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Association of Antipsychotic Treatment With Risk of Unexpected Death Among Children and Youths

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Supplemental content

IMPORTANCE Children and youths who are prescribed antipsychotic medications have multiple, potentially fatal, dose-related cardiovascular, metabolic, and other adverse events, but whether or not these medications are associated with an increased risk of death is unknown.

OBJECTIVE To compare the risk of unexpected death among children and youths who are beginning treatment with antipsychotic or control medications.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted from 1999 through 2014 and included Medicaid enrollees aged 5 to 24 years in Tennessee who had no diagnosis of severe somatic illness, schizophrenia or related psychoses, or Tourette syndrome or chronic tic disorder. Data analysis was performed from January 1, 2017, to August 15, 2018.

EXPOSURES Current, new antipsychotic medication use at doses higher than 50 mg (higher-dose group) or 50 mg or lower chlorpromazine equivalents (lower-dose group) as well as control medications (ie, attention-deficit/hyperactivity disorder medications, antidepressants, or mood stabilizers) (control group).

MAIN OUTCOMES AND MEASURES Deaths during study follow-up while out of hospital or within 7 days after hospital admission, classified as either deaths due to injury or suicide or unexpected deaths. Secondary outcomes were unexpected deaths not due to overdose and death due to cardiovascular or metabolic causes.

RESULTS This study included 189 361 children and youths in the control group (mean [SD] age, 12.0 [5.1] years; 43.4% female), 28 377 in the lower-dose group (mean [SD] age, 11.7 [4.4] years; 32.3% female), and 30 120 in the higher-dose group (mean [SD] age, 14.5 [4.8] years; 39.2% female). The unadjusted incidence of death in the higher-dose group was 146.2 per 100 000 person-years (40 deaths per 27 354 person-years), which was significantly greater than that in the control group (54.5 per 100 000 population; 67 deaths per 123 005 person-years) ($P < .001$). The difference was primarily attributable to the increased incidence of unexpected deaths in the higher-dose group (21 deaths; 76.8 per 100 000 population) compared with the control group (22 deaths; 17.9 per 100 000 population). The propensity score–adjusted hazard ratios were as follows: all deaths (1.80; 95% CI, 1.06-3.07), deaths due to unintentional injury or suicide (1.03; 95% CI, 0.53-2.01), and unexpected deaths (3.51; 95% CI, 1.54-7.96). The hazard ratio was 3.50 (95% CI, 1.35-9.11) for unexpected deaths not due to overdose and 4.29 (95% CI, 1.33-13.89) for deaths due to cardiovascular or metabolic causes. Neither the unadjusted nor adjusted incidence of death in the lower-dose group differed significantly from that in the control group.

CONCLUSIONS AND RELEVANCE The findings suggest that antipsychotic use is associated with increased risk of unexpected death and appear to reinforce recommendations for careful prescribing and monitoring of antipsychotic treatment for children and youths and to underscore the need for larger antipsychotic treatment safety studies in this population.

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The introduction of second-generation antipsychotics led to a marked increase in antipsychotic medication prescribing for children and youths.[1-3] In 2010, more than 1.3 million individuals receiving antipsychotics aged 24 years or younger filled 7 million antipsychotic medication prescriptions.[4,5] The most common diagnoses associated with the antipsychotic prescriptions for these children and young adults were attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorder, and depression.[4,5] However, antipsychotics are often an off-label or secondary therapeutic choice for these diagnoses, given the other well-defined therapeutic interventions available with potentially fewer adverse effects.[5] Antipsychotics also are frequently prescribed to children and adolescents for bipolar disorder or mood instability, although there often are alternative treatments available.[5]

Studies of older adults linking antipsychotics with increased risk of cardiovascular[6,7] and total mortality[8] raise the concern that receipt of antipsychotics may be associated with increased mortality in younger populations. Antipsychotics have potentially life-threatening cardiovascular,[6,7,9-19] metabolic,[20-24] and other[25-39] adverse effects, although in children and adolescents, these adverse effects are most frequently associated with medication overdose and fatal outcomes are rare. However, there is little information from controlled studies of the association of antipsychotics with mortality in younger populations. Thus, we conducted a retrospective cohort study examining unexpected deaths among children and youths beginning therapy with antipsychotics or alternative medications.

