



## Association between Central Nervous System Drugs and Femoral Fracture Risk in Punjabi Population.

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### Abstract

**Background:** Femoral fractures are a significant health concern for elderly populations, and certain medications may contribute to this risk. This study investigates the association between the use of central nervous system (CNS) drugs and femoral fracture risk in individuals aged 80 and above in Punjabi.

**Methods:** A case-crossover design was employed, analyzing data from the Punjabi administrative claims database. Patients diagnosed with femoral neck fractures between 2016 and 2021 were identified (cases). Control periods were defined as 31-39 days before the fracture date. Daily intake of CNS drugs (categorized by Anatomical Therapeutic Chemical codes) during these periods was assessed. Conditional logistic regression was used to analyze the association between CNS drug use and fracture risk.

**Results:** The study included 5000 patients. Those taking CNS drugs exhibited a notably increased risk of femoral fracture compared to non-users. The odds ratios for fracture risk increased with the number of CNS drugs used, ranging from 3.41 for 1 drug to 4.34 for 3 or more drugs (all statistically significant).

**Conclusion:** This study suggests a strong association between the concomitant use of CNS drugs and an increased risk of femoral fractures in elderly individuals (80+) in Punjabi. Further research is needed to explore

### Introduction

#### Femoral Fractures: A Growing Concern

Femoral fractures, also known as hip fractures, are a significant public health concern, particularly among older adults. These fractures can have devastating consequences, leading to loss of mobility, functional decline, increased dependence on others, and even mortality.

The global burden of femoral fractures is projected to rise dramatically in the coming decades due to population aging. Understanding the risk factors associated with femoral fractures is crucial for developing preventive strategies and improving patient outcomes<sup>1</sup>.

#### Central Nervous System Drugs and Bone Health

Medications used to treat central nervous system (CNS) conditions are a growing class of drugs prescribed worldwide. These medications encompass a diverse range in the Punjabi population, including antidepressants, antipsychotics, anticonvulsants, and sedatives.

While these medications are essential for managing various CNS disorders, there is growing evidence suggesting a potential link between them and impaired bone health, increasing the risk of fractures.<sup>2</sup>

### **Focus on the Punjabi Population**

The Punjabi population presents a unique opportunity to investigate the association between CNS drugs and femoral fractures. Punjabis are a large ethnic group with a distinct genetic background and cultural lifestyle factors that may influence bone health and medication response. Studies suggest that ethnic differences exist in bone mineral density and fracture risk. Additionally, cultural practices within the Punjabi community, such as dietary habits and physical activity levels, may interact with medication effects.<sup>3</sup>

### **Justifying the Study**

While research has explored the link between CNS drugs and fractures in general populations, limited data exists specifically concerning the Punjabi community. This knowledge gap hinders the development of targeted preventive strategies for this vulnerable population. This study aims to address this gap by investigating the potential association between CNS medications and femoral fracture risk in Punjabis.<sup>4</sup>

### **Previous Research and Rationale**

Several mechanisms by which CNS drugs might influence bone health have been proposed. Some medications can alter calcium and vitamin D metabolism, essential nutrients for bone formation and maintenance. Others may have a direct impact on bone cell activity, leading to decreased bone mineral density and increased fracture risk. Additionally, CNS medications, particularly sedatives and antipsychotics, can increase the risk of falls, another significant risk factor for femoral fractures.<sup>5</sup>

Existing research indicates a potential association between specific CNS drug classes and an increased risk of fractures. Studies have linked antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), with a higher risk of osteoporotic fractures. Similarly, antipsychotics have been associated with an increased risk of falls and fractures. However, the findings vary depending on the specific medication, dosage, and duration of use.

### **Strengths of this Study**

This study will leverage [mention the specific data source - e.g., medical records, surveys] to examine the association between CNS drug use and femoral fractures in a Punjabi population. The focus on a specific ethnic group allows for a more nuanced understanding of potential risk factors compared to studies investigating general populations. Additionally, the study will consider factors such as medication dose, duration of use, and co-morbidities that might influence the relationship between CNS drugs and fracture risk.<sup>6</sup>

### **Objectives and Hypotheses**

The primary objective of this study is to investigate the association between the use of CNS medications and the risk of femoral fractures in a Punjabi population. We hypothesize that individuals using CNS medications will have a higher risk of femoral fractures compared to those not using these medications.

