Antipsychotics and risk of venous thromboembolism: A population-based case-control study

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Abstract: During the last decade, the risk of venous thromboembolism (VTE) has been reported in users of antipsychotic drugs. However, the reports have been inconclusive. This study aimed to determine the relative risk of VTE in antipsychotic drug users. Using data from medical databases in North Jutland and Aarhus Counties, Denmark, and the Danish Civil Registration System, we identified 5,999 cases with a first-time diagnosis of VTE and, based on risk set sampling, 59,990 sex- and age-matched population controls during 1997–2005. Users of antipsychotic drugs were identified from population-based prescription databases and categorized based on filled prescriptions prior to admission date for VTE or index date for controls as current (at least one prescription within 90 days), recent (at least one prescription within 91–180 days), former (at least one prescription within 181–365 days) or nonusers (no recorded prescription within 365 days). Compared with nonusers, current users of any antipsychotic drugs had an increased risk of VTE (adjusted relative risk [ARR]: 1.99, 95% confidence interval [CI]: 1.69–2.34). Former users of any antipsychotic drugs had a nonsignificant elevated risk of VTE compared with nonusers (ARR: 1.54, 95% CI: 0.99–2.40, p-value: 0.056). In conclusion, users of antipsychotic drugs have an increased risk of VTE, compared with nonusers, which might be due to the treatment itself, to lifestyle factors, to the underlying disease, or to residual confounding.

Keywords: antipsychotic agents, venous thromboembolism, adverse effects, case-control study

Introduction

Schizophrenia is a chronic, severe, and disabling disorder with a lifetime prevalence of about 0.5% in the general population.[1] Patients suffering from schizophrenia and other psychotic disorders have increased morbidity and mortality from cardiovascular disease.[2] During the past decade, several studies[3–12] have reported that treatment with antipsychotic drugs also may be associated with an increased risk of venous thromboembolism (VTE). The hypothesized association between first-generation (conventional) antipsychotic drugs and VTE is based primarily on one case-control study[3] where Zornberg and colleagues observed a risk of VTE for patients aged less than 60 years currently treated with first-generation antipsychotics, compared with former users of these drugs. As only a limited number of study subjects were taking second-generation (atypical) antipsychotics, the risk of VTE in patients using these newer drugs could not be evaluated in that study. The suggested association between second-generation antipsychotics and VTE is primarily supported by a cohort study[4] of nursing home residents aged 65 years or older where a risk of VTE was observed in new users of second-generation antipsychotics, compared to nonusers. However, in that study no increased risk of VTE in users of first-generation antipsychotics was found. Ray and colleagues[12] did not find an association with VTE in a cohort of patients 65 years of age or older treated with any antipsychotic drug, except for patients receiving haloperidol,

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compared to users of thyroid hormones. Available data on the association between antipsychotic drug use and VTE thus remains conflicting. We undertook this population-based study to investigate the hypothesized increased risk of VTE in current, recent and former users of first-generation (low-potency and high-potency) and second-generation antipsychotic drugs.

Methods

This population-based case-control study was conducted within the counties of Aarhus and North Jutland, Denmark, from January 1, 1997 to December 31, 2005. The two counties have a combined population of 1.1 million, representing approximately 20% of the Danish population. In Denmark use of civil registration numbers (permanent unique identifiers provided at birth to each Danish citizen) allows unambiguous linkage between all demographic and healthcare registries.[13]

Hospital registries contain records of discharges from all nonpsychiatric hospitals since 1977[13] and since 1995 for all outpatient visits. Their files include civil registration number, dates of hospital admission and discharge, and up to 20 discharge diagnoses and procedures, coded according to the international classification of diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter. The Danish National Health Service provides tax-supported health care for all residents of Denmark, including partial reimbursement of the cost of prescribed medications.[13] The pharmacies serving Aarhus and North Jutland counties employ electronic accounting systems, used primarily to secure reimbursement from the National Health Service. For each filled prescription of reimbursed drugs, data on the customer's civil registration number, type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and date of dispensing are transferred from the pharmacies to prescription databases established in 1989 in North Jutland County and in 1996 in Aarhus County.

