Evaluation of the link between chronic antipsychotic use and osteoporosis

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ABSTRACT

Background: Patients with schizophrenia are at increased risk for developing osteoporosis, which has historically been attributed to poor diet and lack of exercise. However, more recent data suggest a link between antipsychotic use and osteoporosis due to increased prolactin levels. Hyperprolactinemia can lead to suppression of hypothalamus-pituitary axis regulation of sex hormone production and over time, hypogonadism, which can affect bone health. There have been a few studies evaluating the link between antipsychotic use and osteoporosis; however, the link is not well established and there is very little guidance regarding monitoring of prolactin levels.

Objectives: Determine the prevalence of osteoporosis in patients receiving antipsychotic medications.

Evaluate the duration of antipsychotic therapy, prolactin levels (prevalence of monitoring and mean levels), and incidence of fractures for the study patients diagnosed with osteoporosis.

Methods: The study was a retrospective cohort study evaluating patients 18 years of age and older who were prescribed an antipsychotic at the Dallas VA Medical Center from 1/1/2008-12/31/2009. The patients included had to be taking the same antipsychotic for at least one year. Subjects were excluded if they had significant co-morbidities or were taking other medications that increase osteoporosis risk. Patient demographics, antipsychotic information, and pertinent lab values such as vitamin D, prolactin, testosterone and FSH/LH levels were recorded. The use of other medications that may increase prolactin, smoking status, bone mineral density, and history of fracture were also noted.

Results: This study showed that 26% of patients taking antipsychotics for at least one year developed osteoporosis. The dose or type of antipsychotic (prolactin-sparing versus prolactin-raising) did not appear to be contributing factors. Based on this study's data, the duration of antipsychotic therapy and the concurrent use of other prolactin raising medications may be more concerning.

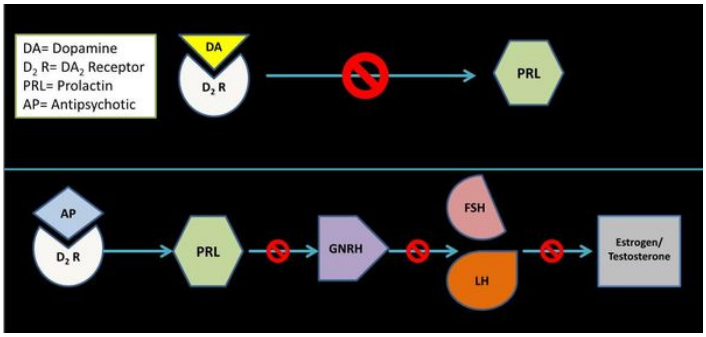
KEYWORDS

antipsychotic, osteoporosis, prolactin

INTRODUCTION

Along with chronic diseases such as obesity, cardiovascular disease, and diabetes, patients with schizophrenia have also been reported to have an increased risk for osteoporosis.[1] Until fairly recently the factors behind this risk were not well understood, but it was demonstrated to be independent of age and gender and attributed mostly to poor diet, smoking, alcohol abuse, and lack of exercise.[2-5] Cross-sectional studies have shown a link between antipsychotic use and osteoporosis due to hyperprolactinemia.[6-8] Antipsychotics typically antagonize dopamine receptors, specifically D_2 receptors, which inhibits prolactin release from the anterior pituitary gland. Use of antipsychotics can therefore increase prolactin levels. Over time, elevated prolactin concentrations may lead to hypogonadism due to the suppression of hypothalamus-pituitary axis regulation of sex hormone production, which is important in maintenance of bone health (Figure 1).[2,8]

Figure 1. Proposed mechanism of antipsychotic induced osteoporosis



GNRH = Gonadotropin Releasing Hormone; FSH= Follicle Stimulating Hormone; LH=Luteinizing Hormone

Prolactin is a hormone that is endogenously produced and released in a pulsatile fashion that is highest during REM sleep. Levels become increased after exercise, meals, sex, general anesthesia, myocardial infarctions, pregnancy, lactation and other stress. Normal levels are 0-20 ng/mL and can increase to >100 ng/mL in patients with prolactinomas and 200-300 ng/ml in pregnant patients. Symptoms of mild elevations (31-75 ng/mL) in prolactin include decreased libido (usually in men), infertility, and oligomenorrhea. Severe elevations (>100 ng/mL) may cause hypogonadism, galactorrhea, and amenorrhea. Long term effects (> 6 years of chronic hyperprolactinemia) include reproductive dysfunction, breast cancer, and osteoporosis.[9-11]

