Supplementary Online Content

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

This supplement provides additional details for the study of antipsychotics and risk of unexpected death in children and youth and should be read in conjunction with the primary manuscript (MS).

1. Sources of Data

All study data were obtained from Tennessee Medicaid files, an efficient data source for identifying the cohort, determining periods of probable exposure to medications, and ascertaining deaths.[1,2] The study Medicaid database included enrollment, pharmacy, hospital, outpatient, and nursing home files and was augmented with linkage to death certificates[1,3] and a statewide hospital discharge database. The linkages used all available identifiers.

2. Study Medications

Antipsychotics, control drugs and other medications were identified from Medicaid pharmacy files. These included the date the prescription was dispensed, drug, quantity, dose, and days of supply. Computerized pharmacy records are an excellent source of medication data because they are not subject to information bias[2] and have high concordance with patient self-reports of medication use.[4-6] The residual misclassification should be limited and, if non-differential, should bias towards the null.[1]

The study included oral antipsychotics available in Tennessee Medicaid during the study period (eTable 1). The control drugs (eTable 2) are alternative treatments for the indications for which antipsychotics are prescribed, including psychostimulants and other medications for attention deficit hyperactivity disorder (ADHD) and other disruptive behaviors, antidepressants commonly used as initial treatment for mood disorders and mood stabilizers.

eTable 1 shows the equivalent doses for study antipsychotics.[7-10]

eTable 1. Study Antipsychotics[a] and Equivalent Doses

Drug	*Equivalent Adult Dose (mg)*	*Drug*	*Standard Adult Dose (mg)*
Acetophenazine	60	Olanzapine[b]	5
Aripiprazole	7.5	Paliperidone	3
Asenapine	5	Perphenazine[c]	10
Chlorpromazine HCL	100	Pimozide	2
Chlorprothixene	50	Quetiapine	75
Fluphenazine HCL	2	Risperidone	2
Haloperidol	2	Thioridazine	100
Iloperidone	6	Thiothixene	5
Loxapine succinate	15	Trifluoperazine HCL	5
Lurasidone	20	Triflupromazine HCL	25
Mesoridazine besylate	50	Ziprasidone	60
Molindone	10		

[a]The use of clozapine or any depot antipsychotic was considered to indicate psychosis and thus was an exclusion criterion. Promazine was not included as a study antipsychotic because 99% of the small number of encounters were for administration of the short-acting injectable formulation.
[b]Includes fluoxetine-olanzapine combination.
[c]Includes perphenazine-amitriptyline combination.

The cohort included new episodes of therapy for the study medications during the period 1/1/1999 through 12/31/2014. Identification of cohort patients began with the filling of the first prescription (fill date t_0) during the study period that qualified the patient as a new user of either an antipsychotic or one of the three classes of a control medication (the cohort entry class).

New users of antipsychotics had no prior antipsychotic prescription filled in the interval $[t_0 -364, t_0-1]$[a]. However, they could have had past prescriptions for up to two classes of control medications. The concurrent use of control medications with antipsychotics was tracked as a study covariate (§6).

New users of a control medication class could have no prior prescription for a medication in the cohort entry class filled in the interval $[t_0 -364, t_0-1]$. Furthermore, they could not have a filled antipsychotic prescription in that interval. However, they could have past use of other control drug classes. Thus, patients in each group could have use of up to three study medication classes.

New users of anticonvulsant mood stabilizers had to meet further criteria to assure that the medication was initiated for a psychiatric indication. The primary issues were: 1) study anticonvulsant mood stabilizers such as the valproates also are frequently prescribed for seizure disorders and other neurologic indications and 2) some anticonvulsants that were not study drugs are occasionally prescribed as mood stabilizers. In order to exclude neurologic patients, we required that patients have no diagnosis indicating a potential neurologic indication in the past year, including seizure disorder/convulsions, migraine, other neuropathic pain or that they have a diagnosis of a bipolar or related disorder in the past year and no diagnosis of a seizure disorder/convulsions in the past 30 days. Furthermore, we did not permit prior prescription (regardless of indication) of either study anticonvulsant mood stabilizers or other anticonvulsants that occasionally are prescribed as mood stabilizers (gabapentin, pregabalin, lacosamide, levetiracetam, tiagabine, topiramate, zonisamide).

eTable 2. Control Medications

2-a. Medications for ADHD or other disruptive behaviors.

Psychostimulants	*SNRI*
Dextroamphetamine + amphetamine	Atomoxetine
Amphetamine	
Dexmethylphenidate	*Alpha$_2$ agonists*
Dextroamphetamine	Clonidine
Lisdexamfetamine	Guanfacine
Methamphetamine	
Methylphenidate	
Pemoline	

2-b. Antidepressants.

