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Z-drugs and risk for falls and fractures in older adults—a systematic review and meta-analysis

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Abstract

Objective: zolpidem, zopiclone, eszopiclone and zaleplon, also known as 'Z-drugs', are commonly used as alternatives to benzodiazepines (BZDs) to treat insomnia. Z-drugs are often perceived as safer than BZDs. We conducted a systematic review and meta-analysis evaluating the association between Z-drugs and fracutres, falls and injuries.
Methods: a systematic review was performed using MEDLINE, EMBASE and ClinicalTials.gov. Pooled effect-sizes were calculated comparing Z-drugs users with non-users, using fixed and random-effect models with corresponding 95% confidence of intervals (CI).
Results: we identified 14 eligible studies reporting on the association between Z-drugs and outcomes of interest. Z-Drugs were associated with a statistically significant increased risk for fractures, with evidence of considerable heterogeneity (OR = 1.63; 95% CI: 1.42–1.87; I^2 = 90%; n = 830,877). Likewise, there was a trend suggesting a 2-fold increase in the odds for falls, however, this result was not statistically significant and there was evidence of considerable heterogeneity (OR = 2.40; 95% CI: 0.92–6.27; I^2 = 95%; n = 19,505). In an analysis assessing the risk for injuries following exposure to zolpidem we found a statistically significant increased risk of injuries, with no evidence of heterogeneity (OR = 2.05; CI 95%: 1.95–2.15; I^2 = 0; n = 160,502). Results were similar in sensitivity analyses, including analyses restricted to studies of high-quality, studies with control groups suffering from insomnia, and with specific Z-drugs.
Conclusion: our results indicate that Z-drugs are associated with an increased risk for fractures, and suggest a possible increased risk for falls and injuries as well. However, studies included were observational and susceptible to confounding. Physicians should consider these potential risks before prescribing these medications in older adults.

Keywords: *Z-drugs, falls, fractures, older adults, hypnotics, zolpidem, systematic review, older people*

Background

Hypnotic non-benzodiazepines (BZDs) (namely, zaleplon, zolpidem, zopiclone and eszopiclone), also known as 'Z-drugs', are the most commonly prescribed hypnotic agents worldwide [1]. Z-drugs use in the UK is reportedly increasing, while that of standard BZDs is falling [2], such that zopiclone has become the most frequently prescribed hypnotic in the UK [3, 4].

Z-drugs have been promoted for use as hypnotics based on various pharmacological characteristics, such as a more natural sleep pattern [5], a reduced propensity of REM sleep supression, and a shorter half-life, compared to most BZDs [6]. Additionally, it has been reported that patients are less likely to develop tolerance and physical dependence upon repeated treatment with Z-drugs [7, 8], and that Z-drugs are perceived to be safer than BZDs by physicians [9]. However, these medications are known to induce drowsiness and impairments in gait, as well as negative effects on vigilance and cognitive function [10], similar to the effects observed with BZDs [11]. Indeed, studies have reported adverse cognitive and psychomotor effects following treatment with Z-drugs, with physical consequences, including falls, fractures, traffic accidents, daytime fatigue,

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addiction and increased mortality [12, 13]. A thorough understanding of the potential consequences of widespread use of Z-drugs is necessary so that implications of prescribing these medications could be considered with care.

Falls are a major risk factor for injuries and hospitalisation among older adults, as they can lead to upper extremity fractures and hip fractures which are strongly associated with disability, morbidity and mortality [14]. The association between exposure to Z-drugs and falls and fractures is unclear. While some studies have reported a significant association between exposure to Z-drugs and the risk for fractures, falls or injuries [15, 16] others have not [17]. In this study, we assessed the association between exposure Z-drugs and the risk for fractures, falls and injuries.

Methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) framework guidelines [18]. Our search included published and unpublished studies through August 2016. We performed the systematic review using MEDLINE, EMBASE and 'clinicaltrials.gov' databases according to pre-selected keywords. We subsequently searched and evaluated published systematic reviews, reviews and original articles, to ensure identification of all studies.