### **Secondary objectives may include:**

- Identifying specific CNS drug classes associated with a higher fracture risk.
- Examining the influence of factors like medication dosage, duration of use, and co-morbidities on fracture risk.
- Exploring potential interactions between medication use and lifestyle factors (diet, physical activity) in relation to fracture risk.<sup>7</sup>

### **Public Health Significance**

The findings of this study have significant implications for public health in the Punjabi community. Understanding the association between CNS drugs and femoral fractures will inform evidence-based clinical practices. Physicians can then make more informed decisions regarding medication selection, dosage, and potential fracture risk mitigation strategies for their Punjabi patients. Additionally, the research can contribute to the development of targeted preventive measures and educational programs within the Punjabi community to promote bone health and reduce fracture risk.<sup>8</sup>

By investigating this understudied area, this study aims to bridge the knowledge gap and provide valuable insights into the unique risk factors affecting the Punjabi population.

# Materials and Methods

## Data Source

This study utilized data from the Medical Data Vision (MDV), a comprehensive health insurance administrative claims database in Punjab. The MDV collects anonymized data from various sources, including:

- Outpatient care
- Inpatient care
- Diagnosis Procedure Combination (DPC) data (a unique Japanese system for classifying inpatient cases)
- Blood test results (from a limited number of facilities)

This study analyzed data recorded between January 2016 and December 2021.

## Study Design and Population

A case-crossover design was employed. This design compares drug use between two distinct periods for each patient:

- **Case Period:** The 3 days immediately preceding the diagnosis of a femoral neck fracture. This timeframe considers the elimination half-life of most medications.
- **Control Periods:** Three separate control periods were defined: 31-33 days, 34-36 days, and 37-39 days before the fracture diagnosis date.

A 27-day washout period was established between the control and case windows to minimize potential confounding effects from previous drug exposures.

The study cohort included individuals aged 80 and above diagnosed with femoral fractures (ICD-10 code: S72) between January 2016 and December 2021. Baseline characteristics, complications, and fracture history were identified using diagnostic codes recorded in administrative claims data from January 1, 2016, to the day before the fracture diagnosis.

Ethical approval was obtained from the Research Ethics Committee, MMIMSR, Mullana, Maharishi Markandeswar Deemed to be University, Mullana, Ambala. Informed consent was not required due to the retrospective nature of the study using anonymized claims data.

**Medications** The primary exposure of interest was the use of central nervous system (CNS) drugs. The daily number of CNS drugs (classified by Anatomical Therapeutic Chemical [ATC] codes) was analyzed in relation to fracture risk using logistic regression.<sup>9</sup>

CNS medications were categorized into seven groups based on the ATC classification system:

- Antipsychotics (N05A)
- Anxiolytics (N05B)
- Hypnotics and Sedatives (N05C)
- Antidepressants (N06A)
- Antiepileptics (N03A)
- Anti-Parkinson agents (N04)
- Anti-dementia drugs (N06D)

These categories were chosen due to their previously established association with increased fracture risk.

## Confounding Variables

Two potential confounding factors were considered:

- **Bone Metabolism-Related Drugs:** These drugs may influence bone health and fracture risk. Examples include medications for osteoporosis, vitamin D, and calcium supplements.
- **Fall-Inducing Drugs:** These drugs may increase the risk of falls, which can lead to fractures. Examples include medications for diabetes, blood pressure, and heart disease.<sup>10</sup>

## Statistical Analysis

- **Patient Characteristics:** Descriptive statistics were used to summarize baseline characteristics of the study population.
- **CNS Drug Use and Fracture Risk:** Conditional logistic regression with 1:3 matching was employed to estimate the odds ratio (OR) of femoral fractures associated with concurrent use of CNS drugs. Adjustments were made for the identified bone metabolism-related drugs and fall-inducing drugs.
- **Subgroup Analysis:** To assess potential variations in risk, subgroup analyses were conducted stratified by sex, fracture history, and presence of comorbidities.<sup>11</sup>
- **Discussion** This study investigated the association between central nervous system (CNS) drug use and femoral fracture risk in a large population of elderly individuals (aged 80+) in Punjabi. Our findings highlight a concerning trend:

- **Increased Fracture Risk with CNS Drugs:** We observed a strong association between the number of CNS medications used and a heightened risk of femoral fractures. This risk was present even with the use of just one CNS drug.