SSRIs	*SNRI*
Citalopram	Desvenlafaxine
Escitalopram	Duloxetine
Fluoxetine	Venlafaxine
Fluvoxamine	
Paroxetine	*Other study antidepressant*
Sertraline	Mirtazapine

2-c. Mood stabilizers.

Anticonvulsants	*Lithium*
Carbamazepine	Lithium
Divalproex sodium	
Lamotrigine	
Oxcarbazepine	
Sodium valproate	
Valproic acid	

The notation denotes a 364 day interval that begins 364 days before t_0 and ends on the day prior to t_0.

3. Cohort Eligibility Criteria
To enter the cohort, patients had to meet the study inclusion/exclusion criteria (eTable 3, criteria 2-8) on t_0

eTable 3. New User Episodes of Study Medications

Criterion	N Antipsychotic	N Control
1. New user. New user of a study medication class 5-24 years of age, with no filled prescription for any medication in that class for the period [t_0 -364, t_0-1].	115,611	427,290
2. Enrollment. Alive and enrolled in TennCare with date of birth and sex known for the period [t_0-364,t_0] (allowing gaps of up to 7 days).	84,199	290,926
3. Medical history. At least one outpatient visit and one filled prescription in the period [t_0 -364, t_0-1].	77,353	255,951
4. Serious illness exclusion. No serious somatic illness in the interval [t_0-364, t_0]. See eTable 4.	70,947	241,973
5. In hospital. Not in the hospital (except for single-day hospitalizations) on t_0.	70,159	241,142
6. Psychiatric diagnosis. A psychiatric diagnosis in the period [t_0-364, t_0+1].	65,946	192,008
7. Psychiatric/neurologic. For the period [t_0-364,t_0+1], no evidence of schizophrenia or other major psychosis or tics (Tourette's syndrome or other).	59,816	189,361
8. Control medication classes. For antipsychotic users, no more than two control medication classes in [t_0-364, t_0].	58,497	189,361

Criteria 2-3 were related to the availability in the Medicaid files of the medical encounters needed to define exposure to study drugs and study covariates. In addition to requiring that cohort members have Medicaid enrollment for at least one year (criterion 2), we also require medical care utilization other than the prescription leading to cohort entry during that year (criterion 3). Given that most study covariates were ascertained from medical care encounters, this assured some degree of medical surveillance.

Criteria 4-5 were designed to identify a population in which the occurrence of unexpected death other than that related to medication adverse effects should be infrequent. This excluded persons with cancer and other life-threatening somatic illnesses, evidence of hospice or other end-of-life care or long-term care residence or who were hospitalized.

Criterion 6 further restricted the new users to those with a psychiatric diagnosis. This excluded use of study drugs for somatic indications (e.g., SSRIs for premenstrual syndrome).

Criterion 7 excluded patients for whom antipsychotics are the only pharmacotherapy option or with a neurologic indication.

Criteria 6 and 7 used information, when available, the day after the cohort entry to determine cohort eligibility. Classifying subjects by a future event may lead to bias if a material proportion of subjects do not remain in the cohort until the date of the future event. However, occasionally medications are started prior to completion of the diagnostic assessment and thus important information becomes known on the day after the initial prescription fill. Since only the first day of followup was affected, with minimal potential for loss to followup, the greater completeness of diagnostic information should outweigh the very limited potential for bias.

Criterion 8 assured that both groups could have use of no more than three study medication classes.