Antipsychotic-induced hyperprolactinemia is estimated to occur in 34%-75% of patients and more often in women than in men.[9-11] It has been proposed that antipsychotics with more specificity for the D_2 receptor are more likely to cause hyperprolactinemia. Therefore, antipsychotics can be classified as prolactin-sparing (olanzapine, clozapine, aripiprazole, ziprasidone, asenapine, iloperidone, lurasidone and quetiapine) and prolactin-raising (risperidone, paliperidone, haloperidol, chlorpromazine, loxapine, fluphenazine and thorazine).[2,4,12-13] Other risk factors for antipsychotic-induced hyperprolactinemia include pre-menopausal and adolescent females and using multiple prolactin raising medications such as morphine, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and metoclopramide. [8,12-13]

Two case-controlled and two cross-sectional studies[1,6,7,14] have been published evaluating the link between antipsychotic use and osteoporosis. However, this link is not well established and there is very little guidance regarding monitoring of prolactin levels.[9] This study attempted to evaluate the risk of developing osteoporosis in patients based on type of antipsychotic used (prolactin-sparing versus prolactin-raising) in a veteran population.

METHODS

This study was a retrospective chart review of patients receiving antipsychotic medications at the Dallas VA Medical Center. Patients were identified by a database search, which listed veterans with an active order for an antipsychotic medication during the time period of 1/1/2008-12/31/2009. Patients must have been 18 years or older, received an antipsychotic within the study period, prescribed the medication for at least one year, and were compliant with therapy based on refill history (refills were requested less than 60 days from the last fill). Subjects were excluded if they were determined to have significant co-morbidities that increase the risk of osteoporosis (e.g., alcohol dependence, heart failure, diabetes, other endocrine disorders, hematologic disorders, end stage renal disease) or were diagnosed with osteoporosis or fracture prior to starting antipsychotics. Patients were also excluded if they were taking concomitant medications that were listed in the 2010 National Osteoporosis Foundation (NOF) guidelines as agents that increase the risk of osteoporosis (e.g., anticonvulsants, lithium, cyclosporine, tacrolimus, gonadotropin-releasing hormone agonists, medroxyprogesterone, chemotherapeutic agents, glucocorticoids - ≥5mg/day of prednisone for ≥3 months).[15] Documented hypogonadism and premature menopause were also considered exclusionary. If patients met inclusion criteria, the chart was retrospectively reviewed to determine if the patient had a diagnosis of osteoporosis. Patients were considered to have osteoporosis if they met any of the following criteria: (1) an ICD-9 code for osteoporosis was noted, (2) osteoporosis was listed on the problem list or in the progress notes by a provider, (3) osteoporosis was noted on a DEXA scan report. Once a diagnosis was confirmed, it was determined whether the patient received an antipsychotic for at least 1 year prior to the diagnosis without receiving more than 1 antipsychotic at a time. This study was reviewed and approved by the Texas Tech University Health Sciences Center and VA North Texas Healthcare System Institutional Review Board.

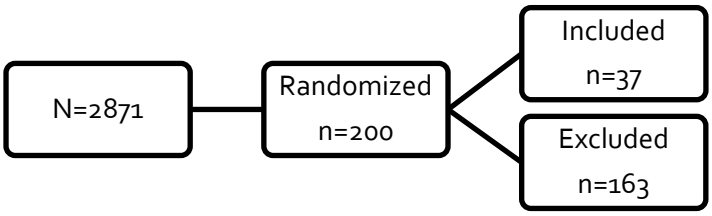
The main outcome of this study was to determine the rate of osteoporosis in patients who received an antipsychotic medication for at least a one year period. Prolactin levels, fracture rates, and other laboratory parameters including testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were recorded, if available. Demographic and baseline antipsychotic information were noted for all patients which included age, sex, smoking status, type of antipsychotic prescribed, duration of antipsychotic use, antipsychotic dose, and the use of other prolactin raising medications. Descriptive analyses, Fisher's Exact, and unpaired t-test were used to compare baseline characteristics and outcomes with alpha set at 0.05.

RESULTS

A total of 2,871 patients were identified as having received an antipsychotic during the study period, of which 200 were randomly chosen for review. For patient randomization, we used a simple program that provided

200 different Arabic numbers. We then selected 200 subjects from the list that correlated with these numbers. Of these patients, 163 met at least one exclusion criteria, leaving 37 patients who were included in the study (Figure 2). The majority of patients were excluded due to diagnoses of diabetes and heart failure or because of past lithium and anticonvulsant use.