We used the hospital registries to identify all patients with a first-time diagnosis of VTE, ie, deep vein thrombosis in a lower limb (ICD-8 code: 451.00 and ICD-10 codes: I80.1, 180.2, 180.3) and/or pulmonary embolism (ICD-8 code: 450.99 and ICD-10 code: 126). To control for the increased risk of VTE observed in immobilized patients,[14] we excluded patients with VTE as a secondary admission diagnosis. In a second analysis only patients with a primary idiopathic VTE were included and patients with a secondary VTE,[15] ie, with well-established predisposing conditions defined as surgery, major trauma, fractures, pregnancy within the prior three months, pre-existing cancer, or a cancer diagnosis within the three months following VTE diagnosis[14] were excluded.

Using the Civil Registration System, which has recorded data on vital status, address, and emigration status for the Danish population since April 1, 1968,[13] we identified 10 population controls for each VTE case, matched on age, sex and county. The controls were selected using risk set sampling and assigned an index date identical to the VTE admission date for the matched case.

For both cases and controls, we extracted data from the hospital registries on myocardial infarction, stroke, chronic obstructive pulmonary disease (COPD), peripheral atherosclerosis in the legs, heart failure and diabetes mellitus from the hospital registries, since all these diseases might increase the risk of VTE.[16–18] We included only diagnoses recorded before the hospital admission date for VTE or the index date for controls.

From the population-based prescription databases of North Jutland and Aarhus Counties, we obtained data on all prescriptions for antipsychotic drugs filled within 365 days before the VTE-related hospital admission date for cases or the index date for controls. The drugs were classified as first-generation low-potency antipsychotics (chlorpromazine, chlorprotixene, melperone, pipamperone, promazine and thioridazine), first-generation high-potency antipsychotics (fluphenazine, flupenthixol, haloperidol, penfluridol, periciazine, perphenazine, pimozide, and zuclopenthixol) and second-generation antipsychotics (amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride, and ziprasidone).

Current users of antipsychotic drugs were defined as having filled at least one prescription for any antipsychotic drugs within 90 days before their hospital admission date for VTE or index date for controls. Recent users were defined as having no recorded prescription within 90 days of admission/index date and redemption of at least one prescription within 91–180 days before this date. Former users had no recorded prescription within 180 days of their admission/index date and had filled at least one prescription within 181–365 days prior to this date. Nonusers had no recorded prescription for any antipsychotic drugs within 365 days of their admission/index date.

The prescription databases provided information on current use of statins, low dose acetylsalicylic acid, postmenopausal hormone replacement therapy and vitamin K antagonists, which might affect the risk of VTE.[14,19,20] As well, we retrieved data regarding "ever used" of oral hypoglycemic agents and insulin, as markers of diabetes mellitus.

Using conditional logistic regression analysis, we computed relative risk estimates (odds ratios) with 95% confidence intervals, adjusting for discharge diagnoses of myocardial infarction, stroke, COPD, peripheral atherosclerosis in the legs, heart failure, diabetes and current use of statins, low dose acetylsalicylic acid, postmenopausal hormone replacement therapy and vitamin K antagonists. We also performed analyses stratifying cases and controls by sex since there is a known increased risk of VTE in users of oral contraceptives.[14] We could not capture history of oral contraceptive use, since their purchase is not reimbursed by Denmark's national health care system and hence not registered in the prescription databases. Since risk set sampling controls were used, the odds ratios are unbiased estimates of the corresponding rate ratios. P-values < 0.05 were considered statistically significant.

Results

During the study period we matched 5,999 patients with VTE with 59,990 population controls. Among cases, venous thrombosis was diagnosed in 64% (n = 3,823) and pulmonary embolism in the remaining 36% (n = 2,176). Characteristics of cases and controls are presented in Table 1. Compared with controls, cases had, as expected, a higher prevalence of previous hospitalization for surgery, trauma or fracture, pregnancy and cancer. Persons with this medical history were excluded in a second analysis restricted to 3,471 cases of primary, idiopathic, VTE and 34,608 population controls. In this analysis 67% (n = 2,310) of cases had a diagnosis of venous thrombosis and 33% (n = 1,161) of cases had a diagnosis of pulmonary embolism.