The search included keywords for all hypnotics and the terms 'Z-drugs', 'non-benzodiazepine' or specific Z-drug agents (zolpidem, zopiclone, eszopiclone and zaleplon), combined with fractures or falls. We included randomised control trials as well as observational studies. No language or date restrictions were applied in these searches. For further detail of search strategy and syntax see Appendix 1 of study protocol. The study protocol was approved by an academic committee on February 2015, and is accessible at: https://medicine.ekmd.huji.ac.il/en/publications/researcherspages/pages/ilanma.aspx

As this study was a systematic review and meta-analysis, no ethical review board was required.

Selection criteria

For our meta-analysis, we included studies that compared adults (≥18 years old) receiving Z-drugs, and a control group of adults who were not treated with Z-drugs. The control group could include participants treated with other, non-Z-drug, sedative medications. We included articles in either English or French languages. Studies were selected only if they reported on one of the three following outcomes: fractures, falls and injuries, and we excluded studies concerning dialysis patients. To facilitate a comprehensive evaluation of the available studies in this area, no restriction was employed for the precise definition of the outcomes (fractures, falls and injuries). The possible impact of variation in terminology and study design was addressed by measuring heterogeneity and by utilising random-effects models and subgroup analyses.

Two investigators identified and extracted independently for potential inclusion (N.T. and L.K.G.). Disagreements were resolved by discussion and consensus. All potentially eligible studies were considered regardless of publication type.

Data extraction and quality assessment

Relevant data was extracted from each article, including age, gender, use of other medications, community dwelling status, exposure (the drugs, doses, timing and treatment duration) and details about the study itself (study design, location, year, number of participants and outcomes).

Study quality was assessed for the risk of bias using 'Newcastle-Ottawa Quality Assessment scale' (NOS). NOS includes a very structured evaluation of a number of specific aspects of study design (e.g. the selection process of the groups study, evaluation of outcome), attaches a similar weight and grade to the various aspects, and calculates the overall quality of the study as a summation process of the strengths and weaknesses in the various aspects. A similar test, Robans was also used to assess the biases in the studies. We also evaluated study quality using the ROBINS-I tool. This tool focuses on a wider range of potential sources of biases in a more thorough manner, and results in a more critical appraisal of study quality. Sensitivity analyses were preformed according to study quality based on these scores.

Data synthesis and analysis

Analyses were performed using RevMan version 5.3 (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). We calculated pooled risk-ratios and corresponding 95% confidence of intervals (CI), to summarise the results for the different outcomes assessed for Z-drugs recipients versus non-Z-drugs users, using Mantel–Haenszel fixed-effect models, or random-effect models. *P* value for statistically significant heterogeneity was set at <0.1. 'Heterogeneity' refers to clinical or methodological differences between studies which can lead to greater variation in the outcomes reported between studies than would be expected by chance. We calculated the quantity I^2 to assess the degree of heterogeneity observed in the analysis, with values of 25, 50 and 75% considered moderate, substantial and considerable, respectively. For substantial and considerable heterogeneity we used DerSimonian and Laird random-effect models. This method provides a summary measure of effects observed in the studies while accounting for between-study variation related to specific study characteristics. Study weights calculated using this method are based on a combination of the variance of the study estimate (which is a function of study size and number of events) and the heterogeneity in the estimates between studies.

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We preformed a series of subgroup and sensitivity analyses to evaluate whether results varied by a wide range of study characterstics. Specifically, we performed subgroup analysis to evaluate whether the association between zolpidem and the risk for fractures, differed from that of all other Z-drugs. Other specific Z-drugs were not assessed individually due to the limited data, and the small number of subjects exposed to each of the other individual Z-drugs [19]. We additionally analysed the risk of fractures with Z-drugs while restricting the analysis to studies using a control group with insomnia. Another subanalysis compared studies performed in the community and studies performed in inpatients. Further analyses included examining the effect of the Z-drugs on the risk for different kind of fractures, focusing on hip fractures and restricting analysis to studies with participants >65 years of age. Lastly, we evaluated estimated associations while stratifying studies by study design (cohort and case–control), and by quality score.

