New Evidence on Benzodiazepine Use and Falls: The Time Factor

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Summary
The objectives of this prospective study were to calculate incidence rates for fall-related hospitalization, to compare the effect of risk factors among benzodiazepine (BZD) users and unexposed controls, and to examine variations in risks according to length of time following a BZD prescription. Data were derived from Saskatchewan Health linked data bases, leading to information on 468 hospitalizations for injury due to falls among a study population of 321,422.

Incidence rates per 10,000 within 28 days of the prescription fill date were 26.2, 12.1 and 9.0 for BZD sedative users, BZD tranquillizer users and for unexposed controls, respectively. Incidence rates increased with age, and were higher for women than for men. Results from multivariate logistic regression models also showed a greater risk of falling for BZD users but the odds ratio was higher for men than for women. A history of treatment for alcohol abuse was a very strong risk factor for falls among both men (odds ratio, 10.7) and women (odds ratio, 4.3).

The highest risk of serious injury due to falls was within 15 days of filling the prescription, with an odds ratio of 3.6 for BZD sedatives and 2.6 for BZD tranquillizers. Risk decreased with further increase of time after the BZD fill date. For the individual BZD, flurazepam and triazolam showed the highest increase in risk with odds ratios of 3.4 and 2.7, respectively, while oxazepam, lorazepam and diazepam showed odds ratios of 2.2, 2.0 and 1.8 (all odds ratios mentioned are statistically significant at p < 0.05).

Introduction
Injuries due to falls represent an important public health concern for all ages, but particularly for elderly people. Falls are the second most important cause of injury-related mortality for all age groups, but the leading cause for those aged over 75. Falls also represent the most important injury-related reason for hospital admissions for all ages [1–4]. Identification of modifiable risk factors [5, 6] could lead to the development of preventive measures that may increase quality of life, reduce premature mortality and lower health care costs.

Risk factors for falls include advanced age, problems in motor control, and a variety of chronic and acute illnesses [7]. Increasing evidence suggests that benzodiazepine (BZD) use represents an important iatrogenic risk factor for older adults in both community and institutional settings [8–13]. The use of tranquillizers and sedatives increases substantially among older age groups, so that more than 10% of men and 20% of women over 65 report using tranquillizers and/or sleeping pills [14, 15]. Clinically, non-pharmacological treatments are available for insomnia (e.g. sleep hygiene measures) and anxiety disorders (e.g. behavioural therapy). An understanding of the risks associated with BZD treatment is essential for informed risk-benefit analysis of the various treatment options.

The associations between individual BZDs and risk of falls or fractures have been the subject of several studies in the past few years. BZDs with long elimination half-life were found to be associated with a higher risk for falls than BZDs with a short elimination half-life [16, 17]. Another study found that the shorter-acting BZDs have a similar increased risk for hip fracture (e.g. 3.5 for temazepam use [12]). Also, several studies have demonstrated an increased risk of falling in older persons who are receiving multiple medications [18–20].

However, the published literature has some important limitations. Many retrospective studies are based on subject recall [21]. Subjects who fall may be more likely to remember drug exposures, since they are motivated to seek an explanation for the fall. It is also often difficult to establish the temporal relationship between BZD exposure and falls. The strength of the present study is that it is designed to address both of these limitations. It has a controlled cohort study design and allows for prospective analysis of fall-related injury after BZD use. In addition, the study permits an
evaluation of the effect of time lapse between a BZD exposure in a previously unexposed person and the risk of falls. The objective of this study is to evaluate the association of a first BZD prescription with subsequent hospitalization for injury due to falls.

**Methods**

The Saskatchewan Health Databases were developed for the province's health care delivery and payment claim systems, but they have also become valuable for population research. The databases used for the present study are the Health Insurance Registration file, the Prescription Drug Claim and the Hospital In-Patient Database [22].

