ORIGINAL ARTICLE

Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

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ABSTRACT

BACKGROUND

Users of typical antipsychotic drugs have an increased risk of serious ventricular arrhythmias and sudden cardiac death. However, less is known regarding the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice.

METHODS

We calculated the adjusted incidence of sudden cardiac death among current users of antipsychotic drugs in a retrospective cohort study of Medicaid enrollees in Tennessee. The primary analysis included 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonusers of antipsychotic drugs. To assess residual confounding related to factors associated with the use of antipsychotic drugs, we performed a secondary analysis of users of antipsychotic drugs who had no baseline diagnosis of schizophrenia or related psychoses and with whom nonusers were matched according to propensity score (i.e., the predicted probability that they would be users of antipsychotic drugs).

RESULTS

Current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than did nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 (95% confidence interval [CI], 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The incidence-rate ratio for users of atypical antipsychotic drugs as compared with users of typical antipsychotic drugs was 1.14 (95% CI, 0.93 to 1.39). Former users of antipsychotic drugs had no significantly increased risk (incidence-rate ratio, 1.13; 95% CI, 0.98 to 1.30). For both classes of drugs, the risk for current users increased significantly with an increasing dose. Among users of typical antipsychotic drugs, the incidence-rate ratios increased from 1.31 (95% CI, 0.97 to 1.77) for those taking low doses to 2.42 (95% CI, 1.91 to 3.06) for those taking high doses ($P<0.001$). Among users of atypical agents, the incidence-rate ratios increased from 1.59 (95% CI, 1 .03 to 2.46) for those taking low doses to 2.86 (95% CI, 2.25 to 3.65) for those taking high doses ($P=0.01$). The findings were similar in the cohort that was matched for propensity score.

CONCLUSIONS

Current users of typical and of atypical antipsychotic drugs had a similar, dose-related increased risk of sudden cardiac death.

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There are extensive data linking the typical antipsychotic drugs to an increased risk of sudden cardiac death. These medications block repolarizing potassium currents in vitro[1,2] and prolong the QT interval,[1,3,4] one important causal mechanism for the ventricular tachyarrhythmias that often lead to sudden cardiac death.[5] There are numerous case reports of torsades de pointes and sudden death in conjunction with the use of the typical antipsychotic drugs.[6,7] Controlled epidemiologic studies have shown a dose-related increased risk of sudden cardiac death associated with the use of these medications.[8-11] Indeed, thioridazine, once one of the most frequently prescribed antipsychotic drugs, now carries a black-box warning of an increased risk of cardiac arrhythmias and sudden death.[12]

Less is known about the cardiac safety of the atypical antipsychotic drugs, which have largely replaced the older agents in clinical practice. Several atypical antipsychotic drugs block repolarizing potassium currents[2] and prolong ventricular repolarization,[1,13] and the electrophysiological effects of some of these drugs are similar to those of the older agents. However, although torsades de pointes has been reported in persons using atypical antipsychotic drugs,[14-16] whether these drugs increase the risk of sudden cardiac death to the same extent as the older medications is unknown. We therefore conducted a large retrospective cohort study that was designed to compare the risk of sudden cardiac death associated with the use of the two classes of antipsychotic drugs.

Methods

Primary Cohort

We obtained the study data from computerized files of Tennessee Medicaid, which have been used extensively for pharmacoepidemiologic research.[17,18] Each person-day of Medicaid enrollment from January 1, 1990, through December 31, 2005 (the study period), was evaluated to determine whether it qualified for inclusion in the analysis. The cohort was restricted to persons 30 to 74 years of age, because among persons younger than 30, sudden cardiac death is very rare and may have a different cause,[19] and among persons older than 74, we found death certificates to be less reliable for identifying sudden cardiac deaths. Inclusion in the cohort required the person to have been enrolled in Tennessee Medicaid for at least 730 days (gaps of <7 days were allowed) and to have been eligible for full pharmacy benefits and made regular use of medical care (defined as having had at least one filled prescription and one outpatient visit in each of the 2 preceding years). Patients at high risk for death from noncardiac causes were excluded from the cohort (see Appendix 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The cohort included every eligible Medicaid enrollee with at least 1 qualifying day of use of antipsychotic drugs during the study period. The first day of follow-up was defined as the first qualifying day. The cohort also included two controls for each user of antipsychotic drugs, matched for age, sex, and first day of follow-up, who were randomly selected from qualifying nonusers of antipsychotic drugs on the first day of follow-up.

Follow-up extended from the first qualifying day until the end of the study period, the death of the person, the termination of Medicaid enrollment, or the date on which eligibility criteria for inclusion in the cohort were no longer met. Controls could become users of antipsychotic drugs, and patients who left the cohort could reenter it. The follow-up time did not include time during hospitalization and the 30 days after discharge from the hospital because in-hospital deaths were not considered to be study end points and Medicaid files do not include drugs dispensed in the hospital.

The Vanderbilt Committee for the Protection of Human Subjects approved the study and waived the requirement for informed consent. Tennessee's Bureau of TennCare and Department of Health also approved the study. The study was funded by grants from federal agencies, which had no role in study conduct or reporting.

Cohort Matched for Propensity Score

To assess residual confounding by factors associated with the use of antipsychotic drugs, we performed a secondary analysis, using propensity scores[20] (i.e., the predicted probability that a person would be a user of antipsychotic drugs) to identify a nonuser control group with a similar psychiatric-illness profile. This matched cohort excluded users of antipsychotic drugs who had a diagnosis of schizophrenia or related psychosis in the 730 days before the first day of follow-up, since treatment with antipsychotic drugs is the standard of

care for these conditions. Thus, this group of qualifying users of antipsychotic drugs primarily had mood disorders (a growing reason for the use of antipsychotic drugs), for which there are alternative medications. For each qualifying user, up to two controls were adaptively matched for propensity score (i.e., controls were selected so as to reduce differences in running mean propensity scores) (Appendix 1 in the Supplementary Appendix), within strata defined by the first day of follow-up, birth year, sex, and a marker of severe psychiatric illness (previous hospitalization for psychiatric cause, diagnosis of bipolar disorder, or lithium therapy).