Figure 2. Study Design



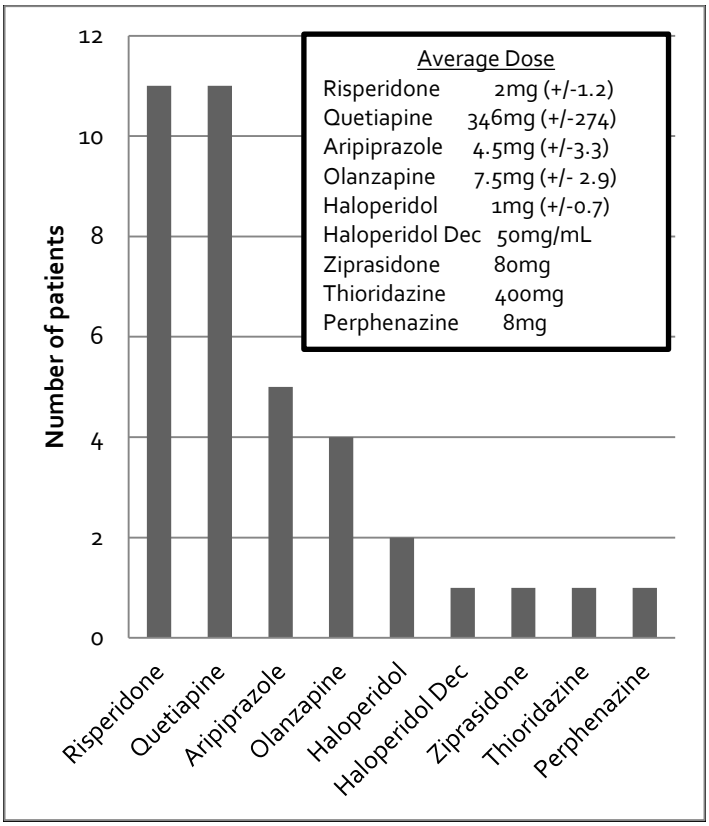
Baseline demographic information is provided in Table 1. Overall, patients were approximately 60 years of age, male and Caucasian, which is consistent with the demographic characteristics of veteran patients. The type of antipsychotic (prolactin-raising versus sparing) was distributed evenly amongst patients. The majority of patients received risperidone (n=11) or quetiapine (n=11). Average doses are listed in Figure 3. Of note, patients were generally receiving low to moderate doses of antipsychotics.

Table 1. Baseline characteristics

	Patients with Osteoporosis (n=10)	Patients without Osteoporosis (n=27)
Age, average years (SD)	61.6 (8.9)	59.6 (8.4)
Gender, n (%)		
Male	8 (80%)	27 (100%)
Female	2 (20%)	0 (0%)
Race, n (%)**		
White	10 (100%)	17 (63.0%)
African American	0 (0%)	9 (33.3%)
Hispanic	0 (0%)	1 (3.7%)
Smokers (during study period), n (%)		
Yes	1 (10%)	9 (33.3%)
No	9 (90%)	18 (66.7%)
Type of antipsychotic, n (%)		
Prolactin Raising	5 (50%)	12 (44.4%)
Prolactin Sparing	5 (50%)	15 (55.6%)

**statistically significant difference between groups (p=0.0359)

Figure 3. BASELINE ANTIPSYCHOTIC USE



Indications for use were variable, which is likely due to the variety of approved and off-labeled use of antipsychotic medications (Table 2). Major depression (n=13) and post-traumatic stress disorder (PTSD) (n=12) represented the majority of cases; the number of patients being treated for psychosis (n=5) or schizophrenia (n=5) was lower than expected, and when combined, represented only 27% of the overall diagnoses.

Table 2. Indications for antipsychotic use, n (%)

Major Depressive Disorder	**13 (34.2)**
Post-traumatic Stress Disorder	**12 (31.6)**
Psychosis	**5 (13.2)**
Schizophrenia	**5 (13.2)**
Bipolar disorder	**3 (7.9)**
Schizoaffective disorder	**2 (5.3)**
Mood disorder	**1 (2.6)**
Alzheimer's Dementia	**1 (2.6)**
Delusional Disorder	**1 (2.6)**

The primary outcome, rate of osteoporosis after at least one year of antipsychotic therapy, was met in 26% of patients. Fifty percent of these patients had an active prescription for a prolactin-raising antipsychotic and 50% for a prolactin-sparing antipsychotic. The majority of these patients (70%) also had a prescription for another prolactin-raising medication in which most cases included

an SSRI. Table 3 shows the antipsychotic type and dose received by patients who developed osteoporosis after receiving an antipsychotic for at least one year. Similar to the primary cohort, doses were generally low to moderate. The average duration of antipsychotic therapy before diagnosis of osteoporosis was 2.8 years. Prolactin concentrations were measured for only 1 of the 37 patients and it was within normal limits. Testosterone, FSH, LH, and vitamin D labs were only available for 5, 2, 4, and 6 patients, respectively. However, it was noted that all vitamin D labs collected were below normal (< 30 ng/ml) with a mean concentration of 20.8 ng/ml. None of the included patients had experienced a bone fracture during the study period.