eTable 4. Serious Illnesses

Disease	Definition
1. Cancer	Cancer (except for non-melanoma skin cancers) diagnosis or selected antineoplastic agents.
2. Hematologic	Sickle cell diagnosis, aplastic anemia.
3. Neuromuscular	Cerebral palsy, muscular dystrophy, multiple sclerosis, ALS, quadriplegia, paraplegia, hemiplegia, or spinal cord injury, stroke.
4. Chromosomal anomalies	Down's syndrome, trisomy 13, trisomy 18, autosomal deletion syndrome and others.
5. Other congenital anomalies-non CV	Cystic fibrosis, anencephalus, spina bifida, hydrocephalus, microcephalus, encephalocele.
6. Congenital anomalies-CV	Common truncus, transposition great vessels, tetralogy of Fallot, common ventricle, endocardial cushion defect , pulmonary atresia, tricuspid atresia, hypoplastic left heart, coarctation of aorta, other anomalies of aorta, total anomalous pulmonary venous connection.
7. Gastrointestinal	Ulcerative colitis, Crohn's disease. Liver disease: acute and subacute necrosis of the liver, chronic liver disease and cirrhosis, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, other sequelae of chronic liver disease, hospitalization for any other liver disease. Acute and chronic pancreatitis.
8. HIV and other serious infections	Diagnosis of HIV or use of antiretroviral agents appropriate for HIV or pentamidine (also used for other major immunocompromised patients), hepatitis B or C, tuberculosis.
9. Other immunologic	Immune deficiencies.
10. Renal	Diagnosis or procedure code for dialysis outside of the hospital. Includes end-stage renal disease diagnosis, also outside of the hospital.
11. Cardio-respiratory	Any diagnosis of primary pulmonary hypertension. Inpatient diagnosis of chronic respiratory failure, cardio-respiratory failure, heart failure, or pulmonary heart disease. Does not include pulmonary embolus. Also includes tracheostomy (excluding temporary), home ventilator, and home oxygen.
12. Organ transplant	Includes kidney, heart, lung, liver, bone marrow, and pancreas.
13. Other serious illness	a. Hospice care. b. Diagnosis of coma, vegetative state, debility, cachexia. c. Total parenteral nutrition, PEG, enteral feeding, malnutrition diagnosis for outpatients. d. Gangrene. e. Intravenous medications outside of the hospital. f. Regular in-home nursing care. g. Severe metabolic disorders. h. In hospital for >30 days.
14. Long term care	Any.

eMethods 1. Study Person-time

4. Study Person-time

Because many antipsychotic adverse effects are acute, the person-time included in the study analysis was restricted to periods of current drug use. These periods were calculated from the prescriptions for drugs in the cohort entry class filled between cohort entry and exit, as described below.

4.1 Cohort Entry and Exit

Patients entered the cohort on the date of the first prescription that qualified them as a new user of a study medication. The cohort exit date was the first of the following dates:

1. End of the study;
2. A period of 364 days with no filling of a study drug prescription in the cohort entry class that led to cohort entry. If t_i was the fill date of the most recent prescription for a medication in the cohort entry class, then the exit date was t_i+364 if there had not been a refill. On t_i+365 the patient would be eligible to reenter the cohort as a new user.
3. Day prior to the 25th birthday;
4. Day prior to failure to meet the TennCare enrollment criteria (eTable 3, criterion 2);
5. The date of death;
6. For control medication patients, the day prior to the filling of an antipsychotic prescription.
7. For antipsychotic patients, the day prior to overlapping use of three control medication classes (eTable 3, criterion 8).

Patients who failed to meet the eligibility criteria related to medical history or illnesses (eTable 3, criteria 3-7) during followup did not exit the cohort. The motivation was to avoid censoring related to a drug-related deterioration in health. Because this could introduce bias if one group of patients had a less favorable prognostic trajectory, a sensitivity analysis restricted study followup to one year, during which time such changes should be minimal. Results were similar to those from the primary analysis (MS Table 3).

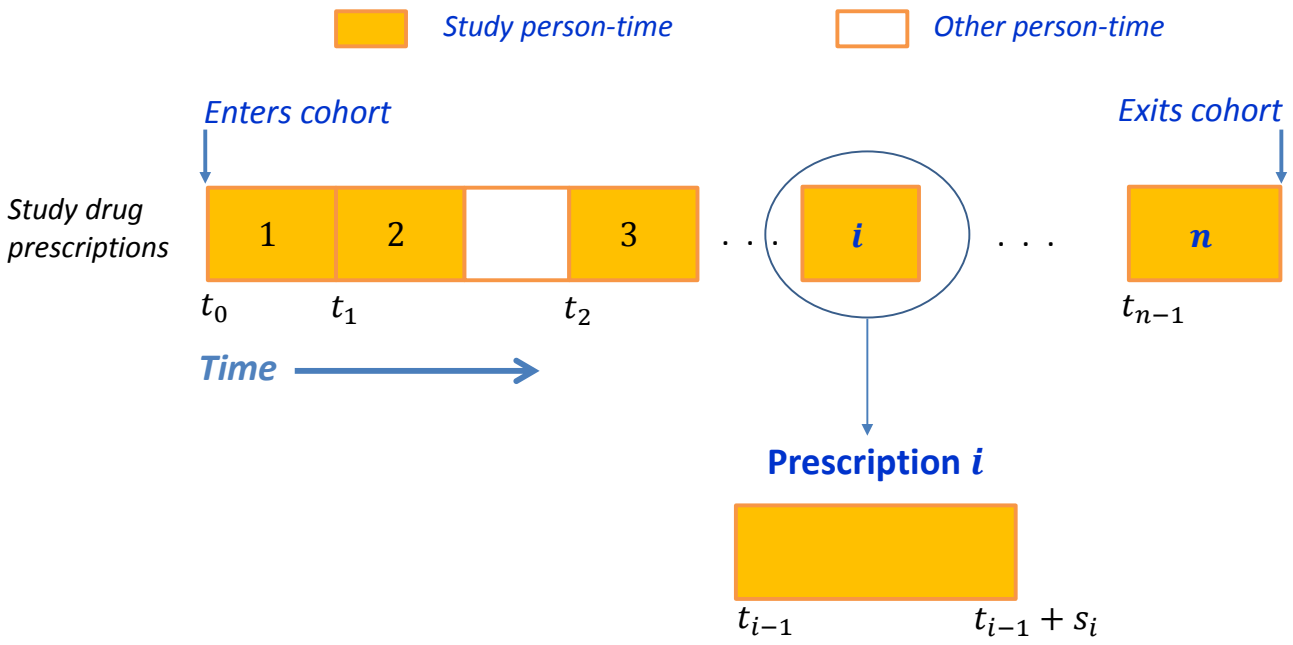
Patients who left the cohort could reenter if they subsequently met the study eligibility criteria. For example, a control patient who started an antipsychotic would enter the cohort as an antipsychotic patient if they qualified for the cohort on the fill date. Since the episodes were non-overlapping and the end point occurred only once, statistical independence assumptions were satisfied.[11]