EXPOSURE TO ANTIPSYCHOTIC DRUGS AND OTHER MEDICATIONS

Antipsychotic drugs and other study medications were identified from Medicaid pharmacy files. Data in the files included the date the prescription was dispensed, the drug, the quantity, the dose, and the number of days of supply (edited to resolve infrequent discrepancies with quantity). Computerized pharmacy records are an excellent source of medication data because they are not subject to information bias[17] and have high concordance with medication use as reported by patients.[21-23] The residual misclassification should be limited, and any bias is likely to be in favor of the null hypothesis.[17]

Each person-day of study follow-up was classified according to the probable use of antipsychotic drugs. Current use included the interval between the time the person filled the prescription and the end of the days of supply (up to a 7-day carryover from previous prescriptions), when the person was most likely to be taking the drug. Indeterminate use included the period up to 90 days after the last current use, and former use included any subsequent person-time that was not classified as current or indeterminate use. Nonuse referred to person-days with no prescribed use of antipsychotic drugs on those days or at any time in the past. Current use was further classified according to the doses of the drugs, which were expressed as approximate equivalents of 100 mg of chlorpromazine (Appendix 1 in the Supplementary Appendix)[24,25] and then categorized as low-dose (<100 mg), moderate-dose (100 to 299 mg), or high-dose (≥300 mg). The individual drugs that were analyzed were thioridazine and haloperidol, the most frequently prescribed typical agents, as well as atypical antipsychotic drugs with 3000 person-years or more of current use in the primary cohort (for which ≥5 cases of sudden death were expected under the null hypothesis): clozapine, quetiapine, olanzapine, and risperidone.

STUDY END POINT

The study end point was sudden cardiac death occurring in the community.[26-28] Sudden cardiac death was defined as a sudden pulseless condition that was fatal, that was consistent with a ventricular tachyarrhythmia, and that occurred in the absence of a known noncardiac condition as the proximate cause of the death.[27] The end point excluded deaths of patients who had been admitted to the hospital, deaths that were not sudden, and deaths for which there was evidence of an extrinsic cause (e.g., drug overdose), a noncardiac cause (e.g., pneumonia), or a cardiac cause that was not consistent with a ventricular tachyarrhythmia (e.g., heart failure).

End points were identified from computerized death certificates linked with computerized Medicaid records. The case definition was developed from and validated by our previous study,[8,29,30] in which medical records were reviewed for deaths that occurred between 1988 and 1993. Qualifying deaths occurred outside the hospital or other institution and had an underlying cause of death that our previous study had determined to be compatible with sudden cardiac death (Appendix 1 in the Supplementary Appendix). These deaths were further restricted to those for which there was no evidence of care in the emergency department on the day of death that was inconsistent with care for sudden cardiac death. In our previous study,[8] we reviewed medical records for 616 of such qualifying deaths that occurred in the present cohort. Of these deaths, 530 (86.0%) were confirmed cases of sudden cardiac death (unpublished data). As long as the accuracy of the definition of sudden cardiac death did not vary according to the use of antipsychotic drugs, the residual misclassification should bias the results toward the null hypothesis.[31]

STATISTICAL ANALYSIS

The relative risk of sudden cardiac death according to current use, former use, or nonuse of antipsychotic drugs, adjusted for dose (Appendix 1 in the Supplementary Appendix), was estimated with the incidence-rate ratio, as calculated from

Poisson regression models. The models (Appendix 1 in the Supplementary Appendix) included demographic characteristics and variables reflecting coexisting conditions at baseline and subsequent changes during follow-up. Baseline coexisting conditions included cardiovascular and other somatic disease as well as psychiatric and neurologic illness.

We calculated a summary cardiovascular risk score from the large number of baseline cardiovascular and somatic variables. The variables included prescribed medications and recorded diagnoses, as well as utilization of medical care and a measure of compliance with drugs (Appendix 1 in the Supplementary Appendix) for long-term use. The summary risk score was defined for the entire cohort as the predicted probability of sudden death, conditional on no exposure to antipsychotic drugs (estimated with Poisson regression analysis among nonusers of antipsychotic drugs), and then expressed as 20 equal parts. This technique permits more parsimonious models when there are numerous covariates and facilitates description of baseline cardiovascular risk.[32]

We performed several supplementary analyses to test key assumptions. These included an analysis that permitted only one cohort entry per person, as well as analyses in which additional baseline and time-dependent variables were included in the model (Appendix 1 in the Supplementary Appendix). The findings were essentially identical to those reported here.

All analyses were performed with the use of SAS software, version 9.0 (SAS Institute). All reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE STUDY COHORTS

The primary cohort included 93,300 users of antipsychotic drugs and 186,600 matched controls. There were 44,218 and 46,089 users of single typical and atypical antipsychotic drugs, respectively, at cohort entry. The cohort that was matched for propensity score included 67,824 users of antipsychotic drugs and 116,069 nonusers.

In the primary cohort, users and nonusers of antipsychotic drugs had similar baseline demographic characteristics (Table 1). The mean age was 45.7 years; 65.2% of the cohort members were women, 70.5% were white, and 56.9% were urban residents. Users of antipsychotic drugs were more likely than nonusers to be enrolled in Medicaid because of disability (62.9% vs. 37.4%), but they had a slightly lower mean baseline cardiovascular risk score (9.2 vs. 9.6 on a scale of 0 to 19, with higher scores indicating increased risk). As expected, users of antipsychotic drugs had a higher prevalence of coexisting psychiatric conditions at baseline than did nonusers; however, there was a substantial prevalence of coexisting conditions, particularly affective disorders, among nonusers as well. In the cohort matched for propensity score, users and nonusers of antipsychotic drugs had identical mean propensity scores and similar baseline rates of coexisting psychiatric conditions.

