



## Sedative Hypnotics and the Risk of Falls and Fractures in the Elderly

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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### ABSTRACT

Older age, poor sleep, and the use of the “Z” sedative hypnotic drugs (zopiclone, eszopiclone, zolpidem, and zaleplon) commonly go together. Each of these can increase the risk of falls and fractures through mechanisms related to cognitive and psychomotor impairment. A recent systematic review and meta-analysis examined the risk of falls and fractures associated with the use of the Z-drugs. The authors of that meta-analysis identified 14 relevant cohort and case-control studies. They found that Z-drugs increased the risk of falls in 2 out of 3 studies that provided information on this outcome; in the third, the increased risk narrowly missed statistical significance. Z-drugs increased the fracture risk in 9 of 10 studies (odds ratio [OR] = 1.63; 95% confidence interval [CI], 1.42–1.87). In secondary analyses, the fracture risk associated with the use of Z-drugs was elevated in studies that included a control group diagnosed with insomnia (OR = 1.28; 95% CI, 1.08–1.53) as well as in studies of samples restricted to subjects aged > 65 years (OR = 1.70; 95% CI, 1.36–2.12). In 2 studies, zolpidem was associated with an increased risk of injuries. Whereas confounding by indication may explain a part of the risk of falls and fractures, there is reason to consider that Z-drugs augment the risk. Either way, the use of Z-drugs emerges as a clear marker for the risk of falls and fractures. Nonpharmacologic interventions for insomnia should therefore be considered as alternatives to the use of Z-drugs. Finally, patients prescribed Z-drugs and caregivers of these patients should be warned about the risk of falls and fractures and counseled about practical measures that can reduce the risk.

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Older age is associated with motor and cognitive slowing and with deficits in coordination; these manifest in many ways, such as in deficits in balance and gait.<sup>1</sup> Because of such slowing, an elderly individual could take a fraction of a second longer to make adjustments while walking on an uneven or slippery surface; that fraction of a second could be sufficiently long for the individual to fall. The fall could result in a fracture because of reduced bone mineral density and fragility of bones in the elderly.<sup>2</sup>

### Risk Factors for Falls and Fractures in the Elderly

Difficulties in activities of daily living, and in instrumental activities of daily living, are a marker for the risk of falls.<sup>3</sup> Many risk factors have been identified for the fall and fracture risk in the elderly<sup>4,5</sup>; the use of psychotropic drugs is one such risk factor.<sup>6–8</sup>

In a systematic review and meta-analysis of 248 studies of the risk of falls in elderly (age 60 years and older) persons receiving psychotropic drugs, antipsychotic, antidepressant, and benzodiazepine drugs were all associated with a significantly increased risk<sup>8</sup>; the odds of falling associated with different groups and subgroups of drugs are presented in Table 1. In another systematic review and meta-analysis of 98 cohort and case-control studies that assessed the risk of fractures in elderly users of neuropsychiatric drugs, all categories of drugs barring hypnotics were associated with an increased risk of fracture.<sup>6</sup> The risks of fracture for different groups of drugs are presented in Table 2. Whereas the indication for which the drug was prescribed could be a contributory reason for the risk, it is reasonable to consider that drug-induced decrease in vigilance as well as psychomotor slowing could also be responsible, or could even primarily be responsible.

### Sedative Hypnotic Drugs and the Risk of Falls and Fractures in the Elderly

The lack of association between hypnotic drug use and fractures was from a meta-analysis<sup>6</sup> published in 2007. In this context, Treves et al<sup>9</sup> published a new systematic review and meta-analysis of the risk of falls and fractures in adults receiving the sedative hypnotic drugs zolpidem, zopiclone, eszopiclone, and zaleplon, collectively referred to as “Z-drugs.” This meta-analysis is important because it included many studies conducted in the elderly, because insomnia is common in the elderly, because Z-drugs are commonly used to treat insomnia, and because older age, insomnia, and sedation resulting from the use of Z-drugs may each impair cognition and psychomotor functioning, predisposing to falls and fractures.

Treves et al<sup>9</sup> searched electronic databases, clinical trial registries, reference lists, and other sources and identified 14 eligible studies: 2 case-crossover studies, 7 case-control studies, and 5 cohort studies. Three studies reported data on falls, 10 on fractures, and 2 on other injuries.

**Fractures.** There were 10 studies that reported data on the association between Z-drugs and fractures; 8 studies focused

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**Table 1. Psychotropic Drugs and the Odds of Falls in the Elderly<sup>a</sup>**

Drug Class	OR	95% CI
Antipsychotics	1.54	1.28–1.85
All antidepressants	1.57	1.43–1.74
Tricyclic antidepressants	1.41	1.07–1.86
Selective serotonin reuptake inhibitors	2.02	1.85–2.20
All benzodiazepines	1.42	1.22–1.65
Long-acting	1.81	1.05–3.16
Short-acting	1.27	1.04–1.56

<sup>a</sup>Data from Seppala et al.<sup>8</sup>

Abbreviations: CI = confidence interval, OR = odds ratio.

