Adverse effects of benzodiazepine use in elderly people: a meta-analysis

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ABSTRACT

Background. Benzodiazepines are commonly prescribed to elderly people for anxiety or insomnia despite adverse effects. This meta-analysis focused on the risk of adverse effects of benzodiazepine use in elderly people.

Study selection. Two reviewers independently searched MEDLINE, EMBASE, and the Cochrane Database of Systemic Reviews for English-language publications from 1950 to June 2010, using the keywords ‘benzodiazepines’, ‘elderly’ and ‘adverse effects’. Retrieved studies were screened according to the inclusion criteria of: (1) mean age older than 65 years, (2) use of benzodiazepines for anxiety or insomnia, (3) randomised controlled trial design, and (4) adverse events in the treatment and placebo groups, including accidental injuries/falls, confusion, dizziness, somnolence, headache, depression, hypertension, and hangover. Seven studies met all the inclusion criteria and had the appropriate data for analysis. Three of the 7 studies contained data suitable as sub-studies and were entered as separate entities.

Data extraction. Data were extracted and synthesised into pooled odd ratios, relative risk, and number needed to harm. Heterogeneity of studies was assessed by the Q-statistic and I² index.

Data synthesis. Of a total of 894 participants, 411 took benzodiazepines and 483 took placebo. 96 (23%) and 46 (10%) of the participants reported adverse effects after taking benzodiazepines and placebo, respectively. The pooled odds ratio was 3.07 (p<0.0001) and relative risk was 2.45. The absolute risk reduction of taking placebo over benzodiazepines was 14%. The number needed to harm was 7. Heterogeneity of studies is deemed acceptable with a Q-statistic of 5.76 (p=0.76) and I² index of 0%.

Conclusion. Use of benzodiazepines lead to various adverse effects in elderly people. These drugs should be prescribed with caution, and the patients should be monitored closely.

Key words: Aged; Anxiety disorders; Benzodiazepines; Depressive disorder; Risk assessment

INTRODUCTION

Benzodiazepine drugs are useful in the treatment of agitation, insomnia, anxiety, seizures, and alcohol withdrawal, as they combine with the γ-aminobutyric acid-A receptor and produce hypnotic, sedative, anticonvulsant, and anxiolytic actions. Their effect can be short, intermediate, or long acting. Long-term use of benzodiazepines may have adverse psychological and physical effects, as these drugs are prone to cause tolerance, physical dependence, and withdrawal syndrome. Benzodiazepines are
associated with confusion, daytime sedation, memory problems, falls, and motor vehicle accidents.\textsuperscript{3-5} Although benzodiazepines are indicated for a limited number of psychiatric disorders, they are the most commonly prescribed psychotropic drugs among elderly people by family physicians and general practitioners.\textsuperscript{6} Elderly people are at increased risk for both short- and long-term adverse effects.\textsuperscript{7} Between 5\% and 33\% of elderly people in North America and the UK are prescribed benzodiazepines or benzodiazepine receptor agonists for sleep problems.\textsuperscript{8,9} Compared with healthy individuals, the safety of benzodiazepines in elderly people is less clear because of the impaired metabolic elimination and increased sensitivity of this population. A meta-analysis on the risks and benefits of sedatives for insomnia among elderly people reported that the risk of adverse events was higher with sedative treatment than with placebo.\textsuperscript{10} Most adverse events were reversible and not severe.\textsuperscript{11} Adverse effects on cognition can be mistaken for the effects of old age.

This meta-analysis evaluated the risks of adverse effects of benzodiazepine use in elderly people.

**METHODS**

Two reviewers independently searched MEDLINE, EMBASE, and the Cochrane Database of Systemic Reviews for English-language publications from 1950 to June 2010, using the keywords ‘benzodiazepines’, ‘elderly’ and ‘adverse effects’. Retrieved studies were screened according to the inclusion criteria of: (1) mean age older than 65 years, (2) use of benzodiazepines for anxiety or insomnia, (3) randomised controlled trial design, and (4) adverse events in the treatment and placebo groups, including accidental injuries/falls, confusion, dizziness, somnolence, headache, depression, hypertension, and hangover. In studies where 2 different benzodiazepines were compared to a placebo, or if there were ≥ 2 different doses of the benzodiazepine used, data from these sub-studies were entered as separate entities (Figure 1).

![Flowchart of the literature search process](image-url)
Odds ratios (ORs) were calculated with appropriate confidence intervals (CIs) based on the number of participants reporting the relevant adverse effects in the study. Where necessary, the value of 1 was added to any arm with zero outcome events according to the Sheehe +1 rule. The random effects model (instead of the fixed effects model) was adopted, as it is usually more appropriate for heterogeneous samples drawn from a wide population, and it accounts for studies that are still in progress or about to be published, and also for data that are either unpublished or included in non-peer reviewed journals. Forest plots were generated based on the OR.

RESULTS

A total of 195 studies were retrieved from MEDLINE, EMBASE, and the Cochrane Database of Systemic Reviews, and 18 studies were added through related sources. After removal of duplicates, 143 studies were considered as potentially eligible. After further analysis by 2 of the authors, 7 studies met all the inclusion criteria and had the appropriate data for analysis. Three of the 7 studies contained data suitable as sub-studies and were entered as separate entities (Table).

Studies that compared benzodiazepines to other hypnotics were included, as long as the numbers of adverse events in both the benzodiazepine and placebo groups were reported. The benzodiazepines used included temazepam, nitrazepam, loprazolam, triazolam, abecarnil, lorazepam, and flunitrazepam.