As compared with users of typical antipsychotic drugs, users of atypical antipsychotic drugs were slightly younger, were less likely to be enrolled in Medicaid because of disability, and had a higher baseline cardiovascular risk score (Appendix 2 in the Supplementary Appendix). They also used higher doses of antipsychotic drugs, in part owing to the preponderance of low-dose use for the typical drug thioridazine (53.9% of thioridazine users took low doses). Users of atypical antipsychotic drugs also were less likely to have a diagnosis of schizophrenia than were users of typical antipsychotic drugs (13.5% vs. 27.1%), with the exception of users of clozapine (which is indicated for treatment-resistant psychosis[24]), of whom 89.1% had a diagnosis of schizophrenia. Users of atypical antipsychotic drugs were more likely to have diagnosed mood disorders than were users of typical drugs (bipolar disorder, 23.3% vs. 12.1%; other mood disorders, 60.2% vs. 36.3%).

SUDDEN CARDIAC DEATH

During the 1,042,159 person-years of cohort follow-up, there were 1870 sudden cardiac deaths, or 17.9 per 10,000 person-years. The unadjusted rate increased from 4.7 deaths per 10,000 for persons 30 to 34 years of age at baseline to 47.6 per 10,000 for those 70 to 74 years of age and was more than twice as high for men as for women (27.1 vs. 12.9 per 10,000).

Current users of typical antipsychotic drugs had an adjusted rate of sudden cardiac death that was twice that for nonusers (incidence-rate ratio, 1.99; 95% confidence interval [CI], 1.68 to 2.34) (Table 2). A similar increased risk was seen for current users of atypical antipsychotic drugs, who had a rate of sudden cardiac death that was more than twice that for nonusers (incidence-rate ratio,

Table 1. Baseline Characteristics of Cohort Members, According to Use or Nonuse of Antipsychotic Drugs at Cohort Entry.*

Characteristic	Primary Cohort		Cohort Matched for Propensity Score†	
	Nonuser (N=186,600)	Current User (N=93,300)	Nonuser (N=116,069)	Current User (N=67,824)
Mean year of cohort entry	1998	1998	1998	1999
Study follow-up (yr)				
Median	2.2	2.9	2.4	2.6
Interquartile range	0.9–4.8	1.2–6.1	0.9–5.0	1.1–5.2
Age (yr)	45.7±11.8	45.7±11.8	46.4±12.0	46.3±11.8
Male sex (%)	34.8	34.8	32.1	30.3
Nonwhite race (%)‡	30.0	28.5	25.8	24.2
Urban residence (%)	56.6	57.5	53.3	54.2
Medicaid enrollment due to disability (%)	37.4	62.9	60.7	57.6
Cardiovascular risk score§	9.6±5.8	9.2±5.8	9.5±5.8	9.4±5.7
Mean propensity score¶	NA	NA	0.52	0.52
Psychiatric characteristics (%)‖				
Use of moderate or high dose of antipsychotic drug**	NA	69.0	NA	62.0
Schizophrenia	1.4	21.3	0	0
Other psychosis	1.0	9.7	0	0
Bipolar disorder	2.6	18.2	14.2	17.1
Major depression or other mood disorder	17.2	48.4	51.3	52.6
Dementia	0.6	3.1	2.9	2.9
Alcohol or prescription-drug dependency	4.9	8.3	9.6	7.9
History of suicide attempt	1.2	3.5	3.5	3.5
Previous stay in psychiatric hospital	3.8	21.7	15.0	14.7
Use of lithium	1.2	9.3	6.1	7.6
Use of mood stabilizer	8.3	24.0	22.2	24.4
Use of antidepressant	41.5	73.0	76.3	79.4
Use of benzodiazepine	34.1	56.0	58.8	61.6

* Factors defined on the basis of medical care encounters reflect any encounter within the 730 days preceding the first day of follow-up, except for the cardiovascular risk score and the dose of antipsychotic drugs, which are those at the start of cohort follow-up. Plus–minus values are means ±SD. NA denotes not applicable.
† Persons with schizophrenia and related psychoses were excluded from this cohort.
‡ Nonwhite race was self-reported.
§ The cardiovascular risk score has a range of 0 to 19, with higher scores indicating increased risk. The variables included in the score are listed in Appendix 1 in the Supplementary Appendix. The score was derived as described in the Methods section.
¶ The propensity score is the predicted probability that persons would be users of antipsychotic drugs.
‖ A cohort member may have had multiple diagnoses.
** Doses were calculated as chlorpromazine equivalents (see Appendix 1 in the Supplementary Appendix): low dose, <100 mg; moderate dose, 100 to 299 mg; and high dose, 300 mg or more.

2.26; 95% CI, 1.88 to 2.72) and that did not differ significantly from the rate for users of the typical agents (incidence-rate ratio for users of atypical as compared with users of typical antipsychotic drugs, 1.14; 95% CI, 0.93 to 1.39). The rates of sudden cardiac death for both current users of typical antipsychotic drugs and current users of atypical drugs were greater than those for former users (P<0.001). Former users did not have a significantly increased risk of sudden cardiac death as compared with nonusers (incidence-rate ratio, 1.13; 95% CI, 0.98 to 1.30). Users of each of the six fre-

Table 2. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death, According to Use or Nonuse of Antipsychotic Drugs.*

User Status	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	624,591	895	Reference group	
Former user	189,981	311	1.13 (0.98–1.30)	0.08
Current user†				
Typical agent				
Any	86,735	255	1.99 (1.68–2.34)	<0.001
Haloperidol	21,728	58	1.61 (1.16–2.24)	0.005
Thioridazine	15,715	65	3.19 (2.41–4.21)	<0.001
Atypical agent				
Any	79,589	223	2.26 (1.88–2.72)	<0.001
Clozapine	4,654	19	3.67 (1.94–6.94)	<0.001
Olanzapine	27,257	75	2.04 (1.52–2.74)	<0.001
Quetiapine	17,355	40	1.88 (1.30–2.71)	<0.001
Risperidone	24,589	85	2.91 (2.26–3.76)	<0.001

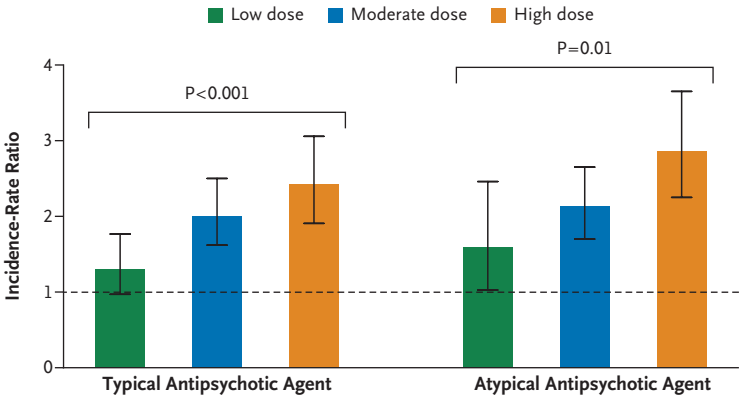
* The total excludes 45,381 person-years and 134 deaths for indeterminate users of antipsychotic drugs, as well as 15,883 person-years and 52 deaths for concurrent users of multiple antipsychotic drugs.
† The analysis of these drugs included an adjustment for dose according to the method described in Appendix 1 in the Supplementary Appendix.

quently prescribed antipsychotic drugs had a significantly increased rate of sudden cardiac death (Table 2).