**Table 2. Psychotropic Drugs and the Risk of Fractures in the Elderly<sup>a</sup>**

Drug Class	RR	95% CI
Antipsychotics	1.59	1.27–1.98
Antidepressants	1.60	1.38–1.86
Benzodiazepines	1.34	1.24–1.45
Non-barbiturate antiepileptics	1.54	1.24–1.93
Barbiturate antiepileptics	2.17	1.35–3.50
Hypnotics	1.15	0.94–1.39
Opioids	1.38	1.15–1.66
Unspecified psychotropic drugs	1.48	1.41–1.59

<sup>a</sup>Data from Takkouche et al.<sup>6</sup>

Abbreviations: CI = confidence interval, RR = relative risk.

specifically on zolpidem. In these studies, there were 146,678 subjects exposed to Z-drugs and 684,199 unexposed controls. Important findings related to fractures are presented in Table 3. In summary, in all but 1 of the 10 studies, Z-drugs were associated with a significantly higher fracture risk. In meta-analysis, Z-drugs were associated with a significantly higher fracture risk in the 2 cohort studies, in the 8 case-control studies, and in the 10 studies combined. There was substantial heterogeneity in the analyses, but even when studies contributing to the heterogeneity were removed, the association between Z-drugs and fractures was statistically significant.

The authors<sup>9</sup> described subgroup and sensitivity analyses. Zolpidem (odds ratio [OR] = 1.39; 95% confidence interval [CI], 1.15–1.67) and the group of other Z-drugs (OR = 1.63; 95% CI, 1.01–2.62) were each found to be associated with a significantly increased risk of fractures. In what should have been an important part of the primary analysis, studies that included a control group diagnosed with insomnia and studies in samples restricted to subjects aged > 65 years also showed a significant association between Z-drugs and fractures (Table 4).

The association between Z-drugs and fractures was significant in both hospitalized and community samples. Finally, the association with fractures was significant in studies rated as low quality as well as in those rated as high quality. There was no evidence of publication bias based on visual inspection of a funnel plot.

**Falls.** There were 2 cohort studies and 1 case-control study that reported data on the association between Z-drugs and the risk of falls. In these studies, 5,269 subjects had been exposed to Z-drugs and 14,235 had not been so exposed.

**Table 3. Z-Drugs and the Risk of Fractures<sup>a</sup>**

1. There were 2 cohort studies with 78,569 subjects exposed to Z-drugs and 83,082 unexposed controls. There were 639 fracture events among the exposed subjects and 491 fracture events among the controls. The risk of fracture was significantly higher in the exposed subjects (OR = 2.10; 95% CI, 1.76–2.49).
2. There were 8 case-control studies with 68,109 subjects exposed to Z-drugs and 601,117 unexposed controls. There were 22,156 fracture events among exposed subjects and 140,495 fracture events among the controls. The risk of fracture was significantly higher in the exposed subjects (OR = 1.53; 95% CI, 1.31–1.77).
3. In a combined analysis of the cohort and case-control study data, the risk of fractures was significantly higher in subjects exposed to Z-drugs than in unexposed controls (OR = 1.63; 95% CI, 1.42–1.87).

<sup>a</sup>Data from Treves et al.<sup>9</sup>

Abbreviations: CI = confidence interval, OR = odds ratio.

**Table 4. Z-Drugs and the Risk of Fractures: Findings in Sensitivity and Subgroup Analyses<sup>a</sup>**

1. Z-drugs were significantly associated with fracture risk even in studies that included a control group diagnosed with insomnia (OR = 1.28; 95% CI, 1.08–1.53).<sup>b</sup> This finding was obtained from 1 cohort and 2 case-control studies with 4,733 exposed subjects and 40,436 unexposed subjects.
2. Z-drugs were significantly associated with fracture risk even in samples restricted to subjects aged > 65 years (OR = 1.70; 95% CI, 1.36–2.12). This finding was obtained from 1 cohort and 6 case-control studies with 8,407 exposed and 166,390 unexposed subjects.

<sup>a</sup>Data from Treves et al.<sup>9</sup><sup>b</sup>Values are as presented in the article. In the supplementary data, the values were OR = 1.40 and 95% CI, 1.07–1.84. Whichever values are correct, the finding is statistically significant.

Abbreviations: CI = confidence interval, OR = odds ratio.