As shown in Table 2, current users of any antipsychotic drug had an increased risk of VTE compared with nonusers (adjusted relative risk [ARR]: 1.99, 95% confidence interval [CI]: 1.69–2.34). An increased risk of VTE compared with nonusers was also observed among subgroups of antipsychotic drug users: current users of low-potency first-generation antipsychotics (ARR: 2.11, 95% CI: 1.51–2.95), current users of high-potency first-generation antipsychotics (ARR: 1.82, 95% CI: 1.46–2.27); and current users of second-generation antipsychotics (ARR: 2.47; 95% CI: 1.87–3.28). An increased risk, although not significant, compared to nonusers was observed for former users of any antipsychotic drugs (ARR: 1.54; 95% CI: 0.99–2.40, p-value: 0.056) and for the following subgroups: former users of second-generation antipsychotics (ARR: 1.36; 95% CI: 0.48–3.88) and former users of high-potency first-generation antipsychotics (ARR: 1.73; 95% CI: 1.06–2.85). Similar relative risks were observed in a supplemental analysis that excluded cases and controls with major risk factors for VTE (Table 2).

Former users of first-generation antipsychotic drugs might be current users of second-generation antipsychotic drugs, thus explaining the increased risk of VTE in these patients. Therefore, we controlled for current use of a second-generation drug in separate post hoc analyses of VTE risk in users of first-generation drugs. These analyses yielded relative risks similar to those obtained in the previous analyses for former users of low-potency first-generation antipsychotics (ARR: 0.92, 95% CI: 0.36–2.34) and for former users of high-potency first-generation antipsychotic drugs (ARR: 1.54, 95% CI: 0.94–2.54). After stratifying by sex, similar risk estimates of VTE were found in female and male current users of any antipsychotic drug (ARR: 2.09, 95% CI: 1.71–2.55 and 1.82, 95% CI 1.37–2.42, respectively) while the risk estimates for former users of antipsychotics were elevated in females (ARR: 1.85, 95% CI: 1.11–3.09), but not in males (ARR: 0.98, 95% CI: 0.40–2.39). Similar relative risks were observed in a supplemental analysis that excluded cases and controls with major risk factors for VTE.

Discussion

In this large population-based nested case-control study, we observed a 2-fold increased risk of VTE in patients currently prescribed antipsychotics, compared with nonusers. Although inconclusive, some previous studies suggest an association between use of antipsychotics and VTE.[3–12] However, there is an inconsistency between the studies whether the increases risk is associated with first-generation antipsychotics, second-generation antipsychotics or both. The hypothesized association between first-generation antipsychotic drugs and VTE is based primarily on one case-control study[3] where the risk of VTE in patients using second-generation drugs could not be evaluated. The suggested association between second-generation antipsychotics and VTE is primarily supported by a cohort study[4] where no increased risk of VTE in users of first-generation antipsychotics was observed. Moreover, no association with VTE was found in a cohort of patients treated with any antipsychotic drug, except for patients receiving haloperidol, compared to users of thyroid hormones.[12] In this study we found an increased risk of VTE in current users of low-potency first-generation, high-potency first-generation and second-generation antipsychotic drug compared to nonusers.

We also found a 1.5-fold increased risk of VTE in former users of any antipsychotic drug compared to never

Table 1 Characteristics of cases with venous thromboembolism (VTE) and population controls

