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A Scoping Review to Assess Risk of Fracture Associated with Anxiolytic Medications

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ABSTRACT

Introduction. Recent research has focused on evaluating the impact of pharmalogical sources on fracture risk. The purpose of this study was to review the literature on anxiolytic medications that may be associated with an increased risk of fracture.

Methods. A search was conducted in MEDLINE and Embase databases to identify primary clinical studies of patients who sustained a fracture while prescribed anxiolytic medications and were published prior to July 2021. Anxiolytics defined by ATC Class N05B, beta blockers, and zolpidem were included. The search terms consisted of variations of the following: ("Psychotropic Drugs" or MeSH terms) AND ("Fracture" or MeSH terms).

Results. Of 3,213 studies, 13 (0.4%) met inclusion criteria and were evaluated. Fractures associated with benzodiazepine were reported in 12 of 13 studies; the highest risk occurred in patients aged 60 years and older (RR=2.29, 95% CI (1.48-4.40)). The ATC Class N05B showed an increased fracture risk for those ≤ 55 years of age that differed by sex: for men (RR=5.42, 95% CI(4.86-6.05)) and for women (RR=3.33, 95% CI (3.03-3.66)). Zolpidem also showed an increase fracture risk (RR=2.29, 95% CI(1.48-3.56)), but only during the first four weeks of treatment. A relative risk of 0.77, 95% CI(0.72-0.83) was observed for beta blockers.

Conclusions. Fractures are a mainstay of traumatic injuries and are accompanied by economical, physiological, and psychological hardship. With proper assessment and prophylactic measures, fracture risk can be reduced dramatically. Anxiolytic medications have been described widely to increase fracture risk, such as benzodiazepines in 60+ year old patients, and ATC Class N05B anxiolytics increased fracture risk in 55+ year old men and in 55+ year old women. Yet, some studies showed that at low doses, nitrazepam lowered fracture risk. Other anxiolytic medications, such as zolpidem and beta blockers, also showed a decrease in fracture risk. Ultimately, this scoping review helped to illuminate the inconsistency of anxiolytic fracture risk assessment while simultaneously illustrating the necessary steps to guide future research.

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INTRODUCTION

Fractures have a significant impact on physical and psychological function, independence, quality of life, and mortality, and may cause devastating economic consequences for patients and their families.[1-6] In 2021, Blankart, et al.[7] estimated end of life hip fracture patients experienced a hospital stay expenditure of $22,508, which did not include emergency department costs, specialist spending, primary care charges, and pharmacotherapy payments. Ultimately, fractures are expensive events that occasionally can be prevented with assessment of a patient's risk for fracture, counseling, and initiation of appropriate preventative measures. Researchers have began identifying pharmalogical sources that increase fracture risk. In the psychotropic arena, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and antipsychotics have been associated with an elevated fracture risk;[8-10] however, the fracture risk of anxiolytics has been evaluated less than other classes of psychotropic medications.

The class of anxiolytics consists of Z-drugs (zopiclone, eszopiclone, zaleplon, and zolpidem) beta-blockers, and members of the World Health Organization's ATC Class N05B (benzodiazepines, diphenylmethanes, carbamates, dibenzo-bicyclo-octadienes, and azaspirodecanediones).[11,12] In this review, some articles discussed benzodiazepines separate from the entire ATC Class N05B anxiolytics. All members in the class of anxiolytics are utilized to mitigate anxiety-provoking stimuli, but the pharmacologic effects could be accompanied by side effects such as blood pressure fluctuations, cognitive impairment, and delirium, which can lead to falls.[13-15] In the geriatric population, falls cause 95% of hip fractures which may result in decreased long term mobility and nursing home admission.[16] While some psychotrophic medications have been associated with an increased risk of fracture, anxiolytics, which are prescribed more commonly, have not been evaluated systematically. This is unfortunate as research shows an increase in the lifetime prevalence of hospital diagnosed anxiety, anxiolytic drug prescriptions, and self-reported anxiety were 4.4%, 6.2%, and 5.1%, respectively.[17]

Moreover, the prevalence of anxiety may have increased substantially due to the COVID-19 pandemic. Thus, there was a critical need to evaluate and identify anxiolytic medications that may be increasing the risks of fractures in individuals. The purpose of this study was to review the literature on anxiolytic medications and ascertain their association with increased fracture risks.

