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Risk of hip/femur fractures in patients using antipsychotics

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Abstract

The objective of our study was to investigate whether use of antipsychotics is associated with hip/femur fractures and whether pharmacological differences between antipsychotics are related to the occurrence of fractures.

A case-control study was conducted, in which cases were defined as patients with a hip/femur fracture. Each patient was matched to one control patient. The association between use of antipsychotics and the occurrence of hip/femur fractures was evaluated using conditional logistic regression.

The study included 44,500 patients from 683 general practices from different geographical areas in the UK, registered within the General Practice Research Database (GPRD). Exposure to antipsychotics was categorized as "no use", "current use" and "prior use".

Both current and prior use of antipsychotics were associated with an approximately two-fold increased risk of fractures. After adjustment for possible confounders, a small significant effect remained (Odds Ratios (OR) of 1.3). We did not find an association between dose of antipsychotics, or between the degree of blockade of the alpha-1 adrenoceptor or histamine-1 receptor and risk of fractures. The total number of days of antipsychotic use was significantly associated with an increased risk of hip/femur fractures.

We conclude that there is a small increased risk of hip/femur fractures associated with the use of antipsychotics. This risk increases with long-term use.

Keywords: Hip; Femur; Fractures; Antipsychotics

Introduction

A hip/femur fracture is a devastating event, especially for the elderly. The 1-year mortality after hip/femur fracture is about 20%, and 20% of those living in the community at the time of their hip/femur fracture have to be admitted to a nursing home [9]. Of those returning to living in the community, the majority will never regain their pre-fracture levels of physical and social activities [9].

The possible association between the use of several psychotropics, especially benzodiazepines and antidepressants, and hip/femur fractures has received much interest during recent years. In contrast, antipsychotics have not been investigated systematically. Some studies, although not directly focused on antipsychotics, have reported an association between the use of antipsychotics and fractures [10,30]. It has been postulated that the use of these drugs may lead to an increased tendency to fall as a result of orthostatic hypotension or sedation [6–8,30,32,38]. Furthermore, long-term use of some antipsychotics has been associated with decreased bone mineralization leading to

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weaker bones [3,5,12,21,25,39], and a higher probability that a fall will result in a fracture. The objective of our study was to investigate whether short- and long-term uses of antipsychotics are associated with hip/femur fractures and whether pharmacological differences between antipsychotics are related to the occurrence of fractures.

Methods

Setting

Data were collected from 683 general practices in different geographical areas in the UK, registered within the General Practice Research Database (GPRD) which is owned by the Department of Health in the UK [36]. General practitioners (GPs) play a key role in the health care system in the UK, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in the GPRD include demographic information, prescription data, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes [36]. Clinical data are stored and retrieved by means of the Oxford Medical Information Systems (OXMIS) and Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Each entry in the GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics [36]. Only data from practices that pass this quality control are compiled and are part of the GPRD. Several independent validation studies have confirmed the high level of completeness and validity of the GPRD [16], specifically with regard to recording of fractures [34,36]. Nazareth et al. found that 74% of all consultations of patients with psychotic disorder were recorded, as were 95% of prescriptions [26].

Study design

A case-control study was conducted using GPRD data collected from 1987 to 1999. We selected patients with a hip fracture (ICD-9 = 820) or with other femur fractures (ICD-9 = 821). A hip fracture is a fracture to the proximal end of the femur, not to the pelvis. The fracture can occur to the femoral head, femoral neck, or at the proximal end of the femur, just below the neck of the bone. In this study, our definition of hip/femur fracture included both types of fractures. We defined cases as permanently registered patients (those residing in the practice neighborhood) with a first record of a hospital admission for a hip/femur fracture recorded in their medical records between the enrolment date of their practice in the GPRD and the end of data collection (July 1999). The date of the occurrence of the hip/femur fracture was termed the index date.

Each case was matched to one control patient by year of birth (within a 1-year margin), sex and medical practice. If no eligible control was available, the age criterion was expanded consecutively at 1-yearly intervals to a maximum of 10 years. If no eligible control patient could be found, then an age- and sex-matched control patient from another practice was selected. Patients who already had a prescription for any antipsychotic at the start of the collection of the GPRD (1987) were excluded, preventing the inclusion of patients who were receiving regular treatment with antipsychotics before 1987. The selected control patient was assigned the same index date as that of their matched case patient. For the small number of control patients who had been transferred to another practice or died prior to this date, an index date was randomly selected between registration and dates of transfer or death.