Two of these studies found a significantly increased risk associated with Z-drug exposure, and the third found an increased risk that narrowly missed statistical significance. Logically, therefore, one might reasonably interpret these findings to indicate that Z-drugs are associated with an increased risk of falls. However, the case-control study was small and the confidence interval was wide, and the cohort studies were large and had narrow confidence intervals, but there was very substantial heterogeneity in their outcomes. As a result, the summary odds ratio in the meta-analysis was not significant (OR = 2.40; 95% CI, 0.92–6.27). This analysis was also associated with substantial heterogeneity. Therefore, it may be prudent to consider the studies as individual studies rather than summarized in meta-analysis.

**Injuries.** Two studies examined the risk of injuries associated with exposure to zolpidem. In these studies, 78,322 subjects had been exposed to zolpidem and 82,180 had not been so exposed. Zolpidem was associated with an increased risk of injuries (OR = 2.05; 95% CI, 1.95–2.15). There was no heterogeneity in this analysis.

### Comments: Confounding by Indication

Z-drugs are prescribed for patients with insomnia. Insomnia could be secondary to medical or neuropsychiatric conditions, and these conditions may be associated with physical and mental impairments that impair vigilance, balance, posture, and gait. Additionally, patients with

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insomnia, even primary insomnia, could feel dull, tired, slow, and listless because of poor sleep. Therefore, sleep deprivation, or whatever condition is responsible for the sleep deprivation, could induce the cognitive and psychomotor deficits that predispose to falls and fractures. In other words, confounding by indication may explain the observed association between Z-drugs and falls and fractures. As an example, 1 case-control study<sup>10</sup> found that whereas current use (last use within 1 year) of anxiolytics and sedatives was associated with an increased risk of fractures, past use (last use > 1 year ago) was also associated with an increased risk. This suggests that it could be the individual that (also) carries the risk rather than the drug alone.

As a counter argument, the meta-analysis<sup>9</sup> found a significant association between Z-drugs and fractures even in studies that had patients with insomnia as controls (Table 4). The authors of the meta-analysis<sup>9</sup> further pointed out that the individual studies in the meta-analysis had made attempts to control for confounds by including covariates in their analyses. As an example, in a retrospective cohort study, Kolla et al<sup>11</sup> examined data of adult inpatients in a tertiary care center. They found that the rate of falls was 3.0% in 4,962 patients who were prescribed and received zolpidem; this figure was only 0.7% in 11,358 patients who were prescribed zolpidem but did not receive the drug ( $P < .001$ ). The association between zolpidem use and fall risk remained significant after adjusting for potential confounders, including age, gender, insomnia, presence of delirium, zolpidem dose, Charlson Comorbidity Index, risk score for falls, duration of hospital stay, presence of visual impairment, presence of abnormalities in gait, and cognitive impairment or dementia (OR = 4.37; 95% CI, 3.34–5.76).

Confounding by indication and confounding due to other variables are eliminated in randomized controlled trials (RCTs). However, falls and fractures are infrequent events, and so RCTs, which are limited in sample size and study duration, would be underpowered to detect differences in risk between treated and control groups; in fact, even meta-analysis of RCTs could be underpowered in this regard. For example, a retrospective population cohort study found that the risk of hip fracture in 6,978 zolpidem users versus 27,848 nonusers was only 3.1 versus 1.4 per 1,000 person years.<sup>12</sup> This may explain why a meta-analysis of 24 RCTs of sedative hypnotics in 2,417 subjects identified only 7 serious psychomotor adverse events: 6 falls (including 3 fractures) and 1 motor vehicle crash.<sup>13</sup>

Injuries, however, are more common events. For example, in a retrospective cohort study, Chung et al<sup>14</sup> found that the incidence rate of soft tissue, orthopedic, or other injury was 6.1% versus 3.0% in zolpidem-exposed ( $n = 77,036$ ) versus unexposed ( $n = 77,036$ ) subjects who were followed up for 90 days. This incidence was 4.8% in 36,528 subjects who had been prescribed zolpidem for < 30 days and 7.2% in those who had received the drug for > 30 days. However, despite the association between longer exposure and higher risk, confounding by indication cannot be ruled out as an explanation for the findings because whatever explains the

### Table 5. Practical Suggestions for Evaluating and Counseling Patients Advised or Receiving Z-Drugs or Other Neuropsychiatric Drugs