The study design is a cohort or prospective study in which the exposed cohort, people who received a prescription for BZD, are compared with the unexposed cohort, a sample selected from the Saskatchewan population. The population included only adults over 20 years old without a BZD prescription in the prior 6 months, from among those eligible for coverage under the Saskatchewan Health Plan (over 95% of the Saskatchewan population). The exposed population represents persons who filled a prescription for a BZD sedative (triazolam or flurazepam) or a BZD tranquillizer (oxazepam, lorazepam or diazepam) between 1979 and 1986. These five BZD covered by far the majority of the BZD use (over 90%) in Saskatchewan at this time. The data collection for this study was discontinued in 1986 because changes in the administration of the drug plan resulted in the drug data being temporarily incomplete. Because this study relates an individual prescription to a potential adverse event, changes in prescribing patterns in more recent years should not affect the conclusions of this study.

To obtain an unexposed group comparable with the BZD exposed population, several criteria were used in the selection of control subjects. Specifically, the population of the Registration File was stratified by sex and 10-year age groups and two control subjects were randomly selected from the appropriate stratum for each triazolam user, so that the age/sex distribution of the control subjects was similar to that of the triazolam group. In order to control for seasonal factors, members of the control group were provided with an artificial prescription date with the same seasonal distribution as the prescription date of members of the BZD users' groups. These dates were used as the start of the follow-up period (up to 60 days) to track hospital admissions for injury due to falls. As with the exposed group, only control subjects who had not received a prescription for one of the study BZDs in the last 6 months before the artificial prescription dates were selected. Further details regarding the sample methodology used in the present study have been provided in an earlier publication [23]. Table I provides the BZD and comparison group sizes and the number of falls occurring in those groups.

The data collected for each individual included age, sex, use of concomitant drugs (other tranquillizers, sedatives, narcotic analgesics, antipsychotics, antidepressants and anticonvulsants) over the 30 days prior to the prescription date, history of treatment for alcohol/drug abuse over the preceding 12 months and the presence or absence of social assistance at the time of the BZD prescription date. The history of treatment for drug or alcohol abuse was determined by previous hospitalization for treatment of those conditions. The outcome variable of injuries due to falls is based on hospital records, using ICD-9 codes E880 to E888 [24]. Within the context of this study, all mentions of falls, injuries due to falls, or hospitalization, refer to hospitalization for injuries due to falls. The diagnosis used is the discharge diagnosis, but the date which determines whether an admission is within the follow-up period of 60 days is the hospital admission date. In case of multiple falls in the follow-up period, only the first hospitalization is included in the analysis.

**Analysis:** Age-specific or age-adjusted incidence rates were calculated for hospital admissions for falls within 4 weeks of filling a BZD prescription. This allows for a comparison of the BZD sedative and BZD tranquillizer users with the unexposed population for men and women of different age groups as well as the calculation of relative risks adjusted for the age distribution of the comparison groups. The exposed and control subjects were categorized by 10-year age groups. The standard population needed for the age adjustment calculation was obtained by summation of the populations of the three comparison groups: BZD sedatives, BZD tranquillizers, and unexposed controls. Multiple logistic regression models, including all relevant risk factors available in the linked Saskatchewan Health Databases (e.g. age, other drug use, receipt of social assistance, alcohol abuse), were calculated separately for men and women aged 60 years and older to examine the independent effects associated with BZD sedative and tranquillizer use. All analyses were performed using SAS-version 6 (SAS Institute Inc., Cary NC).

**Results**

Table II presents age-adjusted and age-specific rates

<table>
<thead>
<tr>
<th></th>
<th>BZD sedatives</th>
<th>BZD tranquillizers</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>No. of</td>
<td>No. of</td>
</tr>
<tr>
<td></td>
<td>subjects</td>
<td>falls</td>
<td>subjects</td>
</tr>
<tr>
<td>Total</td>
<td>77 184</td>
<td>202</td>
<td>146 684</td>
</tr>
<tr>
<td>Men</td>
<td>31 161</td>
<td>71</td>
<td>53 938</td>
</tr>
<tr>
<td>Women</td>
<td>46 023</td>
<td>131</td>
<td>92 746</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–59</td>
<td>41 876</td>
<td>36</td>
<td>100 960</td>
</tr>
<tr>
<td>60–79</td>
<td>28 033</td>
<td>73</td>
<td>38 874</td>
</tr>
<tr>
<td>80+</td>
<td>7275</td>
<td>93</td>
<td>6850</td>
</tr>
</tbody>
</table>