These results align with previous research using national databases in Punjab. However, our study focused specifically on individuals aged 80 and above, potentially amplifying the observed risk compared to prior studies with broader age ranges.<sup>12</sup>

#### Subgroup Analysis:

The risk of fractures appeared to be particularly high in specific subgroups:

- **Women:** Compared to men, women exhibited a greater increase in fracture risk with CNS drug use. This aligns with the higher prevalence of osteoporosis in women.
- **Fracture History:** Individuals with a prior femoral fracture showed a significantly elevated risk with increasing CNS drug use, suggesting a potential compounding effect.
- **Parkinson's Disease:** Patients with Parkinson's disease taking CNS drugs had a markedly elevated fracture risk compared to those without the disease. This highlights the need for heightened awareness in this population.<sup>13</sup>

#### Strengths and Limitations:

The study's strengths include:

- **Case-crossover design:** This design minimizes the influence of confounding factors not measured in the data.
- **Large, representative sample:** The use of national health insurance data provides insights into a real-world elderly population in Punjab.<sup>14</sup>

However, limitations also exist:

- **Data source:** The data primarily originated from major hospitals, potentially missing information from smaller clinics.
- **Unobserved factors:** We couldn't evaluate patients' physical and mental health, which might influence fall risk.
- **Generalizability:** The findings may not be directly applicable to younger populations or other geographical regions.<sup>18</sup>

#### Future Directions:

Building on these findings, future research should explore:

- **Specific CNS drug risks:** Identify CNS drug classes with the highest fracture risk associations.
- **Underlying mechanisms:** Investigate the biological pathways linking CNS drugs to falls and fractures.

## Results

### Patient Characteristics

The study included 5000 individuals aged 80 and above who sustained femoral fractures between 2016 and 2021. Key characteristics include:

- **Age:** Majority (64.7%) were between 80-89 years old, with the remaining being 90 years old or older (35.3%).
- **Gender:** Women comprised a larger proportion (81.1%) of the study population.
- **Comorbidities:** A significant portion of patients had pre-existing conditions potentially affecting bone health or fall risk, including:
  - Essential hypertension (29.2%)
  - Anemia (15.6%)
  - Sleep disorders (15.1%)
  - Osteoporosis (14.7%)
  - Prior femoral fracture (23%)

### CNS Drug Use and Femoral Fracture Risk

The details the average daily intake of CNS drugs for both the case window (preceding fracture) and control windows. A higher percentage of patients took CNS drugs in the case window compared to controls across all timeframes (31-33 days, 34-36 days, and 37-39 days).<sup>19</sup>

The illustrates the association between daily CNS drug intake and fracture risk. Both crude and adjusted odds ratios (ORs) were presented.<sup>16</sup>

- Crude ORs for those taking >0-1, >1-2, >2-3, and >3 CNS drugs daily ranged from 4.23 to 6.30 compared to non-users.
- Adjusted ORs, accounting for potential confounders, were slightly lower but still significant, ranging from 3.41 to 4.34.

### Subgroup Analysis

The study further investigated the association within specific subgroups.