METHODS

Literature Search. This review utilized the Preferred Reporting Items for Scoping Reviews and Meta-Analyses (PRISMA-ScR)[18] guidelines. Approval from our institutional review board was not required. A research focused, university librarian assisted in the development of the search strategy to identify eligible studies (Appendix 1; appendix is only available online at journals.ku.edu/kjm). A search was conducted of MEDLINE and Embase in July 2021, using the following search terms: ("psychotropic drugs" OR related MESH terms) AND ("fracture" OR related MESH terms). These terms included anti-anxiety agents, anxiolytics, anxiety, medication (benzodiazepine, alprazolam, anthramycin, bromazepam, clonazepam, devazepide, diazepam, flumazenil, flunitrazepam, flurazepam, lorazepam, nitrazepam, oxazepam, pirenzepine, prazepam, temazepam, chlordiazepoxide, clobazam, clorazepate dipotassium, estazolam, medazepam, midazolam, olanzapine,

triazolam), accidental fall, accident, road accident, fracture, and adult. See Appendix 2 for exact search strategy for each database and MESH terms (appendix is only available online at journals.ku.edu/kjm).

Study Eligibility. Inclusion criteria consisted of articles with the following description: English language, human studies, anxiolytic medication use, and fracture risk assessment. Studies with level I-IV evidence were considered for inclusion. Animal, cadaver, duplicate studies found between databases, fractures not associated with anxiolytic medications, expert opinion, and review articles were excluded.

Study Selection and Data Abstraction. All studies were gathered initially by a research focused university librarian. Two researchers independently screened articles based on title, followed by an additional round of screening based on abstracts. If disagreement upon gathered articles occurred, a third member of the research team was consulted. Next, the same two researchers reviewed the full articles and gathered data. No automated tools were implemented in the screening process. Data collection included name of medication, number of patients, number of each sex, age range, mean age, follow-up or length of time to event, and fracture risk. Other data that was extracted included a description of the study and the level of the study. When applicable, reported outcomes were converted to risk ratios according to chapter six in Cochrane's Handbook.[19] A risk of bias assessment for non-randomized studies of interventions was conducted using ROBINS-I.[20]

RESULTS

For the initial literature search, 3,213 articles were identified, of which 0.4 % (13 out of 3,213) met inclusion criteria (Figure 1). Table 1 summarizes the included studies: 76.9% (10/13) were retrospective cohorts, with 92.3% (12/13) level III evidence. Length of time to fracture was not discussed in 46% (6/13) of studies; for the remainder, there were substantial variations regarding timeframe that included, 14 to 180 days. Regarding participant demographics, 38.5% (5/13) did not identify sex, and age ranged from 18 to 60+ years. Table 2 shows results of the bias assessment using ROBINS-I.

Of the medications analyzed, benzodiazepines (labeled as benzodiazepines, specific benzodiazepine, or anxiolytics) were the focus in 92.3% (12/13) of the studies, while ATC Class N05B anxiolytics, beta blockers, and zolpidem were investigated in 38.5% (5/13), 7.7% (1/13), and 7.7% (1/13), respectively. The majority of studies analyzing risk of fracture with benzodiazepine appeared to report increased risk of fracture; however, results were inconclusive. For example, a potential benefit was reported for a low dose of nitrazepam (OR=0.4, 95% CI (0.1, 2.9)), though results were not statistically significant.[26] Conversely, a significant increased risk was reported in a case control study of 60+ year old patients (RR=2.29, 95% CI (1.48-4.40)).[25] Moreover, studies with oxazepam and lorazepam[26] reported wide confidence intervals (95% CI (0.5, 57.2), which merit further investigation. Important details of drug regimen were not reported consistently, and these findings