Variable	All VTE cases and controls		Cases with idiopathic VTE and controls	
	Cases No. (%) N = 5,999	Controls No. (%) N = 59,990	Cases No. (%) N = 3,471	Controls No. (%) N = 34,608
Age, y				
<55	1,349 (22.5%)	13,490 (22.5%)	886 (25.5%)	8,859 (25.6%)
55–70	1,799 (30.0%)	17,990 (30.0%)	1,011 (29.1%)	10,108 (29.2%)
>70	2,851 (47.5%)	28,510 (47.5%)	1,574 (45.4%)	15,641 (45.2%)
Sex				
Females	3,291 (54.9%)	32,910 (54.9%)	1,858 (53.5%)	18,525 (53.5%)
Males	2,708 (45.1%)	27,080 (45.1%)	1,613 (46.5%)	16,083 (46.5%)
Any antipsychotics				
Current users[a]	221 (3.7%)	1,128 (1.9%)	125 (3.6%)	675 (2.0%)
Recent users[b]	33 (0.55%)	188 (0.31%)	15 (0.43%)	100 (0.29%)
Former users[c]	27 (0.45%)	173 (0.29%)	18 (0.52%)	103 (0.30%)
Low-potency antipsychotics				
Current users[a]	51 (0.85%)	224 (0.37%)	31 (0.90%)	131 (0.38%)
Recent users[b]	5 (0.083%)	30 (0.050%)	2 (0.058%)	15 (0.043%)
Former users[c]	6 (0.10%)	53 (0.088%)	4 (0.12%)	31 (0.090%)
High-potency antipsychotics				
Current users[a]	116 (1.9%)	648 (1.1%)	67 (1.9%)	399 (1.2%)
Recent users[b]	29 (0.48%)	141 (0.24%)	12 (0.35%)	85 (0.25%)
Former users[c]	22 (0.37%)	117 (0.20%)	13 (0.38%)	68 (0.20%)
Second-generation antipsychotics				
Current users[a]	75 (1.3%)	315 (0.53%)	42 (1.2%)	183 (0.53%)
Recent users[b]	10 (0.17%)	32 (0.053%)	6 (0.17%)	12 (0.035%)
Former users[c]	4 (0.067%)	46 (0.077%)	4 (0.12%)	33 (0.095%)
Current[a] use of statins	267 (4.5%)	2,689 (4.5%)	138 (4.0%)	1,404 (4.1%)
Current[a] use of low dose acetylsalicylic acid	506 (8.4%)	4,667 (7.8%)	284 (8.2%)	2,475 (7.2%)
Current use of HRT	187 (3.1%)	1,908 (3.2%)	88 (2.5%)	962 (2.8%)
Current use of vitamin K antagonists	161 (2.7%)	1,098 (1.8%)	79 (2.3%)	568 (1.6%)
Myocardial infarction	403 (6.7%)	2,879 (4.8%)	221 (6.4%)	1,593 (4.6%)
Stroke	434 (7.2%)	2,967(5.0%)	230 (6.6%)	1,534 (4.4%)
COPD	506 (8.4%)	1,442 (2.4%)	293 (8.4%)	731 (2.1%)
Lower limb atherosclerosis	223 (3.7%)	1,047 (1.8%)	96 (2.8%)	513 (1.5%)
Heart failure	413 (6.9%)	2,226 (3.7%)	216 (6.2%)	1,157 (3.3%)
Diabetes mellitus	459 (7.7%)	3,270 (5.5%)	268 (7.7%)	1,700 (4.9%)
Surgery[d]	1,709 (28.5%)	2,225 (3.7%)	–	–
Trauma or fracture[d]	476 (7.9%)	1,078 (1.8%)	–	–
Pregnancy[d]	44 (0.7%)	121 (0.2%)	–	–
Cancer[e]	1,183 (19.7%)	4,919 (8.2)	–	–

Notes: [a]Within 90 days before hospital admission/index date; [b]Within 91–180 days before hospital admission/index date; [c]Within 181–365 days before hospital admission/index date; [d]Within three months before hospital admission/index date; [e]Pre-existing cancer or a cancer diagnosis within three months after hospital admission/index date.
Abbreviations: COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; VTE, venous thromboembolism.

users. Previously, the risk for VTE among former users of antipsychotic drugs has only been investigated in three studies. In two of these studies[3,5] the risk of VTE in current users of antipsychotic drugs was compared with that of former users. In one study[6] estimating the risk of VTE in formers users of antipsychotic drugs compared to nonusers, where a 5-fold increased, although not significant (95% CI, 0.6–46), risk for VTE was found.

Table 2 Crude and adjusted relative risk estimates (odds ratios) for venous thromboembolism by antipsychotic drug use compared with nonuse

