Bazire S. Psychotropic Drug Directory 2004. Fivepin Publishing. Salisbury 2004
[7]Fick DM et al. Updating the Beers Criteria for potentially inappropriate medication use in older adults. Arch Int Med 2003: 163:2716-24.
[8]British Columbia Therapeutic Initiative: Therapeutics letter November- December 2004
[9]Egan MY et al. High daily doses of benzodiazepines among Quebec seniors: prevalence and correlates. BMC Geriatrics 2001.1:4

2. Figure II describes the percentage of clients with at least one prescription exceeding the equivalent of 40 mg diazepam per day. This data is representative of all age groups, and is not adjusted for age.

Figure II. Percent of Clients with at least one Rx > 40 mg Diazepam Equivalents

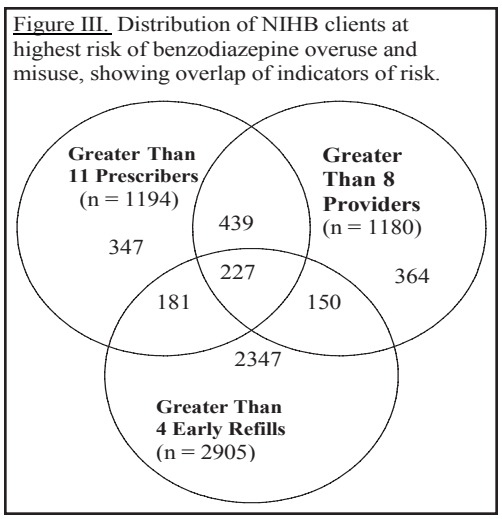


3. Demographics of benzodiazepine use within the NIHB populations match the demographics of populations from both published and unpublished data. About 10 % of NIHB clients had a prescription for a benzodiazepine in the past year. Overall, more females than males use benzodiazepines.[2,8]

4. The use of benzodiazepines in elderly clients is of concern, as there appears to be a higher prevalence of prescribing in the First Nations & Inuit seniors population. Over the two year period, 30.5% of clients > 64 years of age received a benzodiazepine prescription for a dose greater than 1 DDD. This is contrast to a published study from Quebec that showed 17.8% of seniors were prescribed this dose over a one-year period. As well, 24.9% of elderly NIHB clients received two or more benzodiazepines concurrently during the study period.[9]

5. Figure III illustrates the distribution of all clients at highest risk of benzodiazepine overuse and misuse (defined as benzodiazepine prescriptions filled by more than 8 providers (pharmacies), benzodiazepine prescriptions from more than 11 prescribers, and have early refills [refilled less than 2/3 of days supply] on at least 4 occasions).

Figure III. Distribution of NIHB clients at highest risk of benzodiazepine overuse and misuse, showing overlap of indicators of risk.



Limitations of the Analysis

The use of administrative claims data for DUE analysis is not without its shortcomings and as a result, there are three significant limitations to this evaluation.

* For each claim, the recorded quantity and days' supply is not always accurate. This is due to the manner by which the data is entered by the provider. Claims often contain keypunch errors and calculation estimates. For example, the provider may enter the total number of milligrams dispensed instead of the number of tablets dispensed in the claim.

  The method most often employed to detect the effect of these data shortcomings on the analysis was to run the programs with all data included and then to run the program a second time with the questionable claims removed. It was determined that the questionable claims had no significant effects on the results.

* The analysis only includes claims that were paid by NIHB and does not include claims that were paid by other insurers or by cash. This is a limitation for this study since clients who are at risk of benzodiazepine abuse might choose to pay cash for some prescriptions.

* The denominator used when reporting utilization rates as a percent of population (Figure I) was the total number of NIHB eligible persons. It includes persons that are covered under contribution agreements and therefore not captured in NIHB claims data. This has the effect of under-reporting the actual percent values. Therefore, the true population rates can be expected to be marginally higher than the reported rates.

Benzodiazepine Withdrawal Strategies

While the management of benzodiazepine withdrawal is beyond the scope of this report, listed below is information on withdrawal strategies. It is important that health care providers inform patients (and their families) of what to expect during withdrawal. Pharmacists can help physicians and patients keep track of tapering schedules.

* Ashton H. Benzodiazepines: how they work and how to withdraw. Aug. 2002. http://www.benzo.org.uk/manual/bzsched.htm.
* Baillargeon L, Landreville P, Verreault R. et al. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ* 2003;169 (10):1015-20.
* The Addictions Medical Advisory Committee, Government of Saskatchewan. Withdrawal management, protocols, guidelines and services. April 2001, pg. 11-13. http://www.saskatoonhealthregion.ca/your_health/calder_documents/WithdrawalManagementProtocol.pdf

Conclusions

Among First Nations & Inuit, the rate of overuse and potential misuse appears to be the same as the rest of the general population in Canada. A recent bulletin from British Columbia's Therapeutic Initiative describing the use of benzodiazepines within that province confirms overall benzodiazepine use among First Nations & Inuit is similar in usage patterns, demographics (females > males, age) and percentage of users (10%) to other populations.

A very small percentage of First Nations and Inuit clients appear to be at high risk (< 1%) because of benzodiazepine overuse and misuse. "High risk" indicates these clients have prescriptions from several physicians, go to several pharmacies to fill their prescriptions for benzo-diazepines and are early for refills.

There are concerns however, about regional trends, high volume prescribers, use of long-acting benzodiazepines, and continued use in the elderly.

Efforts are underway to review the benzodiazepines listed under the NIHB drug benefit list, with the aim to remove (or restrict access to) certain long-acting benzodiazepines. Prescriber, provider and community profiles are being developed to help monitor benzodiazepine use, with an effort to promote optimal prescribing of these drugs.

Summary of initiatives addressing benzodiazepine use among First Nations and Inuit

* Attempt to address concerns with regional trends and prescribing in the elderly with further DUE activities and consultations with pharmacists and physicians.
* Attempt to identify new benzodiazepine users and address continued use with prescribers and providers.
* Development of prescriber, provider and community profiles.
* Removal of certain long-acting benzodiazepines on the benefit list.

Members of the NIHB DUEAC