4.2 Study Person-Time

For each cohort member, the prescriptions filled for drugs in the cohort entry class between cohort entry and exit defined study person-time (eFigure 1). Study person-time for each individual prescription was restricted to the period of probable current drug use for that prescription. If there was a gap between prescriptions, indicating periods off drug (e.g., eFigure 1, interval between prescriptions 1 and 2), that person-time was not included in the analysis.

For an individual prescription (i), current use began on the date of the prescription fill (t_{i-1}) and extended through the end of the days of supply+1. The additional exposure day allowed for the long half-life of the study drugs. Study person-time for that prescription could include the entire period of current use. However, study person-time could terminate sooner if, prior to the end of current use: 1) a subsequent prescription for a drug in the cohort entry class was filled (defining the beginning of person-time for that prescription); or 2) the patient exited the cohort. For patients admitted to the hospital (not considering single-day hospitalizations) during a period of current medication use, up to the first 7 days of hospitalization was included in study person-time to capture deaths following a short hospitalization, even if the period of current use had ended.

eFigure. Study Person-time



Depicts a single patient who has n filled study drug prescriptions between cohort entry and exit.

Antipsychotic study person-time was stratified according to time-dependent antipsychotic dose, given the strong dose-response for the cardiovascular,[12,13] metabolic,[14] and CNS-depressant[15,16] effects of antipsychotics. The dose cutpoint was >50 mg of chlorpromazine or its equivalent (eTable 1), the median antipsychotic dose on cohort entry.

A single person could have person-time for both the higher and lower dose categories in the analysis. Because these time periods were non-overlapping and the endpoint (death) occurred only once, statistical independence assumptions were not violated.[11]

eMethods 2. Endpoints

5. Endpoints

All deaths were categorized according to the death certificate underlying and multiple cause of death ICD-10 codes (eTables 5 to 8) as follows:

A. Unexpected death
    1. Not drug overdose
        a. Cardiovascular/metabolic (eTable 5)
        b. Other
    2. Unintentional drug overdose (eTable 6)
B. Injury or suicide (eTable 7)
    1. Unintentional injury other than drug overdose
    2. Suicide.

eTable 5. Deaths From Cardiovascular or Metabolic Causes

Codes	Rubric
Cardiovascular	
I00-I02	Acute rheumatic fever
I05-I09	Chronic rheumatic heart disease
I10-I15	Hypertensive diseases
I20-I25	Ischemic heart disease
I26-I28	Diseases of pulmonary circulation
I30-I52	Other forms of heart disease
I60-I69	Cerebrovascular disease
I70-I79	Diseases of arteries, arterioles, and capillaries
I80-I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I95-I99	Other and unspecified disorders of the circulatory system
Q20-Q28	Congenital malformations of the circulatory system
R96.0	Instantaneous death
R96.1	Death in <24 hours
R98	Unattended death
R99	Unknown cause
Metabolic	
E10, E11, E13, E14	Diabetes[a]
E66	Obesity
K859	Acute pancreatitis[b]

[a]Excludes pregnancy-related diabetes.