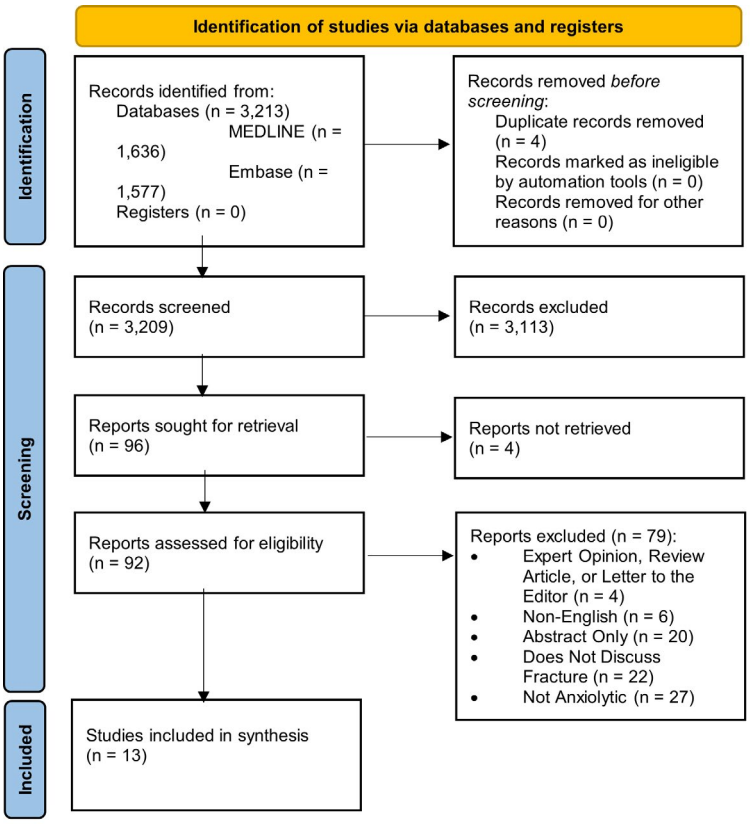

Figure 1. Identification of studies.

may be confounded by dosage. Last, a statistically significant increased risk for fracture was observed across multiple cultures and geographically diverse populations such as those in Spain (RR=1.18, 95% CI (1.07-1.30)), Denmark and the Netherlands (RR=2.20, 95% CI (1.33-3.61)), and the United Kingdom (RR=1.71, 95% CI (1.53-1.91)).[28]

Though ATC Class N05B were not studied as frequently, all reported significant increased fracture risk, for example, in men (RR=5.42, 95% CI (4.86-6.05)) 55+ years of age, but less for women (RR=3.33, 95% CI (3.03-3.66)).[22] Beta blockers were evaluated from one study; results showed a reduced risk of fracture (RR=0.77, 95% CI (0.72-0.83)), and remained beneficial across age groups and sex.[29] Zolpidem, when first started (0-4 weeks), showed a statistically significant increase for fracture risk (RR=2.29, 95% CI (1.48-3.56)).[27] Results for later times were inconclusive. As for beta blockers, the only study showed a statistically significant decrease in fracture risk regardless of patient's age or sex.[29] Overall, depending on study design, specific medication, age, and sex, fracture risk associated with anxiolytic drugs fluctuated greatly.

Table 1. Medications investigated as well as their respective fracture rate for each study analyzed.

