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Antipsychotic use and fracture risk: An evaluation of incidence at a Veterans Affairs medical center

Jabe Weaver, PharmD[1]
Jaclyn Kawsky, PharmD, BCPP[2]
Alexander Corboy, PharmD[3]

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Abstract

Introduction: Recent meta-analyses have found a correlation between schizophrenia and increased fracture risk with one contributing factor potentially being antipsychotic-induced hyperprolactinemia, which may accelerate bone turnover. The objective of this study is to evaluate fracture rates in patients on long-term antipsychotic therapy to see if screening for osteoporosis should be included with routine monitoring.

Methods: Patients exposed to antipsychotics for ≥3 months during a 10-year study period were included in this retrospective analysis. The primary outcome was to compare fracture rates in those exposed to long-term antipsychotics to a control group with similar demographics and comorbidities not receiving antipsychotics. Secondary outcomes included examining the risk of fracture by medication use and comorbid disease states associated with causing osteoporosis, vitamin D level monitoring and fracture presence, and the time to first fracture.

Results: Long-term use of antipsychotics was not associated with an increased rate of fractures compared to the control group in this study. End-stage renal disease, tobacco use, alcohol use, glucocorticoids, antiepileptics, and proton pump inhibitors were associated with higher risk of fracture ($P < .05$). Vitamin D level monitoring and supplementation was found to be a protective factor and lowered the risk of fracture.

Discussion: Long-term antipsychotic use is not associated with an increased risk of fractures. Further long-term prospective studies are necessary to further investigate this correlation. Screening for osteoporosis should follow guideline-driven recommendations for at-risk populations.

Keywords: antipsychotic, osteoporosis, fracture, hyperprolactinemia

[1] (Corresponding author) Post-Graduate Year Two Psychiatric Pharmacy Resident, William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina, jabe.weaver@va.gov, ORCID: https://orcid.org/0000-0001-9896-5537; [2] Clinical Pharmacy Specialist, Mental Health, William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina, ORCID: https://orcid.org/0000-0002-2440-2210; [3] Informatics Pharmacist, William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina, ORCID: https://orcid.org/0000-0002-4022-3423

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Introduction

Antipsychotics are a mainstay of treatment for psychotic and mood disorders. These agents are separated into 2 classes based on affinities for dopamine and serotonin receptors.[1] Side effects of antipsychotics vary between the 2 classes because of differing receptor binding profiles, with high potency dopamine blockade associated with increased risks for movement disorders and hyperprolactinemia.[1] While hyperprolactinemia is commonly described as a class-wide side effect of antipsychotics, it is important to note that this metabolic derangement is most commonly associated with the first generation

antipsychotic class and some second generation agents, such as paliperidone or risperidone.[1] Although the long-term consequences of movement disorders are well established, the long-term effects of untreated hyperprolactinemia are not fully understood.

Hyperprolactinemia results from dopamine blockade in the tuberoinfundibular pathway and is generally asymptomatic.[2] Laboratory monitoring of prolactin is not routinely assessed in clinical practice unless adverse effects develop, which may include galactorrhea, gynecomastia, reproductive side effects, or sexual dysfunction.[3] According to the Endocrine Society Clinical Practice Guideline on the Diagnosis and Treatment of Hyperprolactinemia, normal prolactin levels are $<$25 mg/L and results between 25 and 100 mg/L are typically medication-induced.[3] The use of some antipsychotics (eg, risperidone) has been associated with levels exceeding 200 mg/L.[3] The package inserts of many antipsychotics state that "long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density" in patients of both sexes.[4-8] However, a correlation between the use of antipsychotics and an increased risk for fractures or osteoporosis has not been established.

Osteoporosis is an endocrine disorder that manifests as the deterioration of bone tissue and disruption of bone architecture, compromising bone strength and leading to an increased risk of fracture.[9] While osteoporosis is mostly considered a condition that develops in aging populations, it is important to identify risk factors that increase bone turnover and promote bone loss because of the increased mortality, disability, and diminished quality of life associated with those who experience a fracture.[9] Risk factors for the development of osteoporosis are multifactorial and may include genetic disorders, metabolic disease states, medications, or lifestyle factors such as tobacco and alcohol use.[9] The National Osteoporosis Foundation (NOF) recommends that adults with a medical condition and/or those who are taking a medication associated with low bone mass or bone loss should have bone mineral density (BMD) screening to assess for osteoporosis.[9]

Although antipsychotics are not currently identified as a medication class associated with causing osteoporosis by the NOF, 3 recent meta-analyses have found a correlation between the presence of schizophrenia and an increased risk of fractures and osteoporosis.[10-12] The investigators[10-12] concluded that this correlation is likely complex and multifactorial, especially since patients with schizophrenia are more likely to have substance use disorders, engage in lower levels of physical activity, and use antipsychotics. Further evidence is necessary to fully evaluate the relationship between long-term antipsychotic use and determine if this increases the risk for fractures.