[b]Considered metabolic because acute pancreatitis is a well-recognized antipsychotic adverse effect,[17] antipsychotic effects on glucose, triglyceride, insulin and leptin metabolism are thought to contribute to the development of pancreatitis,[18] and deaths from diabetic ketoacidosis can be difficult to distinguish from those due to acute pancreatitis.[19]

eTable 6. Deaths From Unintentional Drug Overdose

Codes	Rubric
X40-X44	Accidental poisoning by and exposure to medications
Y40-Y57	Adverse effects of medications in therapeutic use[a]

[a]No deaths in the study population had these as an underlying cause of death.

eTable 7. Deaths From Injuries and Suicides

Codes	Rubric
Injury	
Vxx.x, Wxx.x, Xxx.x, Yxx.x	Injuries[a]
Suicide	
X60-X64	Intentional overdose
X65-X84	Intentional injury
Y10-Y14	Undetermined intent overdose
Y15-Y34	Undetermined intent injury
Y87	Sequela of intentional self-harm

[a]Excludes codes in eTable 6 and those for suicide in eTable 7.

All unintentional drug overdose deaths were further described according to the drugs listed in the multiple cause of death data (eTable 8). They were classified as either a) unspecified drug only, b) opioid or drug of abuse only, or c) any prescription medication.

eTable 8. Codes for Specific Drugs From Multiple Cause of Death Data

Codes	Rubric
Unspecified drug	
T50.9	Other and unspecified drugs, medicaments and biological substances
Opioids and drugs of abuse	
T40.0	Opium
T40.1	Heroin
T40.2	Other opioids
T40.3	Methadone
T40.4	Other synthetic narcotics
T40.5	Cocaine
T40.6	Other and unspecified narcotics
T40.7	Cannabis and derivatives
T40.8	Lysergide [LSD]
T40.9	Other and unspecified psychodysleptics [hallucinogens]
Any prescription medication other than opioid	
T36.0-T50.8, excluding T40.x	

The endpoint definitions relied on the ICD10 underlying cause of death codes. Validation studies in non-elderly populations free of severe chronic illness have reported positive predictive values greater than 85% for deaths coded as due to injuries and suicides,[20] medication overdose,[21] and cardiovascular deaths,[22] which accounted for more than 91% of deaths in the study cohort.

eMethods 3. Covariates

6. Covariates

Variables. The covariates were factors potentially associated with both antipsychotic use and the risk of death. They included demographic characteristics, psychoactive medications, psychiatric conditions, neurologic conditions, cardiovascular conditions, respiratory diseases, history of injuries, other illnesses, and medical care utilization. All study covariates are listed in MS Table 1 and eTable 9.

Control medications as covariates. Cohort patients could use control medications not in the cohort entry class. Examples include either a new antipsychotic or bipolar medication user with ADHD medication use. Because the control medication class leading to cohort entry could convey important prognostic information (e.g., ADHD vs bipolar medication), the psychoactive medication covariates included the control medications.

Time-dependent covariates. The values of study covariates were either defined at cohort entry and held fixed throughout followup or were allowed to vary during followup (time-dependent), with the values updated at the time of each prescription fill during followup (eFigure 1).[11] The time-dependent covariates were those thought to be acutely related to mortality and not on the causal pathway for drug-related deaths. Thus, the time-dependent covariates included age and calendar year (given the long study followup period), control medications, and other psychoactive medications (e.g., benzodiazepines, opioids). No other covariates were time-dependent because these could be on the causal pathway between medication use and death. Examples include obesity or diabetes (potentially medication-related adverse effects) and psychiatric hospitalization (possible suboptimal initial medication choice).

A sensitivity analyses that limited the potential for covariate changes by restricting followup to one year from cohort entry had essentially similar findings to those of the primary analysis (MS Table 3).

Ascertainment interval. The ascertainment intervals for the study covariates at the beginning of followup (t_0) were:

Demographic factors:	t_0
Psychoactive medications, control drugs:	$[t_0\text{-}90,t_0\text{-}1]$[b]
Psychoactive medications, other	$[t_0\text{-}90, t_0]$
Medications, other	$[t_0\text{-}364,t_0]$
Diagnoses or procedures	$[t_0\text{-}364,t_0+1]$
Medical care utilization	$[t_0\text{-}364, t_0]$

The psychoactive medication covariates reflected recent use because the acute effects of these drugs could affect mortality (e.g., cyclic antidepressants, benzodiazepines, opioids). The ascertainment for control drugs ended on t_0-1 because use on t_0 could indicate study drug assignment and thus be a surrogate for treatment group. The diagnosis ascertainment extended to t_0+1 because some of the diagnostic workup related to the initiation of drug therapy could occur on the day following the first prescription (see §3 above).