Of a total of 894 participants (mean age range, 65-83 years), 411 took benzodiazepines and 483 took placebo (Table). The duration of the trials ranged from 24 hours to 8 weeks. 96 (23%) and 46 (10%) of the participants reported adverse effects after taking benzodiazepines and placebo, respectively (Table). The difference in adverse effects was significant between the 2 groups, with a relative risk of 2.45 [96/(96+315)]/[46/(46+437)]. The absolute risk reduction of taking placebo over benzodiazepines was 14% (95% CI, 9-19%). The forest plot showed an odds ratio (random effects model) of 3.07 (95% CI, 2.03-4.63) [Figure 1]. The Z value was 5.35 (p<0.0001, 2-tailed). Heterogeneity of studies was acceptable, with a Q-statistic of 5.76 (p=0.76, 2-tailed), I² index

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of benzodiazepine</th>
<th>Benzodiazepine group</th>
<th>Control group</th>
<th>Adverse effects</th>
<th>Duration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meehan et al., 2002</td>
<td>Lorazepam</td>
<td>68/13</td>
<td>67/3</td>
<td>Accidental injury, headache, hypertension, somnolence</td>
<td>1 day</td>
</tr>
<tr>
<td>Bayer and Pathy, 1986</td>
<td>Loprazolam</td>
<td>31/7</td>
<td>28/1</td>
<td>Tiredness, weakness, dizziness, confusion</td>
<td>5 days</td>
</tr>
<tr>
<td>Bayer and Pathy, 1986</td>
<td>Loprazolam</td>
<td>30/3</td>
<td>28/1</td>
<td>Tiredness, weakness, dizziness, confusion</td>
<td>5 days</td>
</tr>
<tr>
<td>Dehlin et al., 1995</td>
<td>Flunitrazepam</td>
<td>52/20</td>
<td>102/17</td>
<td>Vertigo, depression, arthralgia, diarrhoea, headache, myalgia, dry mouth</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Morin et al., 2003</td>
<td>Temazepam</td>
<td>17/8</td>
<td>18/6</td>
<td>Confusion, headache, agitation, diarrhoea, constipation</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Klimm et al., 1987</td>
<td>Nitrazepam</td>
<td>36/1</td>
<td>74/0</td>
<td>Dizziness, confusion</td>
<td>1 week</td>
</tr>
<tr>
<td>Dehlin and Bjornson, 1983</td>
<td>Nitrazepam</td>
<td>26/11</td>
<td>26/5</td>
<td>Drowsiness, nausea, constipation, tremor</td>
<td>2 weeks + 2 weeks</td>
</tr>
<tr>
<td>Dehlin and Bjornson, 1983</td>
<td>Triazolam</td>
<td>26/5</td>
<td>26/5</td>
<td>Drowsiness, nausea, constipation, tremor</td>
<td>2 weeks + 2 weeks</td>
</tr>
<tr>
<td>Small and Bystriksk, 1997</td>
<td>Abecarnil</td>
<td>64/10</td>
<td>57/4</td>
<td>Drowsiness, dizziness, insomnia</td>
<td>6 weeks</td>
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<td>6 weeks</td>
</tr>
</tbody>
</table>

Total 411/96 483/46
of 0% (95% CI, 0-62%), and H value of 1 (95% CI, 1-1.63).

DISCUSSION

These results are in line with the findings from an earlier meta-analysis, which showed that use of benzodiazepines for chronic insomnia in elderly people is associated with a significantly high risk of adverse effects.10

Three of the 7 studies involved multiple arms looking at different dosages of the same class of benzodiazepine or different classes of benzodiazepines at one dosage. One study compared the effects of loprazolam at 0.5 mg and 1.0 mg versus placebo.11 The second study compared the use of triazolam to nitrazepam versus placebo.17 In the third study, adverse effects from 2 dosages of abecarnil (a low dose of 3.0-7.0 mg and a high dose of 7.5-17.5 mg) were compared with those with placebo.18 In addition, one study compared the adverse effects of a benzodiazepine (lorazepam) with a non-benzodiazepine (olanzapine) versus placebo,19 and the pertinent data (for lorazepam) were extracted for analysis.

The sample sizes of the trial and control groups in all studies were comparable, hence minimising weighting bias, except for one study in which all participants acted as both controls and patients at different stages of the study, and the effects of zopiclone were compared with flunitrazepam for insomnia over a 4-week period.20 In the first week, 102 participants were given a placebo. In the second week, they were randomly assigned to receive either zopiclone or flunitrazepam. In the last week, all participants received placebo again as a washout. The adverse events were recorded in the first and last weeks for placebo.

There were several limitations to this meta-analysis. The number of studies satisfying the inclusion criteria was small given the common use of benzodiazepine. The treatment period for benzodiazepines varied from 24 hours to 8 weeks owing to different indications and settings. It was not possible to allocate specific time periods of use. Moreover, all benzodiazepines were included regardless of their duration of action, with expectations that short-acting benzodiazepines would lead to fewer adverse effects. Therefore, the random effects model (instead of the fixed effect model) was used.
to account for this heterogeneity. The exact number of adverse events should have been detailed by categories (i.e. dizziness, drowsiness, insomnia), but such data were not available in all included studies. In addition, several studies did not clarify whether the number of adverse effects was recorded as per participant. One participant could have had more than one adverse event and may bias the analysis. Finally, the studies included were carried out in various inpatient and outpatient settings. Existing comorbidities of the participants were not clearly described and could not be stratified. This would be a potential confounding factor.

**CONCLUSION**

The use of benzodiazepines in elderly people is associated with 2.45 times more risk of developing adverse effects compared with placebo. For every 7 elderly patients treated with a benzodiazepine, one will have an adverse event. Benzodiazepines should be prescribed to elderly people cautiously and preferably only for short periods.

**REFERENCES**