The purpose of this study was to evaluate fracture rates in patients on long-term antipsychotic therapy ($\geq$3 months) to assess if BMD screening should be included in routine antipsychotic monitoring. The primary outcome was to compare fracture rates in patients exposed to long-term antipsychotics in comparison to a control group with similar demographics and comorbid disease states who did not receive antipsychotics. Secondary outcomes included examining the risk of fracture by use of medications and comorbid disease states associated with the development of osteoporosis, the risk of fracture if vitamin D level monitoring occurred prior to study entry, and the time to first fracture for both groups.

Methods

A single-center, retrospective chart review was performed using the institution's electronic medical record for data collection in a veteran population. The study received approval by the local institutional review board. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The electronic medical record was used to identify all patients who were exposed to antipsychotic therapy for $\geq$3 months between April 1, 2007, and April 1, 2017, using International Classification of Diseases (ICD) 9 and 10 coding. We selected the 3 months or more time period for antipsychotic use to mimic the NOF's guidance that reported glucocorticoid use for 3 or more months is a risk factor for osteoporosis.[9] Patients were excluded if they were exposed to antipsychotics for $<$3 months, had a previously reported fracture prior to antipsychotic initiation, a diagnosis of osteopenia or osteoporosis, or received treatment for decreased BMD prior to inclusion to this study (eg, bisphosphonates, calcitonin, denosumab, teriparatide, raloxifene, or hormone replacement therapy). Demographics obtained included age, height, weight, sex, and body mass index. Other data collected included the presence of disease states or use of medications associated with causing or contributing to osteoporosis, presence and timing of fracture, diagnosis of tobacco or alcohol use disorder, 25-hydroxyvitamin D levels, and presence of vitamin D supplementation if available. Patients identified through the inclusion and exclusion criteria were matched to a control group with similar comorbidities who had never received an antipsychotic and were of comparable ages within 5 years of each other. The comorbidities used to match the groups included congestive heart failure, chronic obstructive pulmonary disease, depression, diabetes mellitus, epilepsy, end-stage renal disease, and schizophrenia. The presence of alcohol and tobacco use were also included, however not used in the matching process because of

TABLE 1: Demographics of the study population

	No Antipsychotic (N = 6388)	Antipsychotic Used (N = 6385)	*P* Value
Characteristics			
Age (y), mean ±SD	57.13 ± 13.93	56.28 ± 14.84	<.05
Male, N (%)	5667 (89)	5824 (91)	<.05
Height (in), mean ± SD	69.47 ± 3.33	69.43 ± 3.26	.268
Weight (lbs), mean ± SD	201.95 ± 45.81	200.75 ± 43.41	.075
Body mass index (kg/m^2), mean ± SD	29.39 ± 6.16	29.26 ± 5.93	.119
Comorbid disease states, N (%)			
Congestive heart failure	149 (2)	149 (2)	.997
Chronic obstructive pulmonary disease	526 (8)	526 (8)	.994
Depression	1575 (25)	1575 (25)	.998
Diabetes mellitus	1591 (25)	1591 (25)	.998
Epilepsy	95 (1)	95 (1)	.997
End-stage renal disease	220 (3)	220 (3)	.996
Alcohol use	385 (6)	1252 (20)	<.05
Tobacco use	860 (13)	1649 (26)	<.05
Schizophrenia	29 (0.5)	29 (0.5)	.999
Concomitant medications, N (%)			
Androgen deprivation	48 (0.8)	30 (0.5)	<.05
Antiepileptics	826 (13)	2908 (46)	<.05
Aromatase inhibitors	0 (0)	3 (0.05)	.083
Glucocorticoids	689 (11)	875 (14)	<.05
Heparin	2 (0.03)	0 (0)	.157
Lithium	21 (0.3)	293 (5)	<.05
Methotrexate	28 (0.4)	5 (0.08)	<.05
Proton pump inhibitor	1656 (26)	2720 (43)	<.05
Vitamin D supplementation	0 (0)	248 (4)	<.05

limitations with our statistical software. The medications assessed that could contribute to the development of osteoporosis included androgen deprivation therapy, antiepileptics, aromatase inhibitors, glucocorticoids, heparin, lithium, methotrexate, and proton pump inhibitors.