Results

A systematic search was conducted through August 2016. Of 23 articles reporting on the outcomes of interest with Z-drugs, five did not meet inclusion criteria, three were duplicates or partial results of other included studies, and one did not provide results extractable for inclusion in the analysis. A total of 14 studies were included in our analyses (Supplementary bibliography), five cohort studies and nine case–control studies (Figure 1). Details of the studies

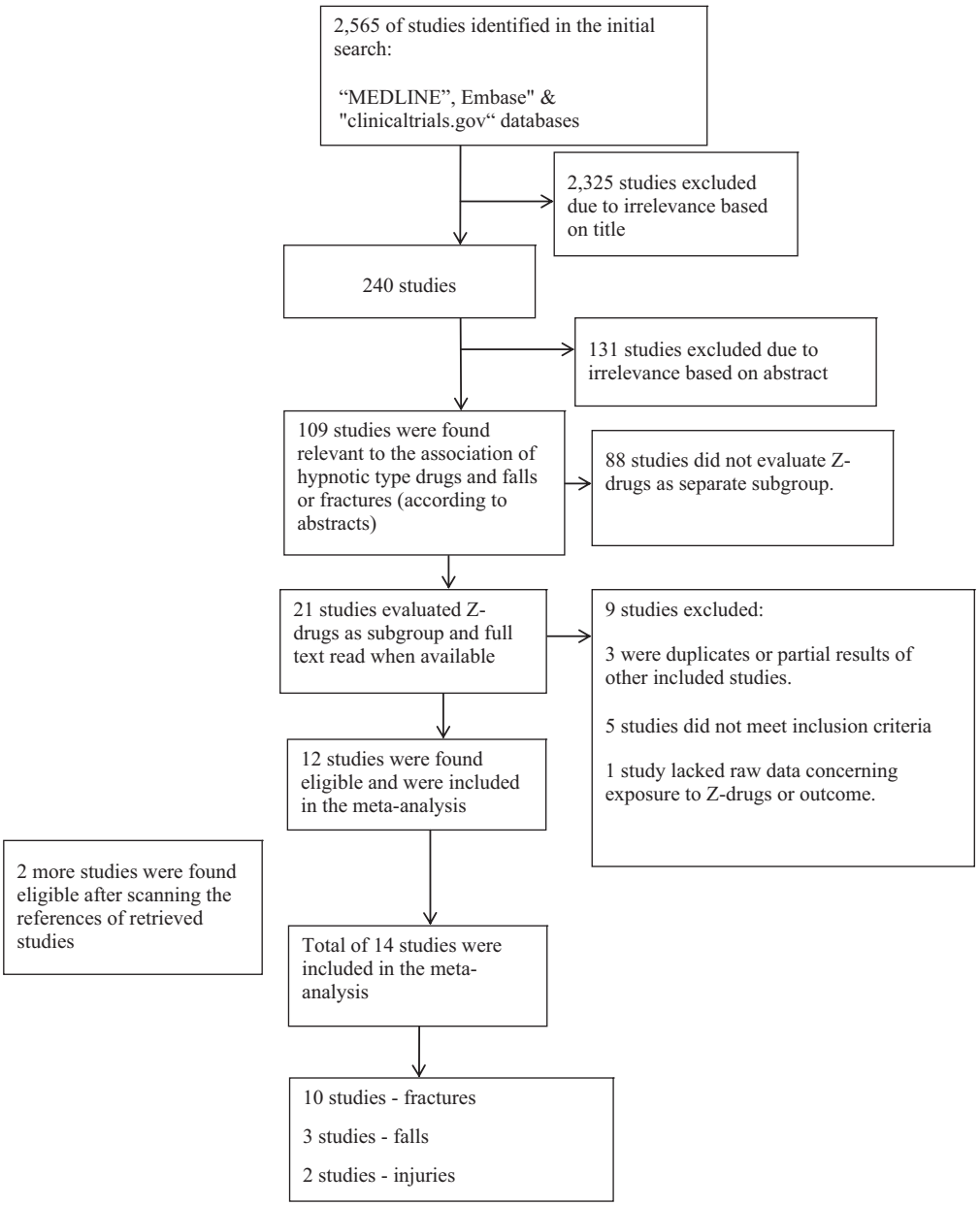

Figure 1. Flow diagram of systematic literature review.