The risk of sudden cardiac death increased with an increasing dose among current users of typical or atypical antipsychotic drugs (Fig. 1). Among users of the typical agents, the incidence-rate ratios increased from 1.31 (95% CI, 0.97 to 1.77) for persons taking low doses to 2.42 (95% CI, 1.91 to 3.06) for those taking high doses (P<0.001 for dose–response relationship). Among users of the atypical drugs, the incidence-rate ratios increased from 1.59 (95% CI, 1.03 to 2.46) for persons taking low doses to 2.86 (95% CI, 2.25 to 3.65) for those taking high doses (P=0.01 for dose–response relationship). There was a dose–response trend for each of the six frequently prescribed drugs (Fig. 2), a trend that was significant in the case of thioridazine (P=0.005) and of borderline significance in the case of risperidone (P=0.05). Current users of thioridazine in high doses (≥300 mg) had the greatest increased risk (incidence-rate ratio, 5.05; 95% CI, 3.09 to 8.27).

In the cohort matched for propensity score (Table 3), both current users of typical antipsychotic drugs and current users of atypical antipsychotic drugs had an increased risk of sudden cardiac death as compared with nonusers, with incidence-rate ratios of 1.84 (95% CI, 1.50 to 2.26) and 1.99 (95% CI, 1.61 to 2.46), respectively. There was a significant dose–response relationship for each class (P<0.001 and P<0.05, respectively). The incidence-rate ratio for users of atypical drugs as compared with users of typical antipsychotic drugs was 1.08 (95% CI, 0.82 to 1.43).

We performed several additional analyses to test the robustness of the study findings. To assess the influence of the adverse metabolic effects of long-term use of antipsychotic drugs,[12] we performed an analysis that was restricted to data from persons whose cumulative use of the drugs was less than 365 days' duration. The respective incidence-rate ratios for current users of the typical and atypical drugs as compared with nonusers were 1.73 (95% CI, 1.09 to 2.72; P=0.02) and 1.87 (95% CI, 1.29 to 2.73; P=0.001). To assess possible bias from inclusion of persons who used antipsychotic drugs before the beginning of follow-up, which could preferentially eliminate patients who might be susceptible to proarrhythmic effects,[33] we analyzed data from cohort members who had not used antipsychotic drugs during the 2 years preceding the first day of follow-up. In this analysis, the respective incidence-rate



No. of Deaths	46	104	105	22	108	93
No. of Person-Years	21,438	33,671	31,626	10,435	41,513	27,641
Incidence-Rate Ratio	1.31	2.01	2.42	1.59	2.13	2.86
95% CI	0.97–1.77	1.62–2.50	1.91–3.06	1.03–2.46	1.70–2.65	2.25–3.65

Figure 1. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Antipsychotic Drugs, According to Type of Drug and Dose.

Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of antipsychotic drugs. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.

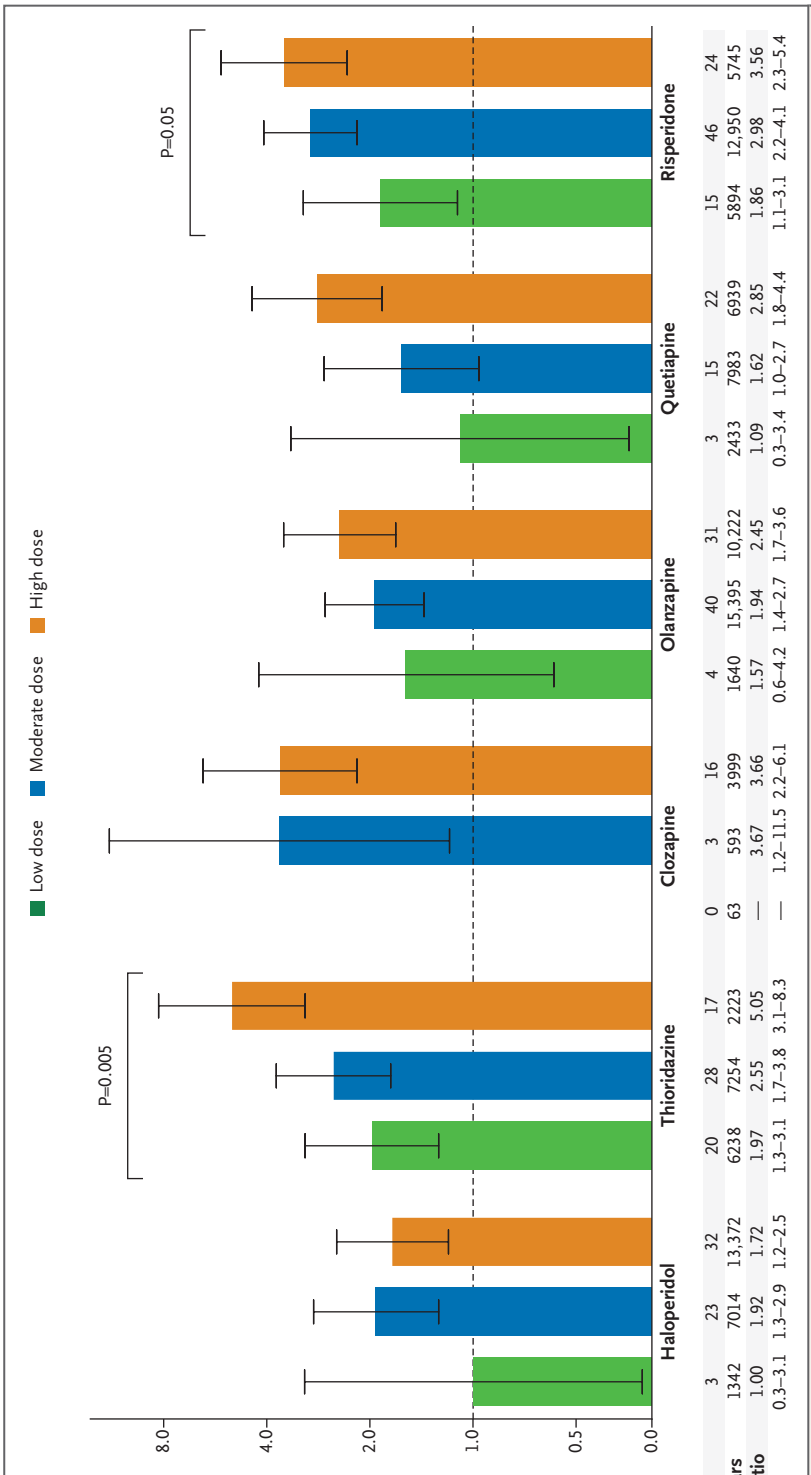
ratios for current users of typical and atypical antipsychotic drugs as compared with nonusers were 1.74 (95% CI, 1.14 to 2.67; P=0.001) and 1.86 (95% CI, 1.35 to 2.57; P<0.001). To assess the effects of secular trends in the use of antipsychotic drugs and the incidence of sudden cardiac death, we performed an analysis that was restricted to data from 1998 through 2005; the respective incidence-rate ratios for current users of typical and atypical antipsychotic drugs as compared with nonusers were 1.78 (95% CI, 1.35 to 2.35; P<0.001) and 2.03 (95% CI, 1.65 to 2.50; P<0.001).

