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Original Study

Zopiclone Use and Risk of Fractures in Older People: Population-Based Study

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A B S T R A C T

Objectives: The primary objective was to evaluate the risk of fractures associated with use of zopiclone, a new Z-hypnotic, in a population-based cohort of older people in New Zealand (NZ) in a real-world setting. The secondary objective was to examine a nonlinear relationship with age and risk for fractures in zopiclone users.
Design: Population-based cohort study with a case-crossover design.
Setting: A nationwide representative sample of New Zealanders aged 65 years and older sourced from the pharmaceutical collections and hospital discharges.
Participants: 74,787 older individuals with a first-time fracture between January 1, 2005, and December 31, 2015, were analyzed using a case-crossover design for fracture risk with zopiclone use.
Measurements: Prescription records (2005–2014) of zopiclone were sourced from NZ Pharmaceutical Collections (Pharms). The first-time coded diagnosis of fracture was extracted from the National Minimal Datasets. Datasets were linked by a unique patient identifier to set up case-crossover designs. Relative risks (RRs) of fracture associated with zopiclone was calculated using conditional logistic regression. A varying-coefficient conditional logistic model was employed to examine the influence of age as a risk factor for fractures.
Results: The risk of fracture associated with zopiclone is higher [RR = 1.45, 95% confidence interval (CI) = 1.37–1.55], compared to non-use. The increased risk of fracture associated with zopiclone [adjusted relative risk (ARR) = 1.36, 95% CI = 1.28–1.45] remained significant after adjusting for concomitant use of alpha blockers, antipsychotics, beta blockers, benzodiazepines, and tricyclic antidepressants. The varying coefficient model showed that the risk of fracture increases significantly and monotonically with age.
Conclusion: The results support that the magnitude of the risk of fracture is higher with use of zopiclone compared to non-use. Prescribers must be aware that the relationship between age and fracture risk is nonlinear, and the oldest old are highly vulnerable to fractures with zopiclone use.

Fractures contribute to a significant burden on societal economy, morbidity, and mortality in older people.[1–3] Several classes of medicines have been implicated to contribute to increased risk of fractures in older people.[4] These include alpha blockers, beta blockers,[5] antipsychotics,[6] antidepressants,[6] hypnotics,[7] and diuretics. Interestingly, benzodiazepines are overrepresented as a medication class contributing to fractures in older people.[8–12] The Z-hypnotic drugs are increasingly being used to treat insomnia in older people because of their perceived safety relative to traditional benzodiazepines.[10] However, recent epidemiologic studies have reported increased risk of fractures in patients taking zolpidem, but the results have been inconsistent.[13–15]

Zopiclone, a cyclopyrrolone derivative, is a short-acting Z-hypnotic that is structurally unrelated to benzodiazepines. Its pharmacologic profile is similar to that of the short-acting benzodiazepines, and peak plasma levels are attained in less than 2 hours. Zopiclone has an elimination half-life of approximately 5 hours, and it is important to note that in older people, the elimination half-life is prolonged to approximately 7 hours.

A recent pharmacoepidemiologic study in New Zealand highlighted that the use of zopiclone rose sharply between 2005 and 2013, by almost 42%.[16] Hence, it is pertinent to examine the risk of fractures posed by zopiclone in older people. A recent meta-analysis found that zolpidem may increase the risk of fractures.[17] We hypothesized that

The authors declare no conflicts of interest.

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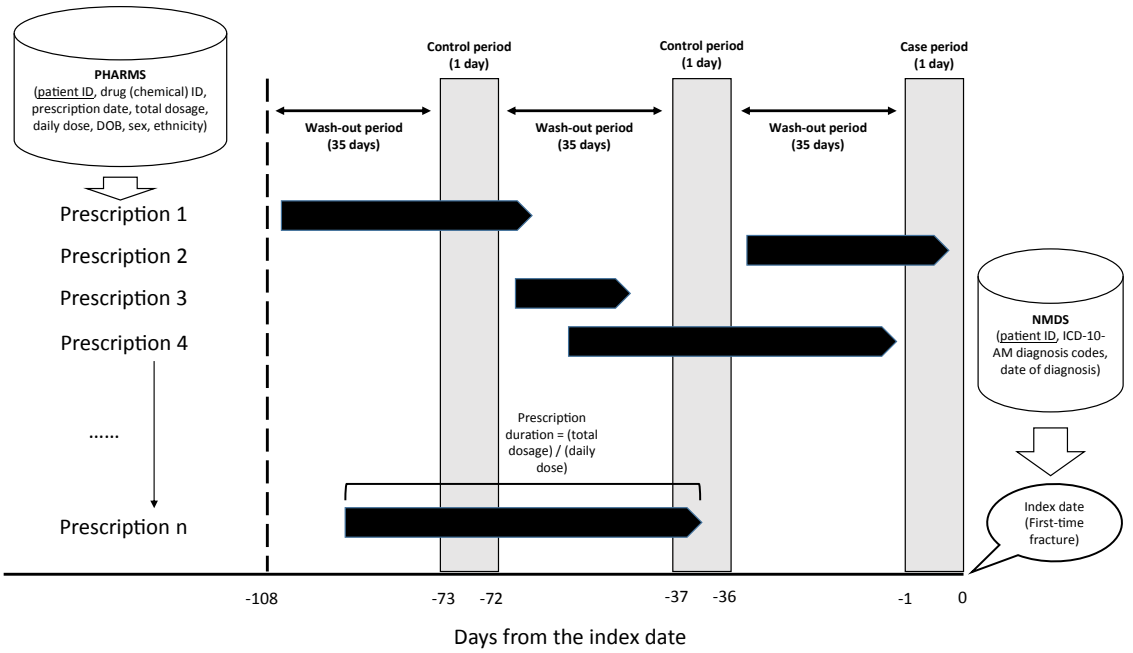