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included in the meta-analysis are presented in Table 1 and Supplementary Table 1.

Z-hypnotics and fractures

The analysis concerning fractures included ten studies with 830,877 subjects (146,678 were exposed to Z-drugs). Z-drugs were associated with a statistically significant increased risk for fractures, with evidence of considerable heterogeneity (OR = 1.63, 95% CI: 1.42–1.87, I^2 = 90%), and estimates obtained from case–control studies were similar to those obtained from cohort studies (Figure 2). We identified three studies which contributed substantially to the observed heterogeneity [20, 21, 25], likely due to clinical and methodological differences in the studies. In analysis excluding these studies, exposure to Z-drugs was

Table 1. Main characteristics of studies included in the meta-analysis

References	Design	Exposure	Outcome	Population of control	Quality score[a]
Chang *et al.* (2011)	Case–control	Zolpidem	Falls	Hospitalised	3
Chung *et al.* [25]	Cohort study	Zolpidem	Injuries and fractures	Cohort	7
Kang *et al.* [15]	Case-crossover	Zolpidem	Fractures	Case-crossover	6
Kolla BP *et al.* (2013)	Cohort study	Zolpidem	Falls	Patients prescribed but not treated with zolpidem	6
Lai MM *et al.* (2014)	Cohort study	Zolpidem	Injuries	Cohort	5
Lai SW *et al.* (2015)	Case–control	Zopiclone	Hip fractures	Randomly selected matched by age	5
Landi *et al.* [24]	Cohort study	Z-drugs[b]	Falls	Cohort	4
Lin FY *et al.* (2014)	Cohort study	Zolpidem	Hip fractures	Cohort	6
Pierfitte C *et al.* (2001)	Case–control	Zolpidem and zopiclone	Hip fractures	Hospitalised for another reason	5
Tamiya *et al.* (2015)	Case–control	Z-drugs	Fractures	Hospitalised	4
Tang *et al.* [21]	Case-crossover	Zolpidem	Fractures	Case-crossover	6
Vestergaard *et al.* (2008)	Case–control	Z-drugs	Fractures	Randomly selected matched by age	5
Wang PS *et al.* (2001)	Case–control	Zolpidem	Hip fractures	Randomly selected matched by age	5
Zint K *et al.* (2010)	Case–control	Z-drugs	Hip fractures	Matched hospitalised control	2

[a]0 indicates lowest quality, 9 the highest.
[b]Z-drugs: including the exposure of zolpidem, zaleplon and zopiclone or eszopiclone.