DISCUSSION

The frequent occurrence of serious movement disorders in persons taking typical antipsychotic drugs limited the use of these drugs.[2-4] Because atypical antipsychotic drugs are less likely to have this adverse effect, they have been considered a safer treatment alternative[3,4] and have rapidly replaced the older drugs in clinical practice. Overall, the use of antipsychotic drugs has increased, with the number of outpatient visits related to the prescription of an antipsychotic drug nearly doubling between 1998 and 2002.[3,4]

Although a link between the use of typical antipsychotic drugs and both torsades de pointes and sudden cardiac death has been established,[5,35] this risk was thought to be lower with the use of atypical drugs.[36] However, the limited data available on the surrogate markers for torsades de pointes — inhibition of the potassium current I_{Kr} and prolongation of the QT interval — suggest that commonly used atypical drugs have electrophysiological effects that are similar to those of the typical antipsychotic drugs.[1,13] There are now case reports that document the occurrence of torsades de pointes among users of several atypical antipsychotic drugs.[14-16] Our data show that in a large retrospective cohort of adults, current users of the atypical antipsychotic drugs had a dose-dependent increase in the risk of sudden cardiac death that was essentially identical to that among users of the typical agents.

The primary limitation of our study is the potential for confounding by factors associated with the use of antipsychotic drugs. For persons with serious mental illness, these factors include cardiovascular and other somatic disease; concurrent use of other proarrhythmic medications; mood disorders; behavioral risk factors, including substance abuse, poor self-care, and smoking; and other effects of mental illness.[12] However, both the study design and analysis included several provisions to manage confounding.



	Haloperidol			Thioridazine			Clozapine			Olanzapine			Quetiapine			Risperidone		
No. of Deaths	3	23	32	20	28	17	0	3	16	4	40	31	3	15	22	15	46	24
No. of Person-Years	1342	7014	13,372	6238	7254	2223	63	593	3999	1640	15,395	10,222	2433	7983	6939	5894	12,950	5745
Incidence-Rate Ratio	1.00	1.92	1.72	1.97	2.55	5.05	—	3.67	3.66	1.57	1.94	2.45	1.09	1.62	2.85	1.86	2.98	3.56
95% CI	0.3–3.1	1.3–2.9	1.2–2.5	1.3–3.1	1.7–3.8	3.1–8.3	—	1.2–11.5	2.2–6.1	0.6–4.2	1.4–2.7	1.7–3.6	0.3–3.4	1.0–2.7	1.8–4.4	1.1–3.1	2.2–4.1	2.3–5.4

Figure 2. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Six Frequently Prescribed Antipsychotic Drugs, According to Dose.
Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of any antipsychotic drug. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.

Table 3. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death in the Cohort Matched for Propensity Score, According to Use or Nonuse of Antipsychotic Drugs and According to Dose.*

Variable	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	390,072	705	Reference group	
Former user	159,415	243	0.93 (0.80–1.08)	0.30
Current user†				
Typical agent				
Any	42,231	125	1.84 (1.50–2.26)	<0.001
Haloperidol	7,189	21	1.39 (0.89–2.19)	0.15
Thioridazine	9,547	41	3.05 (2.15–4.33)	<0.001
Atypical agent				
Any	45,853	116	1.99 (1.61–2.46)	<0.001
Clozapine	418	4	8.06 (2.58–25.23)	<0.001
Olanzapine	15,076	42	1.99 (1.41–2.79)	<0.001
Quetiapine	13,730	26	1.49 (0.98–2.27)	0.06
Risperidone	13,047	41	2.49 (1.72–3.62)	<0.001
Dose‡				
Typical agent				
Low	16,293	36	1.13 (0.81–1.59)	0.47
Moderate	18,203	55	1.59 (1.20–2.11)	0.001
High	7,735	34	2.70 (1.90–3.84)	<0.001
Atypical agent				
Low	8,237	18	1.52 (0.94–2.44)	0.08
Moderate	25,694	58	1.68 (1.28–2.22)	<0.001
High	11,921	40	2.69 (1.93–3.73)	<0.001

* This cohort excludes persons with a baseline diagnosis of schizophrenia or related psychoses. Also excluded are data for 27,775 person-years and 75 deaths among indeterminate users of antipsychotic drugs, as well as for 5119 person-years and 13 deaths among concurrent users of multiple antipsychotic drugs.