For time-dependent covariates, the ascertainment interval was relative to t_i (eFigure 1).

[b] The notation denotes a period beginning 90 days prior to t_0 and ending on the day prior to t_0.

eTable 9. Covariate Distribution After IPT Weighting

See MS Table 1 for definitions.

	Antipsychotic ≤50mg			Antipsychotic >50mg		
	Control	Anti-psychotic	Standardized Difference, %	Control	Anti-psychotic	Standardized Difference, %
Prescriptions during followup, N	1,745,206	232,981		1,745,206	414,741	
Age at prescription fill, years, mean	12.0	12.2	3.6%	12.6	12.8	5.2%
“ “, standard deviation	5.0	5.0		5.2	4.9	
Year of prescription fill	2008.2	2008.0	5.0%	2008.1	2007.9	5.5%
“ “, standard deviation	4.2	4.0		4.2	3.9	
Female	42.1%	42.4%	0.6%	42.6%	42.7%	0.2%
Race white	70.9%	70.3%	1.3%	70.1%	69.3%	1.8%
Medicaid enrollment disabled	13.0%	13.3%	0.9%	14.9%	15.6%	1.9%
Standard metropolitan statistical area	56.0%	56.5%	0.9%	56.9%	57.8%	1.9%
ADHD, conduct disorder, impulsivity	71.9%	70.3%	3.5%	69.9%	68.9%	2.1%
Major depression	6.4%	6.6%	1.1%	7.8%	8.0%	1.0%
Other mood disorder	19.5%	19.5%	0.1%	21.9%	22.6%	1.6%
Bipolar disorder	3.7%	3.8%	0.7%	6.6%	6.7%	0.6%
Anxiety, including panic disorder	13.5%	14.4%	2.5%	14.6%	15.8%	3.3%
Mild/moderate intellectual disability	1.2%	1.4%	1.7%	1.6%	1.7%	0.8%
Autism or Asperger's Syndrome	2.0%	2.2%	1.2%	2.4%	2.4%	0.4%
Alcohol or drug abuse	2.6%	3.4%	4.5%	3.7%	4.0%	1.7%
Suicidal tendencies or ideation	1.9%	2.0%	0.5%	3.0%	3.0%	0.4%
Self-harm	1.2%	1.3%	0.4%	1.7%	1.8%	0.3%
Psychiatric inpatient stay	3.1%	3.2%	0.5%	5.1%	5.2%	0.6%
Learning disability	5.8%	6.4%	2.4%	5.5%	5.2%	1.6%
Sleep disorder	5.5%	6.0%	1.9%	5.9%	6.3%	1.8%
Other psychiatric diagnosis	5.6%	6.0%	1.8%	6.4%	6.4%	0.1%
ADHD Medication: psychostimulant/alpha-agonist	65.6%	65.0%	1.3%	62.1%	61.5%	1.1%
Study antidepressant: SSRI/SNRI/Mirtazapine	26.7%	27.3%	1.4%	27.5%	28.4%	2.0%
Mood stabilizer	7.4%	7.5%	0.3%	10.1%	10.3%	0.6%
Cyclic antidepressant	3.0%	3.3%	1.6%	2.8%	3.2%	1.9%
Trazodone	4.0%	4.5%	2.2%	4.8%	5.2%	1.6%
Benzodiazepine/sBzRA	4.6%	5.4%	3.8%	5.7%	6.3%	2.6%
Anticonvulsants, occasional mood stabilizers	1.9%	2.1%	1.6%	2.5%	2.7%	0.9%
Opioid past 90 days	11.1%	12.0%	2.7%	12.1%	12.9%	2.4%
Arrhythmia	1.2%	1.3%	0.4%	1.3%	1.4%	1.1%
Diabetes	1.9%	2.1%	1.5%	2.1%	2.2%	1.0%
Cardiovascular diagnosis: major	3.5%	3.2%	1.8%	3.6%	3.5%	0.3%
Cardiovascular diagnosis: other	2.7%	2.9%	1.4%	3.0%	3.1%	0.6%
Smoking	4.1%	5.0%	4.2%	5.2%	5.8%	2.5%
Obesity	3.4%	3.4%	0.3%	3.6%	3.3%	1.9%
Cardiovascular medication: major	1.2%	1.3%	1.3%	1.2%	1.3%	0.2%
Cardiovascular medication: other	3.0%	3.5%	2.8%	3.5%	3.6%	0.6%
Seizure disorder or convulsions	3.2%	3.3%	0.6%	3.5%	3.8%	1.8%
Migraine or other neuropathic pain	6.9%	7.8%	3.5%	7.7%	8.2%	2.0%
Asthma: diagnosis or medication	27.6%	26.8%	1.9%	27.6%	27.2%	0.9%
Pneumonia	3.0%	3.5%	3.0%	3.0%	2.8%	1.0%
Sleep apnea	1.2%	1.1%	0.5%	1.2%	1.0%	1.6%
Somatic inpatient stay	8.7%	9.4%	2.7%	9.2%	9.4%	0.8%
Pregnancy	4.4%	5.1%	3.4%	4.7%	5.0%	1.6%
ED injury visit	25.5%	25.9%	0.9%	26.4%	26.9%	0.9%
Prior adverse drug reaction	1.9%	1.9%	0.2%	2.3%	2.3%	0.4%
Two or fewer outpatient visits	61.2%	58.9%	4.6%	59.8%	57.7%	4.3%