Fig. 1. Case-crossover design and data sources.

this may be a class effect, and z-hypnotics such as zopiclone will also increase the risk of fractures in older people. To answer our hypothesis, we performed a nationwide case-crossover analysis to examine the association of fracture with zopiclone in a large population-based cohort of older (aged 65 years and older) New Zealanders.

Methods

Ethical approval was obtained from the Human Ethics Research Committee (approval number HD 16/022).

Data Source

The New Zealand Ministry of Health maintains national collections of prescription use, hospital discharges, and mortality data for community and hospital. Individual records in these national collections include a unique 7-digit alpha-numeric identifier, the National Health Index (NHI) identifier allowing for linking the data collections. Residents in New Zealand who access health and disability support services across New Zealand are assigned an NHI number. Patient-level data with an encrypted NHI enables patient records to be linked between the various national collections while still protecting the

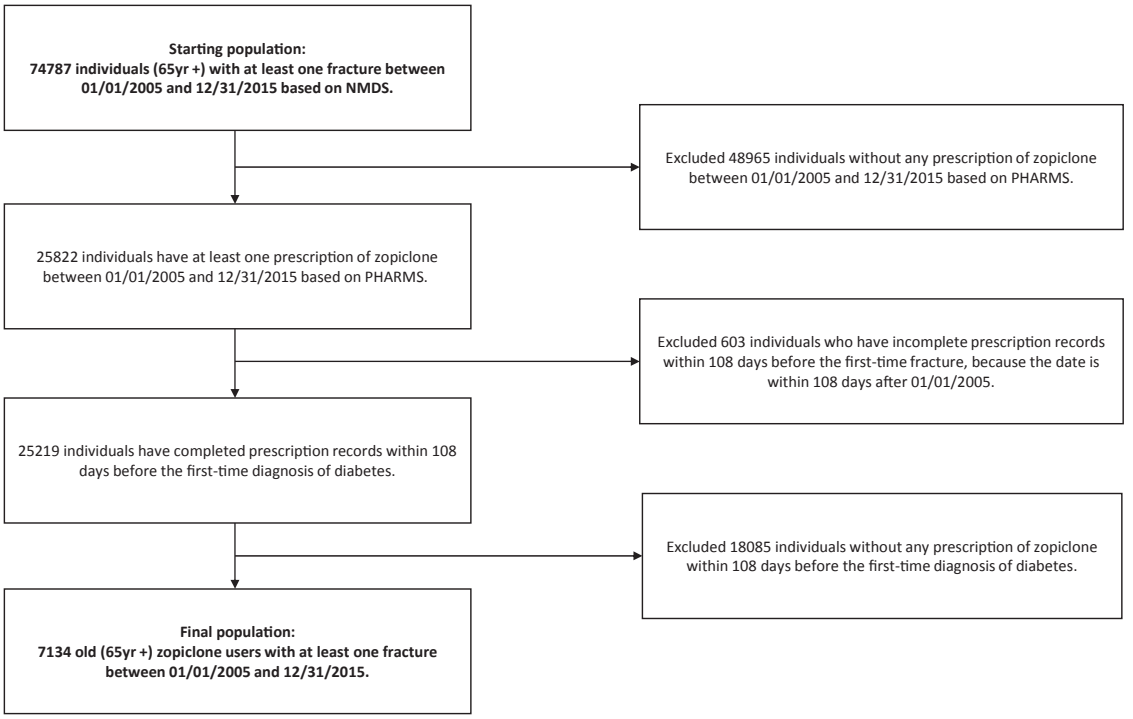

Fig. 2. Process of case selection.