† The analysis of these drugs included an adjustment for dose according to the method described in Appendix 1 in the Supplementary Appendix.

‡ These data are for current users of antipsychotic drugs. Doses are calculated as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. Doses equivalent to 100 mg of chlorpromazine include thioridazine, 100 mg; haloperidol, 2 mg; clozapine, 75 mg; olanzapine, 5 mg; quetiapine, 75 mg; and risperidone, 2 mg. (See Appendix 1 in the Supplementary Appendix for equivalent doses of other drugs.)

We controlled for an extensive set of cardiovascular disease variables. In the Medicaid population studied, users of antipsychotic drugs had a slightly lower baseline prevalence of diagnosed cardiovascular disease than did comparable nonusers, reflecting the fact that many nonusers qualified for Medicaid because of somatic illness. The requirement that cohort members have regular use of medical care, defined by at least one outpatient visit in each of the 2 years before baseline, should reduce the bias from underdiagnosis of cardiovascular disease in patients with mental illness. The analysis also controlled for concurrent use of other proarrhythmic medications, as well as for diagnosed or treated mood disorders.

With regard to behavioral risk factors, the cohort excluded persons with recorded diagnoses of substance abuse and those who did not have regular medical care. Although study data on smoking were limited, the analysis controlled for cardiovascular diseases caused by smoking,[37] diseases that mediate much of the increased risk of sudden death. Furthermore, a sensitivity analysis (Appendix 1 in the Supplementary Appendix) suggested that residual confounding by smoking had at most a minor effect on estimates of relative risk.

Although unmeasured behavioral factors may influence the study findings, the absence of a significantly increased risk of sudden death among former users of antipsychotic drugs and the marked dose–response relationship are evidence of a drug effect per se.

An analysis of the cohort that was matched for propensity score provided an additional check as to whether the study findings were due to confounding by factors associated with the use of antipsychotic drugs. This cohort excluded persons with a baseline diagnosis of schizophrenia or related psychoses, for whom such confounding is of greatest concern, and had a similar distribution of coexisting psychiatric conditions at baseline among users and nonusers of antipsychotic drugs. Findings were very similar to those for the primary cohort. However, some point estimates of relative risk were slightly lower; these differences, although not significant, underscore the fact that in this observational study residual confounding cannot be entirely ruled out.

Our study did not assess the mechanisms by which either class of antipsychotic drugs increased the risk of sudden cardiac death. Although antipsychotic drugs have long-term adverse cardiovascular effects,[1,2] the risk of sudden death was elevated in an analysis that excluded long-term users, which suggests that acute drug effects are involved. We believe that the most plausible explanation is that antipsychotic drugs increase the risk of serious ventricular arrhythmias, probably through blockade of potassium channels and prolongation of cardiac repolarization. However, other mechanisms may be involved, including autonomic effects, inhibition of other ion channels, and other acute cardiotoxic effects, such as the myocarditis associated with the use of clozapine.[3,8]

In conclusion, current users of typical antipsychotic drugs and of atypical antipsychotic drugs in the study cohort had a similar dose-related increased risk of sudden cardiac death. This finding suggests that with regard to this adverse effect, the atypical antipsychotic drugs are no safer than the older drugs.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360:225-35.

Appendix 1. Key study variables and additional details for the statistical analysis.

1. Key Study Variables.

Key study variables are listed in Table A1.1.

Table A1.1. Key Study Variables	
A. Variables leading to study exclusion, defined relative to 730 days preceding t_0 unless otherwise specified	
1. Nursing home	Nursing home residence (except <30 days after hospital discharge)
2. Recent hospital stay	Discharge date in 30 days preceding t_0
3. Serious illness	Cancer other than non-melanoma skin cancer, HIV, renal failure, liver disease, respiratory failure, organ transplantation, multiple sclerosis, home oxygen excluding CPAP, or hospice care
4. Drug dependency	Recorded diagnosis of cocaine, opioid, or other recreational drug dependency
B. Dosage equivalents for the study antipsychotics (in parentheses)	
1. Typical	Acetophenazine (60), chlorpromazine (100), chlorprothixene (50), fluphenazine (2), haloperidol (2), loxapine (15), mesoridazine (50), molindone (10), perphenazine (10), pimozide (2), thioridazine (100), thiothixene (5) trifluoperazine (5), triflupromazine (25)
2. Atypical	Aripiprazole (7.5), clozapine (75), olanzapine (5), quetiapine (75), risperidone (2), ziprasidone (60)
C. Death certificate cause of death codes	
1. ICD9	401.9, 402, 410, 411, 412, 413, 414, 425.4, 427.5, 427.1, 427.4, 427.8, 427.9, 429.2, 429.9, 440.9, 798.2, 798.9
2. ICD10	I10, I11.9, I20, I21, I22, I23, I24, I25, I42.8, I42.9, I46, I47, I47.2, I49.0, I49.8, I49.9, I51.6, I51.9, I70.9, R96.1, and R98
D. Baseline cardiovascular/somatic covariates used for calculation of cardiovascular risk score	
1. Medications	Anti-arrhythmics, angiotensin converting-enzyme inhibitors and angiotensin receptor blockers, anticoagulants, antidiabetics, aspirin, non-aspirin anti-platelet agents, β-blockers, calcium-channel blockers, digoxin and other inotropic agents, statins, other lipid-lowering agents, loop diuretics, thiazide and other diuretics, nitrates, other antihypertensives, and pentoxifylline/related drugs
2. Diagnoses	Prior revascularization, myocardial infarction or other coronary heart disease, heart failure, conduction disorder or arrhythmia, valve disorders, cerebrovascular disease, peripheral vascular disease, hypertension, hyperlipidemia, renal failure, obesity, smoking-related illnesses, and chronic obstructive pulmonary disease
3. Medical care use	Frequency prior inpatient admissions, emergency department visits, and outpatient encounters
4. Compliance index	Medications of interest were statins, beta-blockers, low-dose aspirin, diuretics, calcium-channel blockers, angiotensin-converting enzyme inhibitors, antiotensin 2 receptor blockers, and oral hypglycemics. For persons who neither started or stopped in the 730 days prior to baseline, we counted the number of these medications for which filled days of supply was less than 80% of the interval between the first and last day of supply.
E. Baseline variables in regression model, defined as of t_0 and the preceding 730 days	
1. Demographics	Age, gender, race, urban residence
2. Medicaid enrollment	Disabled indicates those receiving benefits because of disability qualifying for SSI payments; uninsured indicates those ordinarily would not qualify for Medicaid due to elevated income or lack of other qualifying criteria (such as dependent children or disability). In our experience, these enrollees are healthier than others.
2. Cohort entry year	Calendar year
3. Cardiovascular risk score	See D above. After controlling for age and sex, there was more than a 6-fold difference in the rate of sudden cardiac death between the highest and lowest quantiles of the risk score.
4. Psychiatric comorbidity	Schizophrenia and other psychoses, mood disorders (bipolar disorders, major depression, other mood disorders), organic mental illness, dementia, alcohol or prescription drug dependence, history of convulsions or seizure disorder, and psychiatric health care utilization.
F. Time-dependent covariates in regression model, defined for each day from t_0 through the end of followup	
1. Time since t_0	Interval between t_0 and the day of followup classified
2. Antipsychotic use	Nonuser, former user, current user multiple drugs, current user single typical, current user single atypical. Each person-day of followup was placed into one of these mutually exclusive categories. A single person could contribute person-time to each of these categories.
3. Hospital, psych	None prior 365 days, prior 91-365 days, prior 1-90 days
4. Hospital, any	None prior 365 days, prior 91-365 days, prior 1-90 days
5. ED visit, any	None, prior 91-365 days, prior 31-90 days, prior 1-30 days