Exposure assessment

All psychotropic drugs were classified according the ATC-system of the WHO [1]. Drugs starting with the four digit ATC-code N05A were classified as antipsychotics, with the exception of lithium, which is not an antipsychotic. Antipsychotic drugs were stratified according to their alpha-1 adrenoceptor and histamine-1 receptor blocking capacity and on the extent of this effect (low, intermediate or high) [4]. The information recorded by the GPs included the name, dose, frequency and number of dosages prescribed. For this study, we assumed that a subject was exposed for the duration of the prescription supply. If the prescription length was unknown, a 30-day period was presumed (average prescription length was 34 days). We analyzed medication use from 5 years before the index date.

Exposure to antipsychotics was categorized as “no use” when there was no recorded use of antipsychotic medication in the 5-year period before the index date, “current use” when the supply of the most recent prescription lasted at least until the index date or ended no more than 6 days before the index date and “prior use” when the most recent prescription ended 7 or more days before the index date. Current users were subdivided into recent and nonrecent starters (recent starters were patients who had their first prescription of antipsychotic medication 30 days or less before the index date).

The dose of the antipsychotic was based on the last prescription with a record on the dosage regimen and it was standardized to the number of Defined Daily Doses (DDD), a technical unit of measurement defined as the average dose per day for a drug used for its main indication in adults [2]. Daily dosages were categorized as low (<0.5 DDD), normal (0.5–1.5 DDD) or high (≥1.5 DDD). The duration of antipsychotic use was determined by cumulating the number of days of antipsychotic medication that was prescribed before the index date. Treatment episodes were defined as series of subsequent prescription refills for an antipsychotic agent independent of switching to another antipsychotic or changes in dose regimen. Duration of use was subdivided

into no-use, 0–30 days, 30–90 days, 90–180 days, 180 days–1 year, 1–2 years, 2–3 years, >3 years.

Assessment of potential confounders

Potential confounders in this study were clinical variables based on diagnosis and/or medication use that have previously been associated with risk of fractures [35]. The diagnosis of neurologic/psychiatric condition in the year before the index date included cerebrovascular disease, dementia, depression, psychotic disorder and seizures. The diagnosis of somatic condition in the year before the index date included anemia, back pain, heart failure, chronic obstructive pulmonary disease (COPD), diabetes, falls, osteoporosis, rheumatoid arthritis and thyrotoxicosis. Medication use in the 6-month period before the index date included antidepressants [15], anticonvulsants, antiparkinson drugs, benzodiazepines [13,37] as well as somatic drugs: cardiovascular drugs, inhaled corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, calcitonin, vitamin D, thiazides and disease-modifying antirheumatic drugs (DMARDs). Furthermore, the most recent data on smoking status (history of smoking, or nonknown history of smoking) and the last known body mass index (BMI; <20, 20–24, 25–29, ≥30 kg/m^2, or unknown) were gathered at the index date.

Data analysis

The strength of the association between use of antipsychotics and the occurrence of hip/femur fractures was estimated using conditional logistic regression and expressed as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI). Covariates were included in the regression model if they were either independently significantly associated with the outcome ($P < 0.05$), or induced a 10% change or more in the crude matched OR for use of antipsychotics. We evaluated potential confounding by indication by estimating the association between antipsychotic use and hip/femur fractures in patients with a recorded indication for schizophrenia or any other psychotics disorder. Data were analyzed using SPSS for Windows (release 10.0.7 standard version). A trend analysis was performed for the association between cumulative duration of use of antipsychotics and risk of fractures.