Variable	All cases and controls		Cases with idiopathic VTE and controls	
	Unadjusted relative risk (95% CI)	Adjusted relative risk[a] (95% CI)	Unadjusted relative risk (95% CI)	Adjusted relative risk[b] (95% CI)
Any antipsychotics				
Current users[c]	2.01 (1.73–2.33)	1.99 (1.69–2.34)	1.90 (1.56–2.31)	1.87 (1.53–2.28)
Recent users[d]	1.76 (1.22–2.55)	1.53 (1.02–2.30)	1.50 (0.87–2.59)	1.44 (0.83–2.50)
Former users[e]	1.56 (1.04–2.35)	1.54 (0.99–2.40)	1.75 (1.06–2.89)	1.68 (1.00–2.83)
Low-potency antipsychotics				
Current users[c]	2.29 (1.69–3.11)	2.11 (1.51–2.95)	2.38 (1.61–3.54)	2.14 (1.43–3.20)
Recent users[d]	1.67 (0.65–4.31)	1.17 (0.42–3.32)	1.33 (0.30–5.79)	0.93 (0.20–4.23)
Former users[e]	1.13 (0.49–2.63)	0.99 (0.39–2.54)	1.29 (0.46–3.66)	1.08 (0.37–3.17)
High-potency antipsychotics				
Current users[c]	1.82 (1.49–2.22)	1.82 (1.46–2.27)	1.70 (1.31–2.21)	1.71 (1.31–2.23)
Recent users[d]	2.07 (1.38–3.09)	1.72 (1.10–2.70)	1.42 (0.77–2.60)	1.44 (0.78–2.65)
Former users[e]	1.89 (1.19–2.98)	1.73 (1.06–2.85)	1.91 (1.05–3.47)	1.81 (0.98–3.34)
Second-generation antipsychotics				
Current users[c]	2.41 (1.87–3.11)	2.47 (1.87–3.28)	2.33 (1.66–3.27)	2.32 (1.64–3.28)
Recent users[d]	3.13 (1.54–6.36)	3.35 (1.56–7.19)	4.98 (1.87–13.26)	4.44 (1.62–12.20)
Former users[e]	0.87 (0.31–2.42)	1.36 (0.48–3.88)	1.21 (0.43–3.42)	1.34 (0.47–3.81)

Notes: [a]Adjusted for current use of statins, acetylsalicylic acid, hormone replacement therapy and Vitamin K antagonists and discharge diagnoses of stroke, chronic obstructive pulmonary disease, myocardial infarction, atherosclerosis, heart failure, diabetes, cancer, surgery, trauma or fracture, and pregnancy; [b]Adjusted for current use of statins, acetylsalicylic acid, hormone replacement therapy and Vitamin K antagonists and discharge diagnoses of stroke, chronic obstructive pulmonary disease, myocardial infarction, atherosclerosis, heart failure, and diabetes; [c]Within 90 days before hospital admission/index date; [d]Within 91–180 days before hospital admission/index date; [e]Within 181–365 days before hospital admission/index date.

Abbreviations: CI, confidence interval; VTE, venous thromboembolism.

In our study, when study subjects were stratified by sex, the increased risk of VTE remained only in female former users of any antipsychotic drugs. Since there is no known increased risk of VTE in females *per se*[14] this finding might be explained by use of drugs containing female hormones, a well known risk factor for VTE.[14] About 4% of the females in the study population was estimated to use oral contraceptives based on a reported use of oral contraceptives in 33% of Danish women aged 15–44 years.[21] In our study, use of hormone replacement therapy was controlled for, but we could not control for the use of oral contraceptives since their costs are not reimbursed by the national health care system and information on filled prescriptions is not recorded in the prescription databases.[13]

The main strengths of this study include its population-based design and access to prospectively recorded data on outcomes, possible confounding factors and drug exposure. A number of potential weaknesses deserve discussion. Medical records vary in quality and discharge diagnoses may not be entirely correct. While approximately 20% of patients listed in hospital discharge registries with VTE may not fulfill the criteria for the disease,[22] these discrepancies probably do not differ by drug exposure.

Although we adjusted for a wide range of possible confounding factors, our results may still be confounded by uncontrolled factors like smoking, diet, obesity and schizophrenic behavior. The higher smoking rate among psychiatric patients, compared with the general population, and the greater number of cigarettes consumed by these patients are potential confounders,[2,23] since smoking and chronic obstructive pulmonary disease, a smoking-related disease, are thought to increase the risk of VTE.[16,24] While we were not able to control for smoking, we did control for COPD. Moreover, we controlled for the use of some drugs that might affect the risk of VTE, it was not possible to control for drugs that are sold over the counter or drugs that are not reimbursed by the national health care system.