eMethods 4. Propensity Score and Analysis

7. Propensity Score and Analysis

Calculation. The analysis controlled for covariates with a time-dependent propensity score,[11] the probability a cohort member is an antipsychotic user given study covariates.[23-25] A separate score was calculated for each of the two time-dependent antipsychotic dose groups. The propensity score was estimated with logistic regression models with SAS version 9 PROC LOGISTIC. The regressions were performed separately for three strata, defined hierarchically:

1. Major psychiatric illness, as indicated by a) a diagnosis of bipolar disorder or prescription for a mood stabilizer, b) a psychiatric inpatient stay, c) a diagnosis of either major depression, suicidal ideation, or self-harm;
2. Prescription of a study antidepressant or a diagnosis of a mood disorder other than those listed above;
3. All other cohort members.

The propensity score estimation was stratified because the association of covariates with treatment varied for each of these strata. The models to estimate the propensity score included terms for each of the study covariates as well as interaction terms.

Propensity score diagnostics: distribution. eTable 10 shows the distribution of the individual propensity scores for each of the two antipsychotic dose groups. Because the scores largely overlapped, the analysis included all prescriptions.

eTable 10. Distribution of Propensity Scores for Antipsychotic Dose Groups

		Control	Antipsychotic ≤ 50 mg	Antipsychotic >50 mg
N Prescriptions		1,745,206	232,981	414,741
Estimated Probability	Min	0.000647	0.001792	.
	P1	0.006713	0.020099	.
	P5	0.013065	0.043300	.
	P10	0.018394	0.061242	.
	P25	0.034897	0.105004	.
	P50	0.072744	0.181176	.
	P75	0.135666	0.312006	.
	P90	0.223464	0.485591	.
	P95	0.295488	0.594095	.
	P99	0.481661	0.742667	.
	Max	0.943625	0.940985	.
Estimated Probability	Min	0.001639	.	0.005629
	P1	0.007720	.	0.026816
	P5	0.012906	.	0.059622
	P10	0.017647	.	0.092629
	P25	0.035743	.	0.189566
	P50	0.081293	.	0.392934
	P75	0.180229	.	0.632364
	P90	0.344451	.	0.785823
	P95	0.477926	.	0.849500
	P99	0.717940	.	0.925124
	Max	0.981923	.	0.983373

Propensity score diagnostics: balance. A properly formulated propensity score is a balancing score, that is, the distribution of the covariates conditional on the propensity score is the same in both the treated and untreated groups. We assessed balance by examining the distribution of the covariates in each treatment group after stabilized inverse-probability-of-treatment (IPT) weighting,[24] and as recommended calculated the standardized difference, with a difference of less than 10% considered good balance.[25] This criterion was met for all covariates (eTable 9).

Propensity score: use in analysis. There are four general methods for analysis with propensity scores: matching, weighting, stratification, and regression modeling.[24] We used weighting according to stabilized IPT. This creates a pseudo-population in which the distribution of covariates is balanced across the treatment groups.[23-25] If the propensity score is properly constituted, the weighting removes confounding by those covariates included in the score.

One of the key advantages of propensity score is that they allow control for larger numbers of covariates than traditional multivariate methods, which require 7-10 endpoints for every variable in the model. As Haukoos and Lewis note in a review:[25]

> *"Propensity score methods generally allow many more variables to be included in the propensity score model, which increases the ability of these approaches to effectively adjust for confounding, than could be incorporated directly into a multivariable analysis of the study outcome."*

Because IPT weighting uses all of the information available in the propensity score, unlike other propensity score methods, it is not subject to residual confounding by study covariates.[23-25] However, as the number of covariates increases, extreme weights may substantially inflate the variance.[23-25] Thus, as recommended,[26] in the primary analysis the weights were truncated at the 99th percentile. Weights were not truncated in a sensitivity analysis; results were essentially similar to those of the primary analysis (MS Table 3).