Table 1
Characteristics of cases and control patients

Characteristic	Cases (n = 22,250), no. (%)	Controls (n = 22,250), no. (%)
Female gender	16,872 (75.8)	16,872 (75.8)
Age (years)		
18–59	2344 (10.5)	2339 (10.5)
60–79	7616 (34.2)	7920 (35.6)
≥80	12,290 (55.2)	11,991 (53.9)
Mean age	76.9	76.7
Body mass index		
<20	1595 (7.2)*	935 (4.2)
20–24	4121 (18.5)	4080 (18.3)
25–29	2330 (10.5)*	3298 (14.8)
≥30	765 (3.4)*	1253 (5.6)
Unknown	13,439 (60.4)	12,684 (57.0)
Smoking status		
Yes	2705 (12.2)*	2534 (11.4)
Nonknown	19,545 (87.8)	19,716 (88.6)
Neurological/psychiatric condition		
Cerebrovascular disease	3299 (14.8)*	2136 (9.6)
Dementia	2062 (9.3)*	953 (4.3)
Depression	1313 (5.9)*	719 (3.2)
Psychotic disorder	1905 (8.6)*	892 (4.0)
Seizures	686 (3.1)*	292 (1.3)
Somatic condition		
Anemia	1139 (5.1)*	670 (3.0)
Back pain	1911 (8.6)*	1238 (5.6)
Heart failure	3119 (14.0)*	2490 (11.2)
COPD	4508 (20.3)*	3564 (16.0)
Diabetes	1363 (6.1)*	1085 (4.9)
Falls	3444 (15.5)*	817 (3.7)
Osteoporosis	1260 (5.7)*	505 (2.3)
Rheumatoid arthritis	717 (3.2)*	336 (1.5)
Thyrotoxicosis	390 (1.8)*	262 (1.2)
Psychotropic drug use in 6-month period before the index date		
Anticonvulsants	915 (4.1)*	360 (1.6)
Antidepressants	2895 (13.0)*	1607 (7.2)
Antiparkinson drugs	1022 (4.6)*	394 (1.8)
Hypnotics/anxiolytics	4848 (21.8)*	3421 (15.4)
Somatic drug use in 6-month period before the index date		
Cardiovascular drugs	130 (0.6)*	255 (1.1)
Inhalation corticosteroids/bronchial drugs	2243 (10.1)*	1806 (8.1)
NSAIDs	4134 (18.6)*	3212 (14.4)
Systemic corticosteroids	1600 (7.2)*	985 (4.4)
Biphosphonates	202 (0.9)*	72 (0.3)
Calcitonin	5 (0.0)	1 (0.0)
Vitamin D	175 (0.8)*	102 (0.5)
Thiazides	2642 (11.9)*	2872 (12.9)
Disease modifying antirheumatic drugs	256 (1.2)*	120 (0.5)

* $P<0.05$.

Results

The study population consisted of 22,250 patients with a hip/femur fracture and an equal number of matched controls. The characteristics of the study population are shown in Table 1. The majority of subjects were older than 60 years (89.4%) and female (75.8%). Compared to controls, cases had a higher prevalence of medical conditions and used more medication. The most prevalent medical conditions among cases and controls were COPD, heart failure, and cerebrovascular disease. Compared to 3.7% of the controls, 15.5% of cases had a history of falls. The most frequently prescribed drugs among cases and controls in the 6-month time window before the index date were hypnotics/anxiolytics.

Table 2
Association between use of antipsychotics and risk of fractures

Antipsychotic use	Cases (n = 22,250), no. (%)	Controls (n = 22,250), no. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
No use	19,251 (86.5)	20,702 (93.0)	Reference	Reference
Current user	1495 (6.7)	751 (3.4)	2.2 (2.0–2.4)	1.3 (1.1–1.5)
Recent starter	215 (1.0)	135 (0.6)	1.8 (1.4–2.2)	1.2 (0.92–1.6)
Nonrecent starter	1280 (5.8)	616 (2.8)	2.3 (2.1–2.5)	1.3 (1.1–1.5)
Prior user	1504 (6.8)	797 (3.6)	2.1 (1.9–2.3)	1.3 (1.2–1.5)

[a] Adjusted for medical condition: cerebrovascular disease, dementia, depression, psychotic disorder, seizures, anemia, back pain, heart failure, COPD, diabetes, falls, osteoporosis, rheumatoid arthritis and thyrotoxicosis. Medication: antidepressants, anticonvulsants, antiparkinson drugs, hypnotic/anxiolytics, cardiovascular drugs, inhalation corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, vitamin D and thiazides. Also for BMI and smoking status.