Key Points

Question Are antipsychotic medications prescribed for children and youths without psychosis associated with increased risk of unexpected death or deaths other than from injuries or suicides without prolonged hospitalization?

Findings In this cohort study of 247 858 Medicaid-enrolled children and youths in Tennessee who were new users of antipsychotic or control medications, the group that received a higher dose of antipsychotic medication had a significantly increased risk of unexpected death compared with the group that received control medication.

Meaning This study suggests that antipsychotic treatment may be associated with increased mortality among children and youths and appears to underscore recommendations for careful medication use and monitoring in this population.

Methods

Cohort and Follow-up

The cohort was identified from Tennessee Medicaid enrollment, pharmacy, hospital, outpatient, and nursing home files, which were augmented with linkage to death certificates[40,41] and data from a statewide hospital discharge database.[42] These resources provided an efficient source of data for identifying the cohort, determining periods of probable exposure to medications, and ascertaining deaths.[40,43] The study was reviewed and approved by the institutional review boards of Vanderbilt University, Nashville, Tennessee, and the State of Tennessee Health Department, which waived informed consent.

Medications

Medication use was identified from Medicaid pharmacy files, which are not subject to information bias[43] and have high concordance with patient self-reports of medication use.[44-46] Study medications were oral antipsychotics (eTable 1 in the Supplement) and 3 classes of control drugs commonly prescribed for the same indications as antipsychotics (eTable 2 in the Supplement). Control medications included (1) psychostimulants, serotonin-norepinephrine reuptake inhibitors, or α-agonists frequently prescribed for ADHD or other problems of behavior or conduct; (2) antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine, which are commonly recommended as initial therapy for major depression and other mood disorders[47]; and (3) lithium or anticonvulsant mood stabilizers, absent evidence of a neurologic indication.

Cohort Eligibility

The cohort included children and young adults (youths) aged 5 to 24 years enrolled in Medicaid between January 1, 1999, and December 31, 2014. The lower age limit coincides with initiation of school attendance for many children with the consequent social and behavioral demands. The upper age limit coincides with the World Health Organization's definition of youth,[20] corresponds closely to the age of emerging adulthood (defined as ages 18 to 25 years),[48] and is consistent with other studies of psychoactive drugs in younger populations.[3,20,49,50] Sensitivity analyses were performed with an upper age bound of 21 years, which is consistent with the US Food and Drug Administration definition of adolescents,[51] and with a lower age bound of 12 years.

Cohort members (eTable 3 in the Supplement) had at least 1 year of Medicaid enrollment and previous health care use to ensure availability of data for study variables. We excluded patients with life-threatening somatic illnesses (eTable 4 in the Supplement) or who were in the hospital when the medication regimen was started, for whom illness-related deaths might be indistinguishable from those associated with adverse medication events. Individuals were not included if they had a diagnosis of schizophrenia or related psychoses (antipsychotics are the only pharmacotherapy) or a neurologic indication for an antipsychotic. A psychiatric diagnosis in the past year was required to exclude patients with nonpsychiatric indications for study medications.

Antipsychotic Medication and Control Groups

The cohort included new users (no filled prescription in the past year) of antipsychotic and control medications to capture deaths early in therapy and to ensure that baseline covariates were unaffected by long-term medication effects.[52] Patients who received antipsychotics could have previous use of up to 2 control medication classes. Control patients could have no previous use of antipsychotics but could have use of

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the 2 other control medication classes. Thus, on cohort entry, patients in each group could have up to 3 study medication classes (multiple medications within each class were permitted). Sensitivity analyses excluded patients with more severe comorbidities, such as bipolar disorder, autism or Asperger syndrome, or intellectual disability, and patients prescribed a baseline mood stabilizer.