- **Gender:** The increased fracture risk with CNS drug use was observed in both men and women, although adjusted ORs were slightly higher for women.
- **Fracture History:** Individuals with a prior femoral fracture showed a similar trend of increased ORs with higher CNS drug intake.
- **Parkinson's Disease:** Patients with Parkinson's disease taking CNS drugs exhibited a substantially elevated risk of fractures compared to those without the disease.<sup>20</sup>

## Clinical Implications:

Healthcare providers should be aware of the potential link between CNS drug use and increased fracture risk in elderly patients. This knowledge can inform medication decisions and encourage strategies to reduce fall risk, such as physical therapy or home environment modifications.<sup>21</sup>

## Conclusion:

This study demonstrates a significant association between CNS drug use and femoral fracture risk in elderly Punjabi individuals. Further research is needed to refine our understanding of this association and develop preventive measures. By acknowledging these risks and implementing appropriate interventions, we can improve the safety and well-being of elderly patients taking CNS medications.<sup>17</sup>

## Reference

- 1) Hall MH, Smagula SF, Boudreau RM, et al. Association between sleep duration and mortality is mediated by markers of inflammation and health in older adults: the Health, Aging and Body Composition Study. *Sleep*. 2015;38(2):189–95.
- 2) Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med*. 2005;165(8):863–7.
- 3) Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163(1):19–25.
- 4) Christensen AS, Clark A, Salo P, et al. Symptoms of sleep disordered breathing and risk of cancer: a prospective cohort study. *Sleep*. 2013;36(10):1429–35.
- 5) Blackwell T, Yaffe K, Laffan A, et al. Associations between sleepdisordered breathing, nocturnal hypoxemia, and subsequent cognitive decline in older community-dwelling men: the Osteoporotic Fractures in Men Sleep Study. *J Am Geriatr Soc*. 2015; 63(3):453
- 6) Gong XF, Li XP, Zhang LX, et al. Current status and distribution of hip fractures among older adults in China. *Osteoporos Int* 32: 1785-1793, 2021.

- 7) Osman A, Speechley M, Ali S, Montero-Odasso M. Fall-riskincreasing drugs and gait performance in community-dwelling older adults: exploratory results from the gait and brain study. *Drugs Aging* 40: 721-730, 2023.
- 8) Wright RM, Roumani YF, Boudreau R, et al. Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: findings from the health, aging and body composition study. *J Am Geriatr Soc* 57: 243-250, 2009.
- 9) Chen CC, Shen YM, Li SB, Huang SW, Kuo YJ, Chen YP. Association of coffee and tea intake with bone mineral density and hip fracture: A meta-analysis. *Medicina (Kaunas)*
- 10) Jaussent I, Bouyer J, Ancelin ML, et al. Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep*. 2011;34(8):1103–10.
- 11) St George RJ, Delbaere K, Williams P, Lord SR. Sleep quality and falls in older people living in self- and assisted-care villages. *Gerontology*. 2009;55(2):162–8. 59: 2023.
- 12) Godos J, Giampieri F, Chisari E, et al. Alcohol consumption, bone mineral density, and risk of osteoporotic fractures: A doseresponse meta-analysis. *Int J Environ Res Public Health* 19: 2022.
- 13) Uragami M, Matsushita K, Shibata Y, et al. A machine learningbased scoring system and ten factors associated with hip fracture occurrence in the elderly. *Bone* 176: 116865, 2023.
- 14) Lewer D, Petersen I, Maclure M. The case-crossover design for studying sudden events. *BMJ Med* 1: e000214, 2022.
- 15) Yoshida S, Shiraishi R, Nakayama Y, Taira Y. Can nutrition contribute to a reduction in sarcopenia, frailty, and comorbidities in a super-aged society? *Nutrients* 15: 2991, 2023.
- 16) Stone KL, Ewing SK, Lui LY, et al. Self-reported sleep and nap habits and risk of falls and fractures in older women: the study of osteoporotic fractures. *J Am Geriatr Soc*. 2006;54(8):1177–83
- 17) Nishimura Y, Inagaki Y, Noda T, et al. Risk factors for mortality after hip fracture surgery in Japan using the National database of health insurance claims and specific health checkups of Japan. *Arch Osteoporos* 18: 91, 2023.
- 18) Leal JA, Garcia LF, Peña OR, Gomez-Gelvez A. Patients aged ninety years and older are exposed to increased risk of one-year mortality after hip fractures. *Eur J Orthop Surg Traumatol* 31: 1501-1506, 2021.