2. Calculation of propensity score

The propensity score, defined as the predicted probability of being an antipsychotic user, was calculated from a logistic regression model in the primary cohort that included demographic characteristics, cardiovascular risk score, and prior psychiatric diagnoses/medications.

3. Adjustment for antipsychotic dose

The doses were systematically different for the two classes of antipsychotics as well as for individual antipsychotics. For example, 54% of thioridazine current use was for low dose (<100mg chlorpromazine equivalents), whereas only 16% of olanzapine current use was for low dose. Thus, a direct comparison of the two drugs would confound dose (which is very important) with individual drug. For this reason, we performed a dose adjustment for calculation of class- and individual drug-specific IRRs. We first tabulated the overall distribution of current use by dose for all antipsychotic use. Approximately 20% was for low dose, 40% for moderate dose, and 40% for high dose. Then, for each individual drug we calculated the dose-specific IRRs (seen in Figure 2). The log of the dose-adjusted IRR was then calculated from the following contrast: $.2*\beta1 + .4*\beta2 + .4*\beta3 - \beta4$, where $\beta1$, $\beta2$, $\beta3$ are the estimated log IRRs for low, moderate, and high dose respectively and $\beta4$ is that for the nonuser person-time.

4. Supplemental analyses

In addition to the primary and propensity score analyses reported in the paper, we performed several supplemental analyses to test the sensitivity of our findings to certain key assumptions. These are listed in Table A1.2. None of these had findings that differed materially from the primary analysis and thus suggest our findings are not sensitive to these assumptions.

Table A1.2. Supplemental Analyses	
Assumption	**Supplemental Analysis**
1. Independence for persons in cohort multiple times	Restricted cohort to allow only one entry per person.
2. Confounding by additional baseline variables	Ran models that included history of suicide attempts and baseline use of medications for psychiatric or neurological disorders (antidepressants, benzodiazepines, mood stabilizers, other psychotropic medications, anticonvulsants, and narcotic analgesics.
3. Confounding by time-dependent use of proarrythmic drugs	Ran models with time-dependent covariates for cyclic antidepressants,[1] erythromycin,[2] methadone,[3] cisapride,[4] terfenadine,[5] astemizole,[6] anti-arrhythmic medications that can cause torsade de pointes (disopyramide, procainamide, amiodarone, sotalol, quinidine)[7,8] other medications thought to cause torsade de pointes,[9] or prolong QT.[10,11]
4. Confounded by other changes in comorbidity during followup	Included variables important in cardiovascular risk score as time dependent covariates. These included recent psychiatric/neurologic diagnoses (schizophrenia, substance abuse, organic disorder, seizure disorder, dementia, psychiatric ED visit as well as recent evidence of worsening cardiovascular disease (new prescription for ACE inhibitor, digoxin, insulin, or loop diuretic, new diagnosis of coronary heart disease or heart failure, coronary artery revasularization).
5. No bias caused by using controls for typicals in atypical analysis and vice-versa	Performed separate analyses for each antipsychotic drug class, limiting controls to those matched for that class.
6. Cardiovascular risk score can be estimated in nonusers	Performed analysis with risk score estimated using the entire cohort.
7. Dependence not induced by matching on t_0	Ran analysis that estimated variance assuming a possible correlation between members of a matched set.

5. Sensitivity Analysis of Effect of Confounding by Smoking

The information provided by study files on smoking is incomplete, as it relies upon a recorded diagnosis. Given that smoking increases the risk of sudden cardiac death and persons with mental illness have increased prevalence of smoking, there is thus the potential for uncontrolled confounding. The following sensitivity analysis estimates the magnitude of such potential confounding. It does so using the *confounding risk ratio* (see Breslow and Day[12]) which quantifies the degree of confounding due to an unmeasured variable. The confounding risk ratio is calculated as:

$$\omega = \frac{RR_cQ_1 + (1-Q_1)}{RR_cQ_0 + (1-Q_0)} \qquad \textit{Breslow \& Day, Eq 3.1}$$

RR_c = Risk ratio (or rate ratio) for confounder

Q_1 = confounder prevalence in user group

Q_0 = confounder prevalence in nonuser group

Each of these quantities can be estimated for the study cohort, as described below.