Table 3. Antipsychotic information for patients with osteoporosis

Patient	Antipsychotic Name	Total dose (mg)
Prolactin Sparing		
1	Aripiprazole	2.5
2	Quetiapine	300
3	Olanzapine	5
4	Olanzapine	10
5	Quetiapine	100
Prolactin Raising		
6	Haloperidol	1.5
7	Risperidone	1
8	Risperidone	1.5
9	Risperidone	2
10	Thioridazine	400

DISCUSSION

Based on the results from this study, 26% of patients taking antipsychotics for at least one year developed osteoporosis. This is similar to the prevalence observed in schizophrenia patients (25-34%).[5] Except for race, demographic information for patients who developed osteoporosis was similar to the overall sample. The majority of patients in our study were taking antipsychotics for non-psychotic psychiatric illnesses (65.8%) including 7 of the 10 patients who eventually developed osteoporosis. Data showed patients were on antipsychotic therapy for almost 3 years before developing osteoporosis, while generally on low to moderate doses. Previous literature has noted higher antipsychotic doses to be correlated with more bone loss.[6] However, two studies lead by Kishimoto and Bilici showed the duration of antipsychotic therapy, regardless of doses, to be a factor as well.[8,14]

Kishimoto and colleagues conducted a cross-sectional study of 74 male schizophrenic patients.[8] Lower bone mineral density (BMD) was observed in all age groups of the study patients compared with values normally seen in healthy persons. Additionally, the researchers found the duration of antipsychotic treatment was correlated with an increased risk of bone loss. The study lead by Bilici was a case control study which showed patients taking conventional antipsychotics had lower BMD compared to healthy controls and those taking atypical antipsychotics.[14] Duration of antipsychotic treatment was also significantly correlated with bone loss.

Due to lack of laboratory monitoring, we were unable to correlate osteoporosis with hyperprolactinemia; however, this phenomenon has been documented in the literature.[7,16,17] Seventy percent of the patients in this study who developed osteoporosis were taking other prolactin-raising medications in addition to their antipsychotic. This leads us to question whether the combination of prolactin-raising medications increases the risk of bone loss and is a topic that needs more research.

There are several confounding variables that could have affected the results of this study, including age and low vitamin D levels. We were also not able to consistently verify the patients' smoking histories. Ninety percent of the osteoporosis patients were noted to be non-smokers during the study period, but it was difficult to verify whether these patients had been life-time non-smokers or if they smoked in the past. Another large confounding factor was SSRI use (46%) among the selected patients. As noted in the methods section, subjects were excluded if they were taking another medication associated with an increased risk of osteoporosis based on the 2010 NOF guidelines.[15] SSRIs were not listed in these older guidelines, therefore, patients taking SSRIs were included in our study. Several studies have shown an association with SSRIs and bone loss,[18-22] and the class has been included in the recent 2013 NOF guidelines as medications that contribute to osteoporosis.[23]

The limitations of this study included its retrospective study design and lack of DEXA monitoring, which may have limited the rates of reported osteoporosis, as this may not have been consistently documented on the patients' problem lists. Also medication compliance had to be determined on refill history and could not be definitively verified. There was also a lack of prolactin monitoring, which limited insight into the mechanism of antipsychotic induced osteoporosis. Stringent exclusion criteria led to a small patient population; however, this

also allowed for a high quality patient sample in which osteoporosis was more likely to be secondary to antipsychotic use, rather than known risk factors.

While we were able to find a rate of osteoporosis similar to what has been reported previously for the mentally ill population, it would be beneficial to compare these results to a control group in a future trial. Also, studies investigating the use of multiple prolactin-raising medications and the risk of bone loss would be valuable as well.

CONCLUSIONS

This study showed the prevalence of osteoporosis to be 26% for patients who have taken antipsychotics for one year or longer. The type or dose of antipsychotic did not appear to correlate with osteoporosis risk. Duration of antipsychotic use and the concurrent use of other prolactin-raising medications may be factors of concern based on the data of this study.

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