	Year of publication	Level of study	Study description	Total participants	Females	Age range (years)	Length of time to fracture	Medication	Fracture risk
Abrahamsen et al.[21]	2009	3	Retrospective Cohort	Not Provided	Not Provided	50+	Not Provided	Anxiolytics*	PAR = ~2% any fracture risk PAR = ~2% hip fracture risk
Axmon et al.[22]	2018	3	Retrospective Cohort	7,936	3,609	55+	Not Provided	Anxiolytics*	Men: RR = 5.42 (4.86-6.05) Women: RR = 3.33 (3.03-3.66)
Bakken et al.[23]	2014	2	Prospective Cohort	2,009	1,642	60+	Patient must have been on drug for at least 14 days.	Anxiolytics*	Men: RR = 1.6 (1.4-1.7) Women: RR = 1.4 (1.4-1.5)
								Short-Acting Benzodiazepines	Men: RR = 1.7 (1.5-2.0) Women: RR = 1.4 (1.3-1.5)
								Long-Acting Benzodiazepines	Men: RR = 1.3 (1.2-1.5) Women: RR = 1.2 (1.2-1.3)
Bushnell et al.[24]	2020	3	Retrospective Cohort	57,684	37,848	18 to 24	Patients initiating anxiolytic therapy were followed until fracture, discontinuation or switching, disenrollment, 3 months, or study ended.	Benzodiazepines	Incident Rate Ratio: 1.02 (0.86-1.21)
Coutinho et al.[25]	2008	3	Case Control	500	110	60+	Not Provided	Benzodiazepines	RR = 2.29 (1.48-4.40)
Herings et al.[26]	1995	3	Retrospective Cohort	493		55+	A dispensing history of at least a 180 day is required.	Benzodiazepines	Overall RR = 1.44 (1.16-1.75)
								Nitrazepam**	Low Dose: OR = 0.4 (0.1-2.9) High Dose: OR = 1.1 (0.7-1.8)
								Oxazepam**	Low Dose: OR = 0.8 (0.4-1.5) High Dose: OR = 5.1 (0.5-57.2)
								Lorazepam**	Low Dose: OR = 5.1 (1.2-22.2) High Dose: OR = 5.5 (1.3-23.1)
								Temazepam**	Low Dose: OR = 1.0 (0.5-2.1) High Dose: OR = 2.8 (1.3-5.8)
Hwang et al.[27]	2015	3	Retrospective Cohort	6,623	3,562	18+	0-4 week exposure period 4-8 week exposure period 8-12 week exposure period 12-16 week exposure period	Benzodiazepines	0-4 weeks: RR = 1.46 (1.28-1.66) 4-8 weeks: RR = 1.23 (1.01-1.49) 8-12 weeks: RR = 1.09 (0.86-1.37) 12-16 weeks: RR = 1.38 (1.07-1.77)
								Zolpidem	0-4 weeks: RR = 2.29 (1.48-3.56) 4-8 weeks: RR = 1.90 (0.93-3.89) 8-12 weeks: RR = 2.33 (0.92-5.93) 12-16 weeks: RR = 1.83 (0.72-4.64)
Requena et al.[28]	2016	3	Retrospective Cohort	Spain 894: - 418,896 person years UK 436: - 129,857 person-years Netherlands & Denmark 20: - 8,022 person-years	Not Provided	18+	An exposure of at least 30 days is required.	Benzodiazepines	Spain: RR = 1.18 (1.07-1.30 United Kingdom: RR = 1.71 (1.53-1.91) Netherlands and Denmark: RR = 2.20 (1.33-3.61)

Table 1. Medications investigated as well as their respective fracture rate for each study analyzed. *continued.*

	Year of publication	Level of study	Study description	Total participants	Females	Age range (years)	Length of time to fracture	Medication	Fracture risk
Schlienger et al.[29]	2004	3	Case Control	932	640	30+	Last prescription had to be filled 1-59 filled days prior.	Beta-Blockers	Overall: RR = 0.77 (0.72-0.83) Men: RR = 0.66 (0.58-0.75) Women: RR = 0.85 (0.77-0.93) < 50years Old: RR = 0.76 (0.63-0.92) ≥ 50 Years Old: RR = 0.77 (0.71-0.86)
Sgadari et al.[30]	2000	3	Retrospective Cohort	9,752	7,733		Not Provided	Benzodiazepines	RR = 1.09 (0.98-1.19)
Tamiya et al.[31]	2015	3	Case Control	817		50+	Not Provided	Benzodiazepines	RR = 1.38 (1.09-1.72)
van Staa et al.[32]	2002	3	Case Control	231,778	121,615		Not Provided	Anxiolytics*	RR = 1.12 (1.12-1.15)
Vestergaard et al.[33]	2013	3	Retrospective Cohort	Not Provided	Not Provided	40+	Not Provided	Anxiolytics*	< 0.1 DDD/day: RR = 1.22 (1.17-1.27)* 0.1-0.33 DDD/day: RR = 1.38 (1.27-1.49)* ≥ 0.33 DDD/day: RR = 1.51 (1.39-1.63)*

*Includes benzodiazepines, diphenylmethane, carbamates, dibenzo-bicyclo-octadiene, azaspirodecanedione
**A specific benzodiazepine
Note: DDD = defined daily dose; RR = Risk Ratio; PAR = Population Attributable Risk; OR = Odds Ratio

Table 2. Risk of bias assessment of included studies using the ROBINS-I tool.