Descriptive statistics were used to report demographic data, fracture results, and the time to first fracture. Differences in demographic data and outcomes between the 2 groups were compared using χ^2 test analysis for categorical variables and Student *t* test for continuous variables. A multivariate logistic regression was used to assess which comorbid disease states and concomitant medications were associated with a higher risk of causing a fracture. A *P* value of <.05 was considered to be statistically significant.

Results

Demographics of the study population are listed in Table 1. The control group was slightly older (57.13 vs 56.28; $P < .05$) and had fewer male individuals (5667 vs 5824; $P < .05$), which were both statistically significant. The antipsychotic group had a higher percentage of individuals with documented alcohol (20% vs 6%; $P < .05$) and tobacco (26% vs 13%; $P < .05$) use. During the study period, the control group had a higher percentage of individuals who received androgen deprivation therapy (0.8% vs 0.5%; $P < .05$) and methotrexate (0.4% vs 0.08%; $P < .05$), whereas the antipsychotic group was more likely to receive antiepileptics (46% vs 13%; $P < .05$), glucocorticoids (14% vs 11%; $P < .05$), lithium (5% vs 0.3%; $P < .05$), proton pump inhibitors (43% vs 26%; $P < .05$), and vitamin D supplementation (4% vs 0%; $P < .05$).

Overall, the mean fracture per patient and total number of fractures were similar between groups as shown in Table 2. When assessing the fracture rate per 10 000 patient days, the antipsychotic group experienced a higher rate of fractures compared to the control population, but this was not statistically significant (0.552 vs 0.481; $P = .758$).

Secondary outcomes are listed in Table 3. The comorbidities of end-stage renal disease, alcohol use, and tobacco

TABLE 2: Primary outcome: fracture results

Fracture Results	No Antipsychotic	Antipsychotic Used	*P* Value
Fracture rate per 10 000 patient days, mean ± SD	0.481 ± 4.89	0.552 ± 6.41	.758
Patients with fracture, N (%)	371 (6)	359 (6)	
Total fractures, N	657	625	
Fracture per patient, mean	1.77	1.74	
Fracture count by sex, N	Male: 578	Male: 578	
	Female: 79	Female: 47	

use were associated with a higher risk of experiencing a fracture compared to other studied comorbidities: odds ratio (OR) of 1.56 (95% confidence interval [CI] 1.11 to 2.19), 1.25 (95% CI 1.01 to 1.54), and 1.44 (95% CI 1.21 to 1.72), respectively ($P < .05$ for each). The use of antiepileptics, glucocorticoids, and proton pump inhibitors were also associated with a higher risk of experiencing a fracture compared to other studied medications: OR of 1.28 (95% CI 1.09 to 1.5), 1.54 (95% CI 1.26 to 1.88), and 1.29 (95% CI 1.1 to 1.52), respectively ($P < .05$ for each). The presence of vitamin D supplementation was associated with a lower risk of experiencing a fracture (OR of 0.22; 95% CI 0.08 to 0.6; $P < .05$). Vitamin D level monitoring prior to study inclusion was also associated with a statistically significant lower risk of fracture compared to those who did not receive monitoring ($P < .05$). When examining the time to first fracture, the majority occurred during one to six years after study entry in both the control and antipsychotic group (Figure).

Discussion

To our knowledge, this is the first study examining the incidence of fractures in individuals exposed to long-term antipsychotic therapy. Strengths of this study included our ability to control for comorbidities that are associated with causing osteoporosis and having a large patient population. Although there are other comorbidities identified by the NOF, we specifically chose conditions that were more likely to occur in a veteran population to ease the matching process.[9] Additionally, we were able to gain information in regards to which comorbidities and medications are associated with a higher fracture risk.

TABLE 3: Secondary outcomes: Vitamin D monitoring and logistic regression

	Odds Ratio	95% Confidence Interval	*P* Value
Multivariate logistic regression for fracture risk[a]			
Comorbid disease states			
Chronic obstructive pulmonary disease	1.24	0.97 to 1.57	.083
Diabetes mellitus	1.21	0.95 to 1.33	.189
End-stage renal disease	1.56	1.11 to 2.19	<.05
Alcohol use	1.25	1.01 to 1.54	<.05
Tobacco use	1.44	1.21 to 1.72	<.05
Concomitant medications			
Vitamin D supplementation	0.22	0.08 to 0.6	<.05
Antiepileptics	1.28	1.09 to 1.5	<.05
Glucocorticoids	1.54	1.26 to 1.88	<.05
Proton pump inhibitors	1.29	1.1 to 1.52	<.05
	No Fracture, N	**Fracture, N**	***P* Value**
Vitamin D level monitoring and fracture presence[b]			
Monitoring before study inclusion			
Absent	11 214	713	
Present	829	17	<.05

[a]Multivariate logistic regression was used to identify which comorbidities and medications identified in this study were associated with higher odds of causing a fracture, irrespective of antipsychotic use. An odds ratio of >1 identifies factors with higher odds of causing a fracture.