Follow-up

Patients entered the cohort at the filling of the first prescription for an antipsychotic or control drug that satisfied the cohort eligibility criteria. They left the cohort at the earliest of the following times: (1) the end of the study period, (2) 5 years after cohort entry (1 year in a sensitivity analysis), (3) loss of Medicaid enrollment, (4) reached age of 25 years, or (5) death. Follow-up for controls ended with an antipsychotic prescription; for those receiving antipsychotics, follow-up ended with use of all 3 control drug classes. Follow-up also ended after 365 days (30 days in sensitivity analysis) with no filled prescription for the cohort entry drug class.[6,7,20] Both patients who received antipsychotics and control patients who left the cohort could reenter if they subsequently met the study eligibility criteria. Because these episodes were not overlapping and the end point occurred only once, statistical independence assumptions were satisfied.[53]

Because many adverse effects of antipsychotic medications are acute and therapy may be episodic, study person-time was restricted to periods of current medication use, which were calculated from the prescriptions for study drugs filled between cohort entry and exit (eMethods 1 and eFigure in the Supplement). Current use began with the prescription fill and ended with the earliest of the end of the dispensed days of supply (with 1 additional day given for the long half-life of many study medications), filling of a subsequent prescription for a drug in the same class (which initiated a new period of current use), or the end of study follow-up. For patients admitted to the hospital on a day of current study medication use, study person-time extended up to 7 days to capture in-hospital deaths associated with preadmission conditions.

Antipsychotic use was stratified according to time-dependent dose,[6] given the wide dose range for which antipsychotics are prescribed[20] and the strong dose-response for the cardiovascular,[6,7] metabolic,[20] and central nervous system–depressant[54,55] effects of antipsychotics. The dose cut-point was more than 50 mg of chlorpromazine or its equivalent (eTable 3 in the Supplement), the approximate median antipsychotic dose on cohort entry.

End Points

Study deaths were those that occurred out of the hospital or within 7 days after hospital admission. In younger populations free of life-threatening somatic illness, out-of-hospital deaths often reflect disease processes with rapid onset, which would include unexpected adverse events associated with the medication. In the study population, nearly all qualifying in-hospital deaths were attributable to ultimately fatal acute preadmission conditions (eg, severe head injury or drowning). A sensitivity analysis further restricted study deaths to those within 1 day of hospital admission.

Deaths due to injury or suicide had an underlying cause of death of unintentional injury other than a drug overdose or suicide. All other deaths were unexpected deaths, which absent adverse medication events, are rare among children and youths in good or stable health (eMethods 2 and eTables 5-7 in the Supplement). This definition is consistent with a National Institutes of Health and Centers for Disease Control and Prevention research initiative to reduce mortality in younger populations[56] except that it includes deaths due to unintentional overdose, because for both children and adults, antipsychotics are potent central nervous system depressants[54,55] that can impair respiration[25-30] and thus possibly could be synergistically associated with an increase in risk of overdose of other drugs. Unexpected deaths not due to overdose were identified and classified as deaths due to cardiovascular or metabolic causes or other deaths. Deaths due to overdose were described according to specific medications listed as multiple causes of death in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (eTable 8 in the Supplement).

Statistical Analysis

Statistical analysis was performed from January 1, 2017, to August 15, 2018. To control for potential differences in psychiatric and somatic comorbidity, we measured 46 covariates plausibly associated with both antipsychotics and mortality (eMethods 3 and eTable 9 in the Supplement). These factors included demographic characteristics; psychoactive medications; psychiatric, neurologic, and cardiovascular conditions; respiratory diseases; injuries, other illnesses and psychiatric and somatic hospitalizations; and other medical care use. The analysis controlled for covariates with stabilized inverse probability of treatment weights calculated from the propensity score[57-59] defined as the probability that a cohort member was an antipsychotic user given covariates (eMethods 4 and eTables 9 and 10 in the Supplement). If the propensity score is properly constituted, the weighting eliminates covariate imbalances between the study groups and thus controls for confounding by variables included in the propensity score (eMethods 4 in the Supplement).[57-59]