Table 2 shows the association between use of antipsychotics and risk of hip/femur fracture. Both current use and prior use were associated with an approximately two-fold increased risk of fractures. After adjustment for possible confounders, a small effect remained for current users (OR = 1.3; 95% CI: 1.1–1.5) and prior users (OR = 1.3; 95% CI: 1.2–1.5). We found 2797 patients with a diagnosis of psychotic disorder (1905 cases and 892 controls). No statistical differences in risk on hip/femur fractures associated with antipsychotic use were seen in patients with and without a diagnosis of psychotic disorders.

Table 3 shows the association between the effect of dosing, individual antipsychotics and receptor effects of current users and the risk of hip/femur fractures. We found a two-fold increase in the overall crude risk among users of antipsychotics, but no association with dosing regimes, individual antipsychotics or the differential effects on the alpha-1 adrenoceptor or the histamine-1 receptor. After adjustment for possible confounders, no significant associations were found (except for promazine).

Fig. 1 shows the association between days of use of antipsychotics and the risk of fractures. We found a small increased risk on fractures immediately after the initiation of antipsychotic therapy. With longer use of antipsychotics, the risk of fracture further increased. Although the confidence

Table 3
Effect of dose and substance receptor effect on the risk of fracture in current users of antipsychotics

Antipsychotic use	Cases (n = 20,746), no. (%)	Controls (n = 21,453), no. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Dosing				
No use	19,251 (92.8)	20,702 (96.5)	Reference	Reference
<0.5 DDD	1038 (5.0)	532 (2.5)	2.2 (2.0–2.5)	1.1 (0.8–1.4)
0.5–1.5 DDD	113 (0.5)	60 (0.3)	2.1 (1.5–2.9)	0.7 (0.5–1.1)
>1.5 DDD	23 (0.1)	9 (0.0)	2.7 (1.2–6.1)	1.4 (0.5–3.6)
Unknown DDD	321 (1.5)	150 (0.7)	–	–
Last prescribed antipsychotics				
No use	19,251 (92.8)	20,702 (96.5)	Reference	Reference
Thioridazine	741 (3.6)	382 (1.8)	2.2 (2.0–2.6)	1.2 (0.9–1.6)
Trifluoperazine	162 (0.8)	83 (0.4)	2.1 (1.6–2.8)	1.1 (0.7–1.6)
Chlorpromazine	140 (0.7)	59 (0.3)	2.7 (1.9–3.7)	1.5 (0.9–2.3)
Haloperidol	134 (0.6)	70 (0.3)	2.1 (1.6–2.9)	1.0 (0.6–1.5)
Promazine	126 (0.6)	41 (0.2)	3.3 (2.3–4.8)	1.7 (1.0–2.7)
Other antipsychotics	192 (0.9)	116 (0.5)	–	–
Receptor effect (4)				
Strength alpha-1 blocking effect				
No use	19,251 (92.8)	20,702 (96.5)	Reference	Reference
Low	25 (0.1)	8 (0.0)	3.7 (1.6–8.5)	1.4 (0.5–3.5)
Intermediate	198 (1.0)	104 (0.5)	2.1 (1.6–2.7)	0.9 (0.7–1.3)
High	1206 (5.8)	594 (2.8)	2.3 (2.1–2.6)	1.2 (0.9–1.6)
Unknown	66 (0.3)	45 (0.2)	–	–
Strength histamine-1 blocking effect				
No use	19,251 (92.8)	20,702 (96.5)	Reference	Reference
Low	1074 (5.2)	547 (2.5)	2.2 (2.0–2.5)	1.1 (0.8–1.5)
Intermediate	185 (0.9)	88 (0.4)	2.5 (1.9–3.3)	1.1 (0.8–1.7)
High	170 (0.8)	71 (0.3)	2.5 (1.9–3.4)	1.3 (0.9–1.8)
Unknown	66 (0.3)	45 (0.2)	–	–

[a] Adjusted for medical condition: cerebrovascular disease, dementia, depression, psychotic disorder, seizures, anemia, back pain, heart failure, COPD, diabetes, falls, osteoporosis, rheumatoid arthritis, and thyrotoxicosis. Medication: antidepressants, anticonvulsants, antiparkinson drugs, hypnotic/anxiolytics, cardiovascular drugs, inhalation corticosteroids and/or bronchial drugs, NSAIDs, systemic corticosteroids, biphosphonates, vitamin D and thiazides. Also for BMI and smoking status.