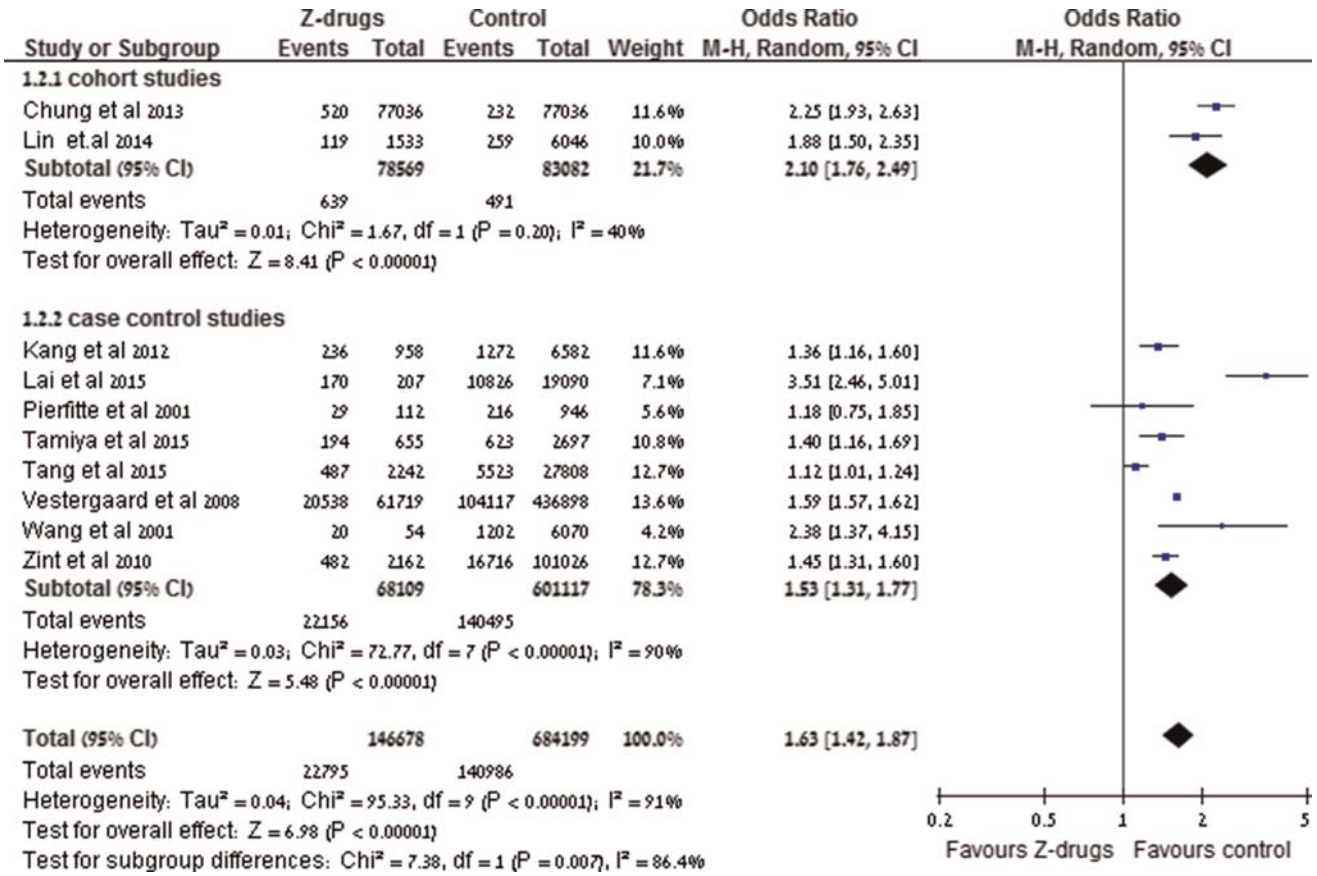

Figure 2. Forest plot of odds ratio for fractures under the exposure of Z-drugs, using a random-effect model.

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similarly significantly associated with fractures, while the heterogeneity decreased substantially (OR = 1.52, 95% CI: 1.39–1.66, I^2 = 58%, 191,598 included) (Supplementary Figure S1).

Z-hypnotics and falls

Three trials, with a total of 19,505 participants (5,269 exposed to Z-drugs), were included in the analysis of the risk for falls with Z-drugs. Z-drugs were not associated with a statistically significant increase in the risk for falls, however, there was a trend suggesting an increased risk and there was evidence of considerable heterogeneity (OR = 2.40, 95% CI: 0.92–6.27, I^2 = 95%) (Figure 3).

Z-hypnotics and injuries

Data on injuries was available only for zolpidem. Two studies were included in the subgroup analysis assessing the risk for injuries following exposure to zolpidem, with a total number of 160,502 participants included (78,322 were exposed to zolpidem). Z-drugs were associated with a statistically increased risk for injuries, with no evidence of heterogeneity (OR = 2.05, CI 95%: 1.95–2.15, I^2 = 0) (Figure S2).

