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).

Reference List

(1) Ray WA, Meredith S., Thapa PB, Meador KG, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2003;75:234-241.

(2) Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin use and the risk of sudden cardiac death. *N Engl J Med.* 2004;351:1089-1096.

(3) Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacol Drug Safety.* 2005;14:747-753.

(4) Wiseman LR, Faulds D. Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. *Drugs.* 1994;47:116-152.

(5) Monahan BP, Ferguson CL, Killeavy ES, Lloyd B.K., Troy J, Cantilena LR. Torsades de pointes occurring in association with terfenadine use. *JAMA.* 1990;264:2788-2790.

(6) Matsumoto S, Yamazoe Y. Involvement of multiple human cytochromes P450 in the liver microsomal metabollism of astemizole and a comparison with terfenadine. *Br J Clin Pharmacol.* 2001;51:133-142.

(7) Murray KT, Roden DM. Disorders of cardiac repolarization: The long QT syndromes. In: Crawford MH, DiMarco JO, Paulus WJ, eds. *Cardiology*. 2nd ed. Mosby; 2004:765-74.

(8) Damkier P, Hansen LL, Brosen K. Effect of diclofoenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol.* 1999;48:829-838.

(9) De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. *Eur J Clin Pharmacol.* 2000;56:1-18.

(10) Curtis LH, Ostbye T, Sendesky V et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med.* 2003;114:135-141.

(11) Gil M, Ssala M, Anguera I et al. QT prolongation and torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol.* 2003;92:995-997.

(12) Breslow NE, Day NE. *Statistical methods in cancer research: Volume 1, The analysis of case-control studies.* 74 ed. Lyon, France: International Agency for Research on Cancer; 1980.

(13) Siscovick DS, Raghunathan TE, Psaty BM et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med.* 1994;330:1852-1857.

(14) Siscovick DS, Weiss NS, Fox N. Moderate alcohol consumption and primary cardiac arrest. *Am J Epidemiol.* 1986;123:499-503.

(15) Cupples LA, Gagnon DR, Kannel WB. Long-and short-term risk of sudden coronary death. *Circulation.* 1992;85:I 11-18.

(16) Shaper AG, Wannamethee G, Macfarlane PW, Walker M. Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. *Br Heart J.* 1993;70:49-55.

(17) Roberts TL, Wood DA, Riemersma RA, Gallagher PJ, Lampe FC. Trans isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. *Lancet.* 1995;345:278-282.

(18) Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. *Circulation.* 1995;91:1749-1756.

(19) Cosin-Aguilar J, Andres-Conejos F, Hernandiz-Martinez A, Solaz-Minguez J, Marrugat J, Bayes-De-Luna A. Effect of smoking on sudden and premature death. *J Cardiovasc Risk.* 1995;2:345-351.

(20) Sexton PT, Jamrozik K, Walsh J, Parsons R. Risk factors for sudden unexpected cardiac death in Tasmanian men. *Aust N Z J Med.* 1997;27:45-50.

(21) Escobedo LG, Caspersen CJ. Risk factors for sudden coronary death in the United States. *Epidemiology.* 1997;8:175-180.

(22) Herlitz J, Wognsen GB, Karlsson T, Karlson B, Haglid M, Sjoland H. Predictors of death and other cardiac events within 2 years after coronary artery bypass grafting. *Cardiology.* 1998;90:110-114.

(23) de Vreede-Swagemakers JJM, Gorgels APM, Weijenberg MP et al. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. *J Clin Epidemiol.* 1999;52:601-607.

(24) Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-Based prevalence study. *JAMA.* 2000;284:2606-2610.

(25) Kotov R, Guey LT, Bromet EJ, Schwartz JE. Smoking in Schizophrenia: Diagnostic specificity, symptom correlates, and illness severity. *Schizophrenia Bulletin.* 2008;1-9.

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.