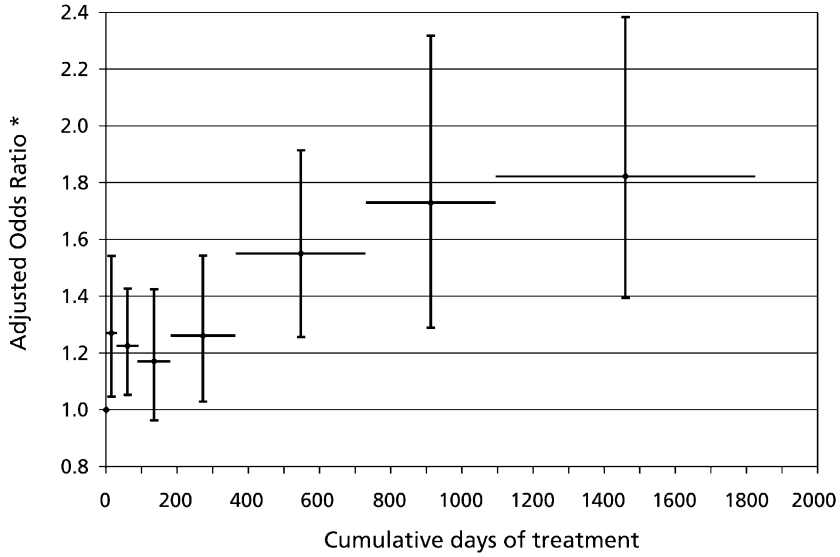

Fig. 1. Association between cumulative days of use of antipsychotics and risk of fractures.

intervals overlaid, the linear trend analysis showed a significant slope ($r^2 = 0.88$).

Discussion

In this study, we found evidence for an increased risk of hip/femur fractures among patients with current or prior use of antipsychotics. We did not find major differences between individual antipsychotics, dosing effects, nor an association with affinity for the alpha-1 adrenoceptor and the histamine-1 receptor. Finally, the cumulative dose (total number of days of antipsychotic use) was significantly associated with an increased risk on hip/femur fractures.

It has been estimated that 90% of hip/femur fractures are associated with falls [40]. Risk factors for fractures can be classified into those that pertain to the risk of falling and those that relate to the propensity of fracturing following a fall [9]. Risk factors involved in falling are physical impairments (e.g. dizziness, vision problems), and use of medication (e.g. benzodiazepines) [19]. In our analyses, we adjusted for a range of medical conditions and medications that are associated with falling, as described in Methods.

Patients who are vulnerable for orthostatic hypotension or sedative effects of antipsychotics are likely to be at risk for fracture shortly after initiating treatment. Antipsychotics like clozapine and risperidone are associated with blocking of the alpha-1 adrenoceptor. It has been advised that the hemodynamical effects of such drugs are monitored in elderly patients, as they are more vulnerable to the vasodilatory side effects of alpha-1 blocking agents. Adverse events that have been reported in clinical trials of alpha-1 blocking agents include dizziness, weakness, postural hypotension and syncope [6,20]. Antipsychotics like clozapine and the phenothiazines cause histamine-1 receptor blocking in the central nervous system, which can cause sedation. Sedation is also a well known cause of fractures [8,13,29,38]. Remarkably, we did not find an association between different doses of antipsychotics, or between the degree of blockade of the alpha-1 adrenoceptor or histamine-1 receptor and risk of fractures. The lack of association with the risk of fractures is perhaps explained by the alpha-1 blocking effect of antipsychotics not being as strong as alpha-1 adrenergic blockers used in the treatment of hypertension or benign prostate hyperplasia [33], for which the cardiovascular effects are well known. Also, no association between dosing and no association for the strength of the histamine-1 blocking effect and risk of fractures were found. The lack of association can perhaps be explained by patients being treated with multiple medications, with sedative effects.