Authors	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Abrahamse et al.[21]	moderate	low	low	low	low	low	moderate	moderate
Axmon et al.[22]	moderate	moderate	low	low	low	low	low	moderate
Bakken et al.[23]	moderate	low	low	low	low	low	moderate	moderate
Bushnell et al.[24]	serious	moderate	low	low	moderate	moderate	low	serious
Coutinho et al.[25]	moderate	low	serious	low	low	low	low	serious
Herings et al.[26]	moderate	moderate	low	low	moderate	moderate	moderate	moderate
Hwang et al.[27]	moderate	moderate	low	moderate	low	moderate	low	moderate
Requena et al.[28]	moderate	low	moderate	low	moderate	moderate	moderate	moderate
Schlienger et al.[29]	low	low	low	low	low	low	low	low
Sgadari et al.[30]	moderate	moderate	low	low	low	moderate	low	moderate
Tamiya et al.[31]	serious	serious	moderate	low	low	moderate	moderate	serious
van Staa et al.[32]	moderate	moderate	moderate	low	low	moderate	moderate	moderate
Vestergaar et al.[33]	moderate	moderate	low	low	low	low	low	moderate

DISCUSSION

In this scoping review, anxiolytic medications were evaluated to determine if they put individuals at an increased risk of fracture. Overall, ATC Class N05B medications, as well as benzodiazepines, were studied more frequently in terms of fracture risk analysis. In patients utilizing either, there was an observed increased fracture risk according to numerous studies in this review, while another study reported decreased relative risk only in the lose dose cohorts. Therefore, it is important to consider the risk benefit analysis when prescribing these medications, especially in high risk populations, such as those over the age of 65 or those with independent risk factors such as chronic glucocorticoid use (defined as over three months of prednisone use (minimum 5 mg per day)), personal history of previous low energy fracture of the hip or spine, personal history of metabolic bone disease, chronic kidney disease more than or equal to stage 3 (GFR< 60 mL/min), high fracture risk as calculated by FRAX (fracture risk assessment tool), alcohol use (three or more units/d), vitamin D deficiency, current smoking, limited mobility, wheelchair bound, current cancer treatment (known to impact bone health), and diabetes mellitus (> 10 years and poor control).[34] Moreover, the inclusion of benzodiazepines as one of the medications in ATC Class N05B acts as selection bias for other medications in this group given the known risk for fracture specifically associated with benzodiazepines. As for zolpidem and beta blockers influence on fracture risk, each were only investigated in one study, respectively, which indicated more research needs to be conducted to identify the actual fracture risk associated with these medications.

Lastly, throughout the literature, a uniform method for statistically measuring and comparing fracture risk for medications was lacking. Within this review, 46% (6/13) of the articles did not quantify the amount of time a patient must be on a medication before considering that a fracture could be due to a medication. Additionally, more studies need to be conducted analyzing fracture risk in younger populations that do not have as many comorbidities. Plus, the medications investigated in multiple studies only listed "anxiolytics" and were not specified. Due to the ambiguity of the medications analyzed in the study, information gathered from these articles cannot be categorized. Lastly, the comorbidities of included patients were widely unavailable. There are numerous comorbidities that could be the cause of the resulting fractures which need to be revealed within the study population. These studies identified fracture risk in different ways, including relative risk, odds ratio, and percentage which made comparison difficult. Ultimately, for an increased understanding of the role anxiolytics play in fractures, additional research and a more consistent way of reporting information are needed. Future studies should include more specifics regarding medications being evaluated, including total daily dose and duration of use, the comorbidities of participants, and a uniformly accepted comparison strategy.

Limitations. A major limitation of this study included the paucity of literature regarding this subject, especially regarding zolpidem and beta blockers. With that said, a standardized comparison strategy must be established due to the inability to compare fracture risks. Moreover, the studies that met the inclusion criteria for this review did not include the concurrent medications and comorbidities of the patients in these studies. Lastly, sex, body mass index, and other patient demographics rarely were discussed, which contributed to confounding results in these studies and review.

CONCLUSIONS

Fractures are a mainstay of traumatic injuries and are accompanied by economical, physiological, and psychological hardship. With proper assessment and prophylactic measures, fracture risk can be reduced dramatically. Anxiolytic medications have been described widely to increase fracture risk, such as benzodiazepines in 60+ year old patients, and ATC Class N05B anxiolytics in 55+ year old patients.[22,25] Yet, some studies showed that at low doses, nitrazepam, as well as beta blockers, lowered fracture risk.[26,29] Ultimately, this scoping review helped to illuminate the inconsistency of anxiolytic fracture risk assessment while simultaneously illustrating the necessary steps to guide future research.

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