Subgroup and sensitivity analyses

We performed subgroup analyses to estimate the risks for fractures with zolpidem alone and with Z-drugs other than zolpidem (Supplementary Figures S3 and S4). Both the zolpidem, as well as the other Z-drugs, were found to be associated with a statistically significant increased risk for fractures (OR = 1.39, 95% CI: 1.15–1.67, I^2 = 93%; and OR = 1.63, 95% CI: 1.01–2.62, I^2 = 88%, respectively).

In order to estimate the effect of insomnia as a potential confounder, we performed a subgroup analyses for studies which included a control group diagnosed with insomnia. This analysis resulted in an attenuated, though still statistically significant risk increase for fractures with Z-drugs exposure (OR = 1.28, 95% CI: 1.08–1.53, I^2 = 71%; Figure S5).

We performed additional subanalysis to evaluate whether results differed in studies performed in the community and in inpatients. Only one study reporting on fractures was performed in hospitalised patients. This study reported a statistically significant 40% increase in the risk for fractures with Z-drugs. This effect size was numerically smaller, but not statistically significantly different, compared to the community studies, which reported an overall increase of 67% in the risk for fractures (Figure S6).

As studies differed in the type of fractures evaluated as outcome, we preformed a subanalysis comparing the reported association in studies evaluating the risk for hip fractures and studies evaluating all fractures. No substantial differences were found in this analysis (Figure S7). While the precise definition of injury also differed between studies, subgroup analysis was not feasible due to the small number of studies and absence of injury specific data, including traumatic brain injury.

Subanalysis of fractures restricted to studies of Z-drugs in older adults (age > 65) resulted in a similar estimate of risk of fractures as the overall analysis (OR = 1.70, 95% CI: 1.36–2.12, I^2 = 71%; Figure S8).

Using the ROBINS-I tool to assess study quality, most of the studies were graded 'serious risk of bias' due to limitations in their ability to control for all potentially confounding factors. In the analysis of results by quality, studies were designated 'high-quality' if they scored ≥6 on