To our knowledge, there has been no other systematic study of the association between fractures and long-term use of antipsychotics, although concern for this topic has been raised [39]. Multiple lines of evidence suggest that dopamine, which is secreted by the tuberoinfundibular dopaminergic neurons into the portal hypophyseal vessels, is the primary prolactin-inhibiting factor [17]. Hyperprolactinemia is associated with reduced bone mineral density, which is probably mediated by the inhibition exerted by prolactin on the hypothalamic–pituitary–gonadal axis and the resulting hypogonadism [31]. Patients with tumors that secrete prolactin have reduced bone densities at vulnerable sites [11,22]. Bone demineralization could lead to a higher risk of fractures with long-term use. Recently, Meaney et al. [21] found reduced bone mineral density after long-term prolactin-raising antipsychotic medication. In our study, the long-term use of antipsychotics was indeed associated with an increased risk of hip/femur fracture. Which is probably caused by the effect of antipsychotics on decreasing bone mineralization, leading to weaker bones [3,5,12,21,25,39]. This will result in a higher probability that a fall will result in a fracture, increasing the risk of fractures.

We found an increased risk for hip/femur fractures in prior users of antipsychotics. Since our "prior users" of antipsychotics ended their most recent prescription 7 or more days before the index date, no significant amount of antipsychotic would be present in the patient. The increased risk can probably be explained by the fact that damage done to the bone structure is irreversible [23]. Although there are effective bone resorption inhibitors for osteoporosis (bisphosphonates, estrogen and calcitonin), these drugs essentially stabilize bone mass and do not cause substantial increases in bone mass or restore trabecular bone microarchitecture [24]. Damage to the bone structure caused by antipsychotics is probably also irreversible.

There are some limitations to this study. Drug treatment in observational studies is not randomized and is vulnerable to bias and confounding. In our analysis, we controlled for a range of medical conditions and prescription drugs that are associated with an increased risk of hip/femur fracture. However, we cannot rule out the possibility that residual confounding occurred or that alternative causes for our findings exist. Psychiatric patients are exposed to other risks to bone health, particularly excessive nicotine and alcohol consumption [14,27]. To overcome this, we adjusted for weight and smoking. But this study cannot address with certainty the aetiology of the increased risk of fracture in patients using antipsychotics. There remains the possibility that a higher risk of fractures is caused by the underlying disease (e.g. psychosis). Kuruvilla et al. [18] found that prolactin levels in patients with schizophrenia are generally within the normal range prior to treatment for psychosis; schizophrenia itself does not appear to affect prolactin levels. Furthermore, we found no differences in the association between antipsychotic use and the occurrence of hip/femur fractures in patients with and without psychotic disorders, reinforcing the idea that hip/femur fractures are associated with antipsychotic use rather than the underlying disease.

Typical antipsychotics and risperidone raise prolactin levels, but clozapine, quetiapine and olanzapine are not associated with significant prolactin increase because they spare dopamine blockade within the tuberoinfundibular tract [28]. Unfortunately, we did not have enough patients who were treated solely with these atypical antipsychotics.

In conclusion, our findings suggest that use of antipsychotics is associated with a small increased risk of hip/femur fractures. This risk increases with long-term use of antipsychotics. The clinical implication is that patients starting treatment with antipsychotics have a higher risk of hip/femur fractures, regardless of the antipsychotic prescribed.

Acknowledgments

We would like to thank the participating general practitioners for contributing to the research database and EPIC for providing the data.

Appendix A. Antipsychotics categorized according to the affinity for the alpha-1 adrenoceptor and the histamine-1 receptor

Drug	Alfa-1 receptor	Histamine-1 receptor
Amisulpride	Low	Low
Benperidol	Low	Intermediate
Chlorpromazine	High	Intermediate
Clozapine	High	High
Flupentixol	Unknown	Unknown
Fluphenazine	Intermediate	Low
Fluspirilene	Unknown	Unknown
Haloperidol	Intermediate	Low
Levomepromazine	High	High
Loxapine	High	High
Olanzapine	Intermediate	High
Pericyazine	Unknown	Intermediate
Perphenazine	Intermediate	High
Pimozide	High	Low
Pipothiazine	Unknown	Unknown
Promazine	High	High
Quetiapine	Intermediate	High
Risperidone	High	Intermediate
Sertindole	High	Low
Sulpiride	Low	Low
Thioridazine	High	Low
Trifluoperazine	High	Low
Zotepine	High	High
Zuclopenthixol	Intermediate	Intermediate

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