1. Ask about a history of falls and fractures. Ask about problems related to walking and balance. Ask about other risk factors for falls and fractures, including symptoms such as dizziness, muscle and joint pain, and numbness in the feet. Evaluate cognition, gait, balance, and muscle strength.
2. Inform patients and caregivers that the medications that the patients have been prescribed or are receiving are associated with an increased risk of falls and fractures. Clarify that whereas the medications are a marker of risk, they may not necessarily be wholly responsible for the risk; for example, the condition for which the medications are prescribed may contribute to or drive the risk.
3. Encourage the implementation of recommendations to reduce the risk of falls and fractures.<sup>20,21</sup> Evaluate and correct problems with vision, evaluate bone mineral density, supplement with calcium and vitamin D, suggest exercises that strengthen muscles and improve balance, etc, as appropriate.
4. Provide practical advice, as appropriate, to patients and their caregivers. Some examples:
  - Keep a night light on so that you can see where you are going should you need to get out of bed at night
  - Wear footwear that fits well and that gives a good grip on the floor
  - Carpet the floor if the floor is slippery
  - Do not leave objects, cords, or cables on the floor
  - Do not leave loose mats or rugs on the floor
  - Use a walking stick, if you need one, and keep it handy at all times
  - Install antiskid mats and handrails in the bathroom
  - Take special precautions in the bathroom and on stairs

longer use of zolpidem may also be responsible for the higher fracture risk.

Other recent meta-analyses have also found a significant association between benzodiazepines, Z-drugs, and the risk of fractures, especially at the hip.<sup>15,16</sup> Perhaps the best way to view the matter is to consider that, whether or not Z-drugs are causal for falls and fracture risks, their use is a marker for these risks and for the risk of injuries in general. Therefore, all patients who are receiving or are advised Z-drugs need to take precautions as discussed in a later section.

### Other Comments

Control subjects in the meta-analysis by Treves et al<sup>9</sup> were not necessarily medication-free. Thus, some or many may have been taking psychotropic drugs, including benzodiazepines, that might have increased the risk of falls, thereby narrowing the differences in the Z-drug and control group comparisons. This implies that the effect sizes of Z-drugs on the falls and fractures risks could be larger than what was estimated in the meta-analysis.

There is need in future studies to better identify predictors of risk. Examples of potential predictors include age, sex, osteoporosis, and medical and neuropsychiatric comorbidities.

### Action Points

Patients with insomnia do not necessarily need to receive Z-drugs. In many cases, behavioral interventions may be of considerable short- and long-term benefit. Readers

**Table 6. Key Messages**

1. Sedating and hypnotic drugs with long half-lives are associated with an early morning hangover, daytime sedation, slowed cognitive functioning, slowed psychomotor reflexes, and an increased risk of accidents, falls, and fractures. All Z-drugs have short half-lives and are substantially washed out of the body by the time the patient awakens in the morning. Possible exceptions are eszopiclone, which has the longest half-life among the Z-drugs, and extended-release zolpidem.
2. It is possible that disease processes or comorbidities that make insomnia sufficiently severe or bothersome to necessitate Z-drugs treatment may be an important factor contributing to the risk of falls and fractures associated with these drugs. However, the Z-drugs can slow psychomotor reflexes in patients who get out of bed during the night, and in those in whom blood levels remain high during morning hours. Therefore, there is a plausible mechanism for the occurrence of falls and fractures in association with Z-drugs, and patients should be counseled about the risk.
3. Whereas persons at all ages are at risk of injuries, falls, and fractures related to the psychomotor effects of sedative-hypnotic drugs, it goes without saying that the elderly are at greater risk because of the slowed psychomotor reflexes and increased bone fragility associated with aging.
4. These comments apply to all drugs that have sedative and hypnotic activity, and not to Z-drugs alone.

are referred to the appendix of the article by Sharma and Andrade<sup>17</sup> for practical suggestions for nonpharmacological and behavioral interventions for patients with insomnia.

Many interventions have been studied for the prevention of falls in elderly persons in hospitals, in care facilities, and in the community.<sup>18,19</sup> Recommendations have been issued for the prevention of falls and fractures in the elderly.<sup>20,21</sup>

However, these are long-term interventions and would serve little purpose if initiated at the time of initiation of treatment with Z-drugs. Therefore, in patients for whom Z-drugs are inevitable, more immediate and commonsense, practical advice should be provided (Table 5). Key messages are stated in Table 6.

Because most or all psychotropic drugs are markers for an increased risk of falls and fractures in the elderly, the suggestions provided here apply to all elderly subjects who are started on treatment with psychotropic drugs or who are already receiving psychotropic drugs.

### Parting Note

Readers take authors on trust when data are reported and results of analyses are presented. In their meta-analyses, Treves et al<sup>9</sup> showed that a case-crossover study<sup>22</sup> had found an increased odds of fractures associated with zolpidem use (OR = 1.12; 95% CI, 1.01–1.24). However, the study<sup>22</sup> actually showed that, after adjusting for comorbid conditions, zolpidem use was *not* associated with fracture risk; this was also the conclusion presented in the abstract and in the text. Additionally, the numbers cited by Treves et al<sup>9</sup> for this study are not found anywhere in the text of the study. Therefore, Treves et al<sup>9</sup> either selectively extracted data from the study to drive the findings of the meta-analysis in a desired direction or made mistakes in data extraction. Either way, one is tempted to wonder how many other problematic issues such as this the meta-analysis may contain.

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