Proportional hazards model. The regression models used modified sandwich variance estimation (Allison,[27] p.266) to correct for weighting-induced dependencies. Hazard ratios (HRs) were estimated via a counting process formulation that accommodates non-proportional hazards (Allison,[27] p.172). The time origin was the fill date of the first study prescription and the time variable[28] corresponded to cumulative days of drug therapy, which adjusts for treatment duration.

8. Additional Findings

eTable 11. Prescribed Study Medications on Cohort Entry[a]

	Control Medications		Antipsychotics	<= 50mg		> 50mg	
	N	%		N	%	N	%
All	189,361	100.0%		28,377	100.0%	30,120	100.0%
ADHD Medications	*81,310*	*42.9%*	Risperidone	18,729	66.0%	3,387	11.0%
Dextroamphetamine-amphetamine	21,587	11.4%	Quetiapine	2,029	7.2%	10,570	34.3%
Methylphenidate	21,003	11.1%	Aripiprazole	3,523	12.4%	7,222	23.4%
Lisdexamfetamine	9,693	5.1%	Olanzapine	1,626	5.7%	5,108	16.6%
Dexmethylphenidate	6,954	3.7%	Ziprasidone	342	1.2%	1,701	5.5%
Clonidine	6,213	3.3%	Perphenazine	584	2.1%	111	0.4%
Atomoxetine	5,891	3.1%	Haloperidol	188	0.7%	312	1.0%
Guanfacine	2,670	1.4%	Chlorpromazine	312	1.1%	145	0.5%
Other or multiple	7,299	3.9%	Thioridazine	321	1.1%	77	0.2%
Antidepressants	*93,864*	*49.6%*	Other or multiple	723	2.5%	2599	8.6%
Sertraline	26,008	13.7%					
Citalopram	18,781	9.9%					
Fluoxetine	16,192	8.6%					
Paroxetine	14,688	7.8%					
Escitalopram	5,170	2.7%					
Mirtazapine	4,740	2.5%					
Venlafaxine	3,735	2.0%					
Other/multiple	4,550	2.4%					
Mood stabilizers	*14,187*	*7.5%*					
Divalproex sodium	4,929	2.6%					
Lamotrigine	3,235	1.7%					
Oxcarbazepine	3,088	1.6%					
Lithium	1,094	0.6%					
Other or multiple	1,841	1.0%					

ADHD: attention deficit hyperactivity disorder.

A control patient can have multiple medication classes. For the counts, priority is given to ADHD medications, then antidepressants, then mood stabilizers.

eTable 12. Unintentional Drug Overdose Deaths—Specific Drugs Listed in the Death Certificate Multiple Causes of Death

	Control	*Antipsychotic >50mg chlorpromazine-equivalents*
All overdose deaths	11 (100.0%)	10 (100.0%)
Unspecified drug only	4 (36.4%)	4 (40.0%)
Opioid or drug of abuse[a] only	4 (36.4%)	1 (10.0%)
Any non-opioid prescription medication	3 (27.3%)	5 (50.0%)

[a]For the study population, the only drugs of abuse mentioned were cocaine and cannabis.

eTable 13. Effects of Unmeasured Confounder on the Risk of Unexpected Death for Higher-Dose Antipsychotic Users

		Confounder Hazard Ratio			
		2	**3**	**4**	**5**
Confounder Prevalence					
Antipsychotic	**Control**				
		True Hazard Ratio			
25%	25%	3.51	3.51	3.51	3.51
25%	0%	2.81	2.34	2.01	1.76
50%	50%	3.51	3.51	3.51	3.51
50%	25%	2.93	2.63	2.46	2.34
50%	0%	2.34	1.76	1.40	1.17
75%	75%	3.51	3.51	3.51	3.51
75%	50%	3.01	2.81	2.70	2.63
75%	25%	2.51	2.11	1.89	1.76
75%	0%	2.01	1.40	1.08	0.88

eTable 13 presents a sensitivity analysis for the effect of an unmeasured confounder across a range of values for confounder strength and the difference in confounder prevalence between the higher-dose antipsychotic patients and controls. The Table shows the hazard ratio that would result after adjustment for an unmeasured confounder, using the method originally described by Breslow and Day.[29,30] Confounding would completely explain an increased risk of unexpected death only for a confounder that increased the risk of unexpected death by a factor of 5, was present for at least 75% of higher-dose antipsychotic users, and was not present in any of the controls

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