[b]Vitamin D level monitoring prior to study inclusion was assessed to identify if this lowered the risk of developing a fracture during the study period.

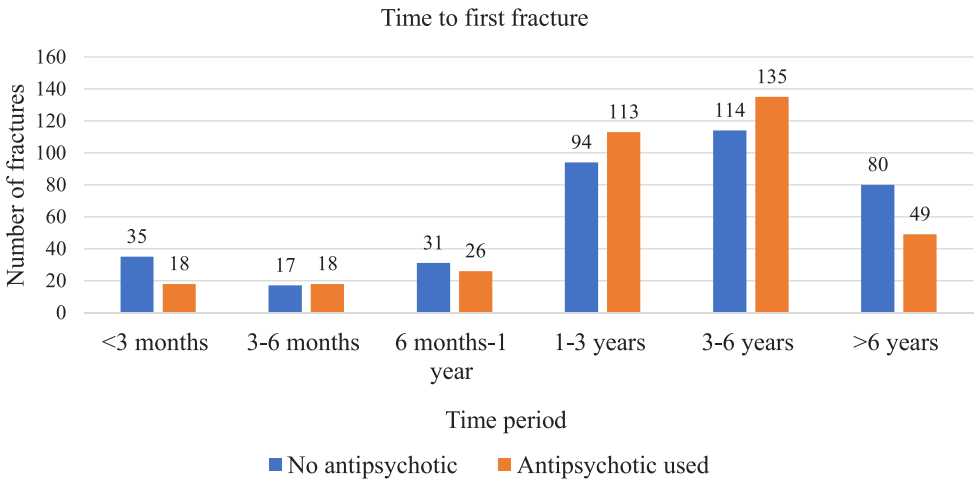

FIGURE: Time to first fracture (time to first fracture examines the length of time from which the first fracture occurred after inclusion to this study; this period does not reflect the duration of antipsychotic use, and the majority of fracture events occurred 1 to 6 years after entering the study)

Despite the many strengths of our protocol, there are limitations. Our study used a veteran population, which limits the generalizability of the results since it was predominately male. As hyperprolactinemia is more prevalent in females,[3] it is possible that there may have been a difference between groups if more females were present. We did not assess prolactin levels in this study as it is not routinely monitored unless adverse effects develop. This study was also designed retrospectively, and the data was limited to information documented through ICD coding. There is a possibility that not all fracture events were obtained because of inaccurate or missing coding. We attempted to pull ICD codes for psychiatric diagnoses entered in the medical record when the antipsychotic was initiated to identify the indication, however only 10% of individuals had this documented. Many of these individuals had multiple psychiatric conditions coded on the date of initiation, which made it difficult to assess the true indication. Despite alcohol and tobacco use being more prevalent in those who received antipsychotics, no statistically significant difference in fracture rates was found between groups. We were also unable to determine the causation of the fracture (eg, because of low bone mineral density, trauma, or other means). The higher use of vitamin D supplementation in the antipsychotic group may have also confounded results by decreasing the risk for fractures since this was not controlled for in our protocol. Finally, we were unable to assess if a difference in fracture rates exists between first generation and second generation antipsychotics based on time of total exposure to either class or if there is a dose-response relationship. The risk of developing a fracture with antipsychotics may be dependent on the total time of exposure to this class of medication. We recognize that the 3-month period of antipsychotic exposure for this study may not fully reflect the same risk for individuals receiving therapy for longer periods. In the future, we would like to increase the period of time that an individual must be exposed to an antipsychotic to see if fracture rates change. We would also like to assess prolactin levels and bone mineral density screening reports, if available, to correlate if the fracture occurred because of low BMD. Other factors to consider would be to evaluate whether there are any specific antipsychotics that may have a higher risk of causing a fracture compared to others, especially those with anticholinergic or alpha adrenergic antagonistic activity, which could theoretically increase the risks for falls.

In conclusion, the use of antipsychotics for 3 months or more does not appear to increase the risk for developing a fracture based on our study results over this 10-year period. Long-term prospective studies are necessary to further investigate if a correlation exists, especially since the risk of fracture could differ based on the type of antipsychotic initiated and the duration of use. At this time, we recommend that clinicians continue to follow NOF screening guidance to identify at-risk populations.

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