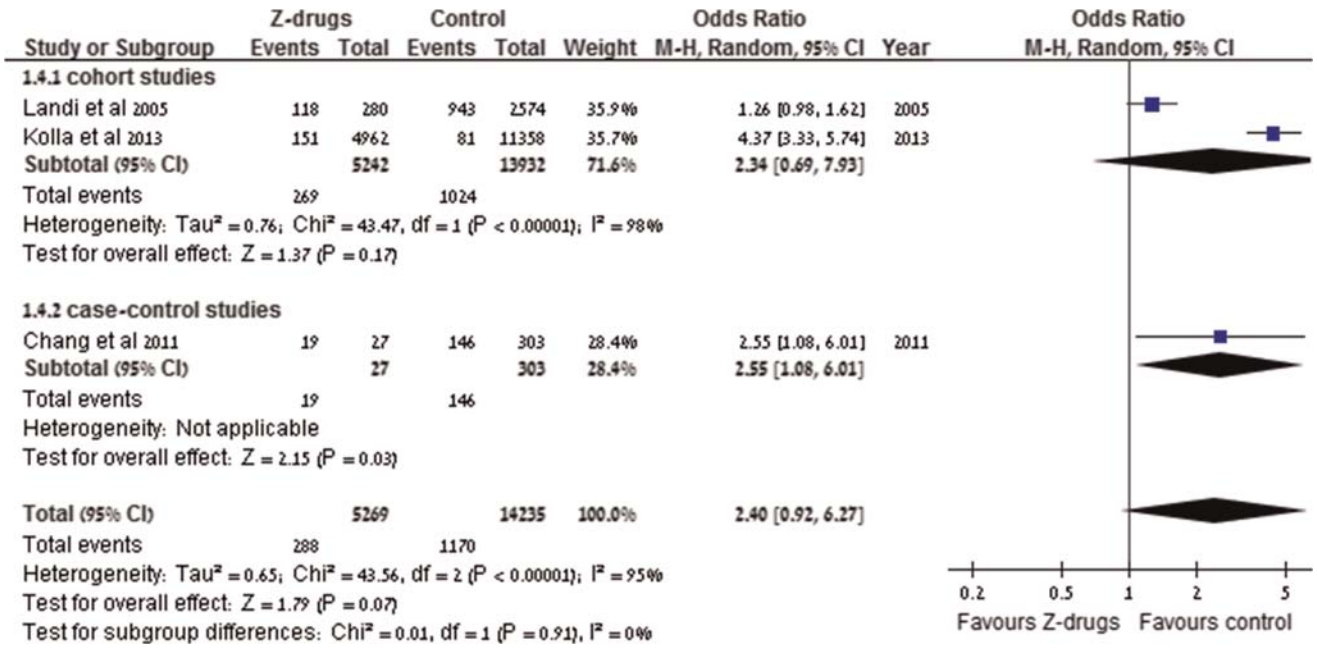

Figure 3. Forest plot of odds ratios for falls under the exposure to Z-drugs, using a random-effect model.

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the NOS, had ≤1 item indicating bias in Robans, and had ≤1 domain with serious risk of bias on the ROBINS-I tool. Three of the studies were included in the high-quality group, while the seven others were designated 'low-quality'. In both groups Z-drugs use was associated with a statistically significant increase in the risk for fractures, however, in the high-quality group the size of the association was more moderate (OR = 1.40, 95% CI 1.07–1.84), compared to that observed in the lower quality studies (OR = 1.83, 95% CI 1.56–2.14). (Figures S9 and S10).

A funnel plot was created based on the studies included in the meta-analysis of fractures. Visual inspection of the funnel plots revealed no indication of publication bias in this analysis (Figure S11).

Discussion

To our knowledge, this is the first meta-analysis assessing the links between Z-drugs as a class and the risk for fractures, falls and injuries. We found that exposure to Z-drugs is associated with a >60% increase in the risk for fractures, that exposure to zolpidem is associated with a doubling of the odds for injuries, and a trend suggesting exposure to Z-drugs may be associated with a doubling of the odds for falls.

Our findings mirror reports of previously published meta-analyses, evaluating the association between BZDs and the risk for fractures and falls (OR ranging between 1.48 and 1.6 [22, 23]). However, we did not perform a direct comparison of the reported risk for these outcomes between Z-drugs and BZDs.

The absence of a statistically significant association between Z-drugs and falls, despite a trend suggesting more than doubling of odds, is likely the result of insufficient power, as only three relatively small studies reported results for this outcome. Additionally, compared to fractures and injuries, data on falls are more often based on self-report (such as in Landi *et al.* [24]). Self-reported outcomes are more prone to imprecision, thus reducing the ability to detect existing effects, and Z-drugs users may be less likely to recall a fall. It is also possible the link between Z-drugs and fractures could be mediated by non-fall related events, such as road accidents [25]. Lastly, as the studies were observational, the comparison groups included some people using other hypnotic agents known to increase the risk of falls, such as BZDs, thus potentially masking the risk associated with Z-drugs.

Though all three studies included in the analysis of Z-drugs and falls pointed towards an increased risk for falls with Z-drugs, there was significant heterogeneity between the studies in the point estimate of this risk, and we therefore utilised a random-effect model to pool these estimates. Using this model reduces the precision of the estimated risk and the ability to establish a statistically significant result [19]. The heterogeneity in the observed effect, could be the result of methodological differences in the terminology of the outcome, as differences in the definition of fall lead to variable results [26].

The precise definition of injuries and of fractures used in the various studies varied with study design and data source as well. We addressed variation in study design, and evidence of heterogeneity, by employing random-effects models, by stratifying analysis according to study type (case–control and cohort), specific Z-drug (zolpidem vs non-zolpidem), study population (hospitalised and community setting), and study quality. The results of all models supported our main results, indicating an increased risk with exposure to Z-drugs.

