Study finds moderately elevated fracture risk following use of sedative–hypnotics

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Global consumption data show that there is an increasing trend of sedative–hypnotic prescriptions, especially in more developed affluent countries and regions, such as Hong Kong. Researchers in the Center for

Safe Medication Practice and Research (CSMPR) of the Department of Pharmacology and Pharmacy in the LKS Faculty of Medicine, the University of Hong Kong (HKUMed), conducted a study investigating the connection between particular sedative–hypnotics and the risk of bone fractures on more than 6 million individuals in 11 countries/ regions.

The findings revealed that the use of certain sedative–hypnotic medications was moderately associated with an increased risk of bone fractures, estimating at 30% to 40%. The study highlights the importance of carefully evaluating the benefits and risks when prescribing sedative–hypnotics, particularly for patients with a high risk of bone fracture. The findings were published in *Sleep Medicine Reviews*.

Sedative–hypnotics are drugs that are commonly used to reduce anxiety and tension, and improve sleep quality. They can be categorized into three generations: barbiturates and chloral hydrate, benzodiazepines (BZD), and z-drugs. Numerous studies show a potential risk of bone fractures following the use of sedative–hypnotics.

The risk may be related to certain side effects of these medications, such as dizziness, drowsiness, and hypotension, which can increase the likelihood of falls and injuries. However, the existing evidence is inconclusive, possibly due to the complex mechanisms and various factors that can contribute to fractures.

In view of this, researchers from CSMPR conducted a systematic review and performed a meta-analysis to synthesize the existing evidence and determine the association between sedative–hypnotic use and the risk of fractures.

The research team examined 20 observational studies conducted in 11 countries/ regions, involving more than 6 million individuals. The studies

comprised six cohort studies, eight case-control studies, and six case-crossover studies, one of which also incorporating a self-controlled case series design. Eleven of the studies were included in a subsequent meta-analysis. All the studies were rated as good quality, receiving scores ranging from 7 to 9 out of 10 stars, according to the Newcastle-Ottawa Scale, a widely recognized instrument for assessing the quality of studies.

The review found that 18 out of the 20 studies showed a significant association between the use of sedative–hypnotic medications and an increased risk of fractures. A meta-analysis estimated that sedative–hypnotic users have a 30% higher risk of fractures compared to non-users. Specifically, a pooled analysis showed that the use of BZD was associated with a 32% higher risk of hip fractures, and the use of z-drugs was linked to a 41% higher risk of fractures at any site in the body. The risk was similar for both long-acting and short-acting sedative-hypnotics.

Despite limitations such as unmeasured confounding effects, the study highlights the rare but possible side effect of fractures from the use of sedative–hypnotic medications. The underlying cause of the elevated fracture risk needs further research, but falls likely contribute to this association.

The study suggests that patients who have a higher risk of fractures, such as those aged 85 years or above or living alone, should be prescribed sedative–hypnotics with caution. Appropriate counseling should be provided to patients before prescribing these medications, and fall and fracture risks should be monitored and mitigated. Taking preventive measures to prevent falls by sedative–hypnotic users can also help reduce the risk of fracture.

"With the increasingly prevalent use of sedative-hypnotics worldwide,

including off-label use, we believe a more careful clinical assessment should be conducted for patients based on the overall safety profile of the specific sedative–hypnotic agents before prescription," said Dr. Francisco Lai Tsz-tsun, assistant professor in the Department of Pharmacology and Pharmacy and the Department of Family Medicine and Primary Care, School of Clinical Medicine, HKUMed, also the senior author of the study.

More information: Chong Xu et al, Sedative-hypnotics and osteoporotic fractures: A systematic review of observational studies with over six million individuals, *Sleep Medicine Reviews* (2023). DOI: 10.1016/j.smrv.2023.101866

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