a. Increased risk conferred by smoking: RR_c

RRc is the relative risk conferred by smoking. Several studies suggest that current smokers have a two-fold increased risk of sudden cardiac death.[13-23]

b. Prevalence of smoking in Tennessee Medicaid: Q_0

The estimated prevalence of current smoking among all persons in Tennessee was 27% in 1997 (*Prevalence of Tobacco Use in Tennessee, 1997-2007*. Tennessee Department of Health, 2008). The prevalence of smoking in adult Medicaid enrollees is 50% higher than that of the general population (MMWR 2001; 50(44):979-982). Thus, the estimated prevalence of current smoking among antipsychotic nonusers in the cohort is 40%.

c. Prevalence of smoking in persons with serious mental illness: Q_1

The National Comorbidity Survey reported the prevalence of current smoking in 1990-1991 to be 45% in adults with schizophrenia or major depression and 61% in adults with bipolar disorders.[24] A study of newly diagnosed schizophrenics admitted to a psychiatric hospital between 1989 and 1995[25] reported a 52% prevalence of current smoking at the time of admission. The highest figure, that of 61%, is used for the sensitivity analysis.

d. Calculations

Given these assumptions, the estimate of the confounding risk ratio is 1.15. That is, the observed relative risk estimate is 15% greater than the relative risk completely adjusted for the effect of current smoking. This is likely to be an overestimate for two reasons. First, smokers with a recorded diagnosis are identified in the study files, which would reduce misclassification. Second, some of the effects of smoking are mediated by factors that are measured in our study. For example, smokers have greater prevalence of prior (eg, history of AMI) and current (eg, angina) cardiovascular disease, which would be adjusted for in our analysis.

6. Supplemental Analysis: Atypical vs Typical Antipsychotics in Persons with Schizophrenia or Related Psychosis

To quantify the extent to which the risk of sudden cardiac death varied between the two classes of antipsychotics in patients with schizophrenia-related psychoses, we performed an analysis that restricted the primary cohort to persons with a baseline diagnosis of schizophrenia or related psychoses. The analysis compared current use of atypical versus typical antipsychotics. Nonusers were not the reference category because treatment of these serious psychoses with antipsychotics is the standard of practice. The resultant IRR was 1.24 (0.87-1.77).

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Appendix 2. Baseline characteristics* according to antipsychotic type and use of frequently prescribed individual drugs.

	*All Typical***	*Haloperidol*	*Thioridazine*	*All Atypical***	*Clozapine*	*Olanzapine*	*Quetiapine*	*Risperidone*
Cohort members, N	44,218	9,287	7,711	46,089	681	16,687	13,366	12,144
Demographic characteristics and somatic comorbidity								
Year of cohort entry, mean (std)	1994.4 (3.9)	1994.6 (4.0)	1993.9 (3.6)	2002.1 (2.2)	1997.5 (3.5)	2001.8 (1.9)	2003.0 (1.6)	2001.4 (2.5)
Study followup, years, median (iqr)	5.5 (7.3)	5.0 (7.4)	5.8 (7.3)	1.9 (2.5)	5.2 (6.2)	2.2 (2.6)	1.5 (2.0)	2.3 (3.1)
Age in years, mean (std)	47.1 (12.6)	47.8 (13.5)	47.6 (12.9)	44.5 (10.8)	39.5 (10.0)	45.0 (11.0)	44.5 (10.4)	44.7 (11.1)
Male, %	35.2%	43.6%	35.9%	33.5%	62.0%	35.9%	28.7%	34.7%
Race non-white, %	33.2%	43.2%	26.2%	23.6%	23.9%	22.0%	20.2%	28.7%
Urban residence, %	57.6%	62.9%	55.7%	57.2%	74.0%	54.3%	55.2%	60.4%
Medicaid enrollment due to disability, %	73.3%	78.1%	76.4%	52.4%	77.8%	49.1%	50.5%	56.6%
Cardiovascular risk score, mean (std)	9.1 (5.7)	9.4 (5.6)	8.7 (5.7)	9.4 (5.9)	6.6 (5.6)	9.4 (5.8)	9.7 (5.9)	9.4 (5.8)
*Psychiatric characteristics****								
Antipsychotic dose moderate or high****, %	61.8%	88.6%	46.1%	73.9%	97.7%	84.4%	76.7%	51.4%
Schizophrenia, %	27.1%	41.3%	19.2%	13.5%	89.1%	12.9%	5.9%	17.8%
Other psychosis, %	9.8%	16.9%	8.3%	8.8%	18.4%	8.3%	5.2%	12.7%
Bipolar disorder, %	12.1%	13.5%	11.3%	23.3%	20.9%	21.5%	23.0%	23.4%
Major depression or other mood disorder, %	36.3%	29.5%	37.7%	60.2%	31.6%	53.1%	67.8%	62.0%
Dementia, %	2.9%	6.0%	3.1%	3.3%	2.6%	3.0%	3.0%	4.3%
Alcohol or prescription drug dependency, %	7.3%	8.0%	7.3%	9.2%	7.3%	8.8%	10.4%	8.8%
History of suicide attempt, %	1.9%	1.8%	1.9%	5.0%	3.5%	4.3%	6.1%	4.4%
Prior psychiatric hospital stay, %	19.2%	25.0%	16.9%	22.6%	44.6%	19.8%	19.9%	27.6%
Lithium, %	10.5%	11.5%	9.8%	7.9%	18.5%	7.7%	6.4%	9.0%
Mood stabilizer, %	11.7%	12.7%	11.8%	35.0%	30.5%	30.3%	39.7%	33.2%
Antidepressant, %	60.5%	46.3%	55.7%	85.2%	51.2%	83.6%	90.9%	82.4%
Benzodiazepine, %	45.6%	37.0%	46.8%	66.1%	44.3%	65.2%	74.0%	60.1%

*Factors defined from medical care encounters reflect any encounter within the 730 days preceding t_0, except for cardiovascular risk score and antipsychotic dose, which are those at the start of cohort followup. 'std' = standard deviation, 'iqr' = interquartile range.
**Excludes 2993 baseline users of multiple antipsychotics.
***A cohort member may have multiple diagnoses present.
****Doses equivalent to ≥100mg chlorpromazine: cutpoints for thioridazine, 100mg; haloperidol, 2mg; clozapine , 75mg; olanzapine, 5mg; quetiapine, 75mg; risperidone, 2 mg. See Appendix 1 for other drugs.