Our analysis included an assessment of the association of zolpidem in specific with fractures and injuries. Zolpidem is a commonly used Z-drug in the UK, accounting for over 722,000 prescriptions dispensed annually [4]. There are some pharmacodynamic differences between zolpidem and other Z-drugs [5, 27], however, our analysis revealed similarly increased risks for fractures under the influence of zolpidem and other Z-drugs.

The results of our analysis indicate an association between exposure to Z-drugs and the risk for fractures and injuries, and a likely, though statistically insignificant, association with the risk for falls. These results can most likely be explained by the CNS effects of these medications, which include drowsiness and impairments in gait, as well as negative effects on vigilance and cognitive function [10], and are similar to the effects observed with BZDs [11].

The possibility that the associations observed in our meta-analysis are the result of confounding by indication, should also be considered. As the studies identified in our systematic review were all observational, it is difficult to differentiate the effect of the drugs and the effects of insomnia [28, 29]. However, a number of studies included in our analysis employed various methods to control for this risk, and nevertheless found an increase in risk. Additionally, our analysis indicated this risk is observable also when focusing on the high-quality studies with relatively low risk for bias. Lastly, our analysis restricted to studies using a control group with insomnia, also found a statistically significant increased risk with Z-drugs.

Other notable potential confounders are dementia and delirium. The majority of the included studies addressed this issue, using various measures. These studies nevertheless reported an increased risk for the examined outcomes under the exposure of Z-drugs. Furthermore, as differential use of Z-drugs among participants with dementia or delirium would likely be related to differences in insomnia, such a confounding effect is less likely in studies employing a control group with insomnia.

Another potential limitation of our meta-analysis is that we did not evaluate the effect of the drug formulation on the observed outcomes. Extended-release formulations may lead to longer lasting effects, including drowsiness and impairment in gait, which in turn could increase the risk for fractures. However, a crossover study assessing the impact of zolpidem extended-release 12.5 mg on next-day cognitive

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and psychomotor performance did not report a statistically significant difference compared with immediate release zolpidem [30].

Lastly, it has been shown that the effects, and the elimination, of Z-drugs are related to gender and age. Most of the studies included in our meta-analysis did not provide data on outcomes by gender or by age. Kang *et al*. reported that the increased risk associated with zolpidem was modified by age, such that over the age of 85 the risk for fractures among zolpidem users increased by more than 300%. This elevation can be explained by the frailty and sensitivity of older adults, as well as by reduced metabolism and elimination of the drug. Additional studies are needed to further evaluate age and gender dependent changes in the effects of Z-drugs.

Conclusions

In this meta-analysis, we evaluated the association between Z-drugs and the risk for fractures, falls and injuries. Our results show that Z-drugs are associated with an increased risk for fractures and injuries, and a non-statistically significant trend suggesting a doubling in the odds for falls. Given the widespread use of these medications, these findings are reason for concern. Physicians should be aware of the potential risks of Z-drugs use, especially among older patients, and consider limiting the treatment of Z-drugs when possible. Additionally, these finding suggest that the regulatory processes governing medication approval should be reviewed. The evaluation of these medications received prior authorisation was likely insufficient to fully evaluate their potential safety implications, considering current patters of use. Notwithstanding, additional research is warranted evaluating these associations—especially concerning the link to falls and injuries as they have been evaluated by relatively few studies.

Key points

- Z-drugs are commonly prescribed and are perceived to be safer than benzodiazepines, however, data on their safety is limited.
- The results of this study suggest that Z-drugs are associated with an increased risk for fractures, falls, and injuries in comparison to non-users.
- Physicians should be aware of the potential risks of Z-drugs use, especially among older patients.
- Studies reporting on safety outcomes with Z-drugs are limited and heterogenous, additional research of their safety is needed.

Supplementary Data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Conflict of interest

None.

Funding

None.

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