**Table I.** Study population size, and number of hospital admissions for falls within 4 weeks after the first BZD prescription, by age and sex
Table II. Age-adjusted and age-specific rates per 10,000, unadjusted relative risks and risk differences for falls within 4 weeks after the first BZD prescription, by age and sex

<table>
<thead>
<tr>
<th>Rates of hospitalization for falls per 10,000</th>
<th>Unadjusted risk estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZD sedatives</td>
<td>BZD tranquillizers</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Total</td>
<td>26.2</td>
</tr>
<tr>
<td>Men</td>
<td>22.8</td>
</tr>
<tr>
<td>Women</td>
<td>28.5</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>20–59</td>
<td>8.6</td>
</tr>
<tr>
<td>60–79</td>
<td>25.5</td>
</tr>
<tr>
<td>80+</td>
<td>127.8</td>
</tr>
</tbody>
</table>

* The relative risk for this table was calculated by dividing the exposed rate by the unexposed rate.

b The relative risk difference was calculated by subtracting the unexposed rate from the exposed rate.

for falls for BZD sedative users, BZD tranquillizer users and the control group. Hospitalization rates are highest for those exposed to BZD sedatives, followed by users of BZD tranquillizers and lowest for the control group. Among the three age groups, individuals 80 years and over show a much higher rate of hospitalization due to falls than the other two groups. Table II also presents the unadjusted relative risks and risk differences for the comparison groups. The BZD sedative exposed men have a risk of hospitalization due to falls 4.0 times that of unexposed men, while similarly exposed women have a risk of 2.5 times that of the unexposed women. Among the three age groups, the relative risks are highest for the under-60-year age group, with risk estimates of 10.8 and 7.1 for those exposed to BZD sedatives and tranquillizers, respectively. Conversely, the older subjects (aged 80 years and older) have the highest risk difference at 94.5 per 10,000 and 52.8 per 10,000 for those exposed to BZD sedatives and tranquillizers, respectively.

Table III shows adjusted odds ratios for risk of falls by BZD use and other variables for the population 60 years and older, stratified by sex. The odds ratios for BZD sedative use in this table are consistent with the relative risks reported in Table II. Specifically, compared with unexposed controls, male BZD sedative users had approximately a four-fold increase in risk while female BZD sedative users were approximately twice as likely to experience a fall-related hospitalization. For both men and women, the adjusted odds ratios associated with BZD tranquillizer use were somewhat lower than those observed for BZD sedative use. Use of antipsychotics and other sedatives was associated with a statistically significantly increased

Table III. Adjusted odds ratios for hospitalization for falls within 4 weeks of filling a first BZD prescription among men and women aged 60 years and over

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n* = 110)</td>
</tr>
<tr>
<td>BZD sedatives</td>
<td>4.0* (2.4–6.6)</td>
</tr>
<tr>
<td>BZD tranquillizers</td>
<td>2.5* (1.4–4.3)</td>
</tr>
<tr>
<td>Age (10-year intervals)</td>
<td>2.6* (2.0–3.4)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.5 (0.8–2.9)</td>
</tr>
<tr>
<td>Other sedatives</td>
<td>1.1 (0.6–1.9)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1.6 (0.6–4.5)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0.4 (0.1–1.2)</td>
</tr>
<tr>
<td>History of alcohol/drug abuse</td>
<td>10.7* (5.4–21.0)</td>
</tr>
<tr>
<td>Social assistance recipient</td>
<td>0.8 (0.3–2.3)</td>
</tr>
</tbody>
</table>

* Obtained from multiple logistic regression models, adjusted for all variables listed above. In this and subsequent tables: * Statistically significant at p < 0.05; *n = number of falls.
risk of hospitalization for falls for women, but not for men. A history of treatment for alcohol and drug abuse was strongly associated with risk of falls for both men and women, with a particularly high odds ratio for men (10.7).

Table IV presents adjusted odds ratios for risk of hospitalization for falls by length of time after first prescription. The odds ratios are highest for the first 2 weeks after the prescription was filled and then decrease with increasing length of follow-up for both BZD sedatives and tranquillizers.