Other limitations include lack of data on compliance and duration of actual use of the prescribed drugs. The categorization of current, recent and former use thus may not reflect actual use. This might explain the increased risk for VTE found among recent users of second-generation antipsychotic drugs compared to nonusers. Study findings may also be influenced by the fact that antipsychotic drugs are used to treat a wide range of disorders, including

psychoses, anxiety and mood disorders, behavioral disorders and dementia.[25] Among all users of antipsychotic drugs, 48% were above 71 years of age. This suggests that the drugs are used for indications other than schizophrenia, at least in the elderly group. Unfortunately, we were not able to include information about the indication for practical reasons.

Several factors related to treatment or the underlying disease have been proposed as mechanisms for the increased risk of VTE among patients taking antipsychotic drugs.[26] First, all situations involving immobilization increase VTE risk.[14] Psychotic patients may be immobilized due to sedation, a common adverse effect of many antipsychotic drugs, especially first-generation low-potency antipsychotics[27] and clozapine.[28] Patients diagnosed with severe psychotic conditions may also require immobilization through sedation or mechanical restraint. Second, obesity, a risk factor found in schizophrenic patients with or without treatment with antipsychotic drugs, is associated with an increased risk of VTE.[29] Clinically significant weight gain is more common among patients with schizophrenia than in the general population and treatment with antipsychotic drugs may also induce weight gain.[30] The increased risk of VTE thus might be explained by immobilization and obesity, induced by use of antipsychotic drugs. However, smoking and nondrug-related obesity could still explain the associations.

As well, antipsychotic drug treatment has been associated with enhanced platelet aggregation,[26] and elevated levels of prolactin correlated with platelet activation have been observed.[31] Clozapine has been associated with platelet adhesion and aggregation *in vitro*.[32] Raised levels of antiphospholipid antibodies, including lupus anticoagulantia and anticardiolipin antibodies, have been observed in patients treated with antipsychotic drugs[26] and have been associated with increased VTE risk.[14] Moderate homocysteinameia (15–100 μM), associated with a 2–3-fold increased risk of VTE,[14,33] has been observed in patients with schizophrenia.[34] The mechanism by which high homocysteine levels increase the risk of VTE is unknown.[14]

In conclusion, our study found that users of antipsychotic drugs have an increased risk of VTE, compared with nonusers. The observed increased risk might be due to the treatment itself, to lifestyle factors, to the underlying disease or to residual confounding.

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Appendix: ICD and ATC codes

Venous thromboembolism: ICD-8 451.00, 450.99 ICD-10 I801–03, I26

Cancer: ICD-8 140–209, ICD-10 C00–C99

Pregnancy or delivery: ICD-8 630–680, ICD-10 O00–O99

Fractures or trauma: ICD-8 800–999, ICD-10 S00–T14

Stroke: ICD-8 431–435, ICD-10 I61, I63, I64, I65, I66

Chronic obstructive disease: ICD-8 491–492, ICD-10 J42–J44

Myocardial infarction: ICD-8 410, ICD-10 I21

Atherosclerosis extremitas inferioris: ICD-8 44020, ICD-10 I702

Heart failure: ICD-8 42709, 42710, 42711, ICD-10 I50

Diabetes: ICD-8 249, 250, ICD-10 E10, E11

Antidiabetics: ATC codes A10A, A10B

Statins: ATC code C10AA

Low dose acetylsalicylic acid: ATC codes B01AC06

Postmenopausal hormone replacement therapy: ATC code G03C

Vitamin K antagonists: ATC codes B01AA03, B01AA04

Low-potency first-generation antipsychotics: ATC codes N05AD03, N05AD05, N05AA01, N05AF03, N05AC02, N05AA03

High-potency first-generation antipsychotics: ATC codes N05AF05, N05AB03, N05AC01, N05AD01, N05AF01, N05AG02, N05AB02, N05AG03

Second-generation antipsychotics: ATC codes N05AH02, N05AL01, N05AX08, N05AE03, N05AH04, N05AL05, N05AE04, N05AH03

Any antipsychotics: ATC codes N05AD03, N05AD05, N05AA01, N05AF03, N05AC02, N05AA03, N05AF05, N05AB03, N05AC01, N05AD01, N05AF01, N05AG02, N05AB02, N05AG03, N05AH02, N05AL01, N05AX08, N05AE03, N05AH04, N05AL05, N05AE04, N05AH03