Table V presents adjusted odds ratios for fall-related hospitalizations associated with the individual BZD. The highest odds ratios were found for flurazepam (3.4) and for triazolam (2.7). The three BZDs categorized as tranquillizers—diazepam, lorazepam, and oxazepam—had odds ratios ranging from 1.8 to 2.2.

Discussion

The present study is among the first to report incidence rates for fall-related hospitalizations after a first prescription for a BZD. Both relative risks and odds ratios showed a strong association between BZD exposure and subsequent falls (Tables II and III). This association is particularly strong in the period shortly after the receipt of the BZD prescription (Table IV) and is not accounted for by the various potential confounding variables examined here.

The present findings report new information not discussed elsewhere in the literature, but there are some shortcomings to be noted. Exposure to BZD is based on filling a prescription at a pharmacy. Some of the BZD group may not have consumed the BZD while a few of the control group may have obtained BZD from acquaintances. However, the rate of misclassification is highly unlikely to differ depending on whether falls occurred. Biases based on non-differential misclassification would tend to decrease the observed differences between the comparison groups, leading to a more conservative estimate of effect (i.e. a lower relative risk or odds ratio). Another limitation relates to the paucity of information on each patient, including details on the indications for BZD use and measures of the patient’s physical and mental health status. The data presented in Table III address comorbidity to some extent, but alternative explanations may not be accounted for entirely. Conditions that lead to BZD use might also increase the risk of hospitalization due to falls. Comorbidity is a problem that increases with age and might lead to a greater propensity to falls.

The present study offers several advantages for the study of BZD use and risk of falls. The data used in this analysis have the advantage of a reliable outcome measure, as detection rate for hospitalization due to falls is very high, probably complete, and the specificity for diagnoses is also high. That is, it is unlikely that coders would favour falls as the diagnosis for BZD users over non-users, because the coders could not be aware of BZD use. Also, the prospective nature of the data allows for the establishment of a temporal order between BZD use and falls. The higher odds ratio associated with the shorter follow-up period after BZD exposure may reflect the greater likelihood of current BZD use. Use of BZD is likely to decrease over time, with or without adverse side effects [25] and this may explain a weaker association with falls over time. Another explanation for the reduced odds ratio with longer follow-up could be an increase in tolerance of the effects of BZD.

The present results are consistent with evidence reported in the literature examining a variety of outcomes for falls. The strength of the association in this study is somewhat higher than that of other studies [8-11], but this could be explained by the closer time relation between BZD use and the falls in this study. This is especially likely in the light of the data of Table IV. Table V shows the risk for individual BZD which is somewhat at variance with two other studies which found that long-acting BZD (e.g. diazepam, flurazepam) had a higher risk while the shorter-acting BZD (e.g. triazolam, lorazepam, oxazepam) were associated with little or no risk [12, 16, 17]. The present study shows that flurazepam and triazolam have the higher risk, although the three other BZD studied also have a statistically significant increase in risk.
Some of the covariates also show some interesting results. The strong association for history of treatment for alcohol abuse shown in this study is consistent with some other publications [26], while other studies failed to find an association between alcohol use and fall-related injuries [27, 28]. The present study suggests that there may be a long-term risk for falls related to drug and alcohol abuse, because not all those with a history of abuse would continue to have that problem. The odds ratios shown here are sufficiently high to warrant further research.

An evaluation of the number of falls attributable to BZD (and thus, the impact of BZD use) was made by subtracting the incidence of falls in BZD non-users from that in BZD users. Table II presents the risk differences between the exposed and unexposed comparison groups. Given the assumption of a causal relation between BZD use and falls, these data suggest that for those 80 years of age and older exposed to BZD sedatives, 94.5 falls per 10 000 exposed could have been prevented by not giving the BZD sedatives. Similarly, 52.8 per 10 000 could have been prevented in this age group exposed to BZD tranquilizers.

Because of the numbers of falls that could potentially be prevented in a population that is very vulnerable to major disability because of falls, it is important to continue to study the elderly population in order to elucidate the causal mechanisms at work. Intervention studies examining alternatives to BZD use are of the highest priority. Falls have repeatedly been shown to represent a serious public health problem and BZDs are consistently implicated as major risk factors. Intervention studies can advance our understanding of the mechanism linking BZD use with falling and suggest effective ways of dealing with this problem.

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References

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