Because the factors leading to lower- vs higher-dose antipsychotic use could differ, we calculated a time-dependent propensity score[53] for each group. Antipsychotic dose, age, calendar year, and psychoactive medications were time-dependent because changes during follow-up may be associated with the risk of death. Other covariates were fixed at cohort entry given that they could be on the causal pathway for antipsychotic-associated deaths (eg, obesity or type 2 diabetes).

The adjusted relative risk of death was estimated with a weighted proportional hazards regression with weights truncated at the 99th percentile[60] (eMethods 4 in the Supplement). A 2-sided $P < .05$ was considered to be statistically significant. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc).

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Results

Cohort

The study included 189 361 new users of control medications (control group) (eTable 11 in the Supplement), including 81 310 (42.9%) who received ADHD medications (most frequently psychostimulants), 93 864 (49.6%) who received antidepressants (most frequently selective serotonin reuptake inhibitors), and 14 187 (7.5%) who received mood stabilizers (most frequently anticonvulsants). The cohort included 28 377 new users of antipsychotic medications who received initial doses of 50 mg or less chlorpromazine equivalents (most commonly risperidone [18 729 patients; 66.0%]) (lower-dose group) and 30 120 who received doses higher than 50-mg chlorpromazine equivalents (most commonly quetiapine [10 570 patients; 34.3%], aripiprazole [7222; 23.4%], and olanzapine [5108; 16.6%]) (higher-dose group).

Of the 189 361 patients in the control group, 82 088 were female (43.4%), with mean (SD) age, 12.0 (5.1) years; of the 28 377 patients in the lower-dose group, 9157 were female (32.3%), with a mean (SD) age of 11.7 (4.4) years; and of 30 120 patients in the higher-dose group, 11 804 were female (39.2%), with a mean (SD) age of 14.5 (4.8) years (**Table 1**). In the study, 70.6% of the cohort had a diagnosis of behavioral symptoms (ADHD, conduct disorder, or impulsivity). Control patients more frequently had been prescribed ADHD medications (125 414 patients [66.2%] for all 3 symptoms together), whereas antipsychotic users were more likely to have disability-related Medicaid enrollment (16 452 users [28.3%]), had greater prevalence of diagnosed mood disorders and other psychiatric comorbidities, and were more frequently prescribed mood stabilizers and other psychoactive drugs (Table 1). These differences were more pronounced in the higher-dose group. The prevalence of diagnosed or treated cardiovascular illness was low and differed little between the study groups. After adjustment for the propensity score, the distribution of study covariates was comparable in all 3 groups (eTable 9 in the Supplement).

Deaths

Cohort follow-up included 123 005 person-years in the control group, 16 159 person-years in the lower-dose group, and 27 354 person-years in the higher-dose groups. There were 67 deaths in the control group (54.5 per 100 000 person-years; 95% CI, 42.9-69.2 per 100 000 person-years) (**Figure**), with injuries and suicides accounting for 67.2% of deaths. There were 8 deaths in the lower-dose group (49.5 per 100 000 person-years; 95% CI, 24.8-99.0 per 100 000 person-years), which did not differ significantly from the incidence in the control group ($P = .80$). There were 40 deaths in the higher-dose group (146.2 per 100 000 person-years; 95% CI, 107.3-199.4 per 100 000 person-years), which was significantly greater than the incidence in the control group ($P < .001$). The difference was primarily attributable to the increased incidence of unexpected deaths (higher-dose group vs control group, 76.8 per 100 000 person-years vs 17.9 per 100 000 person-years), which accounted for 52.5% of deaths in the higher-dose group.

After adjustment for covariates, the risk of death in the higher-dose group was 80% greater than that in the control group (hazard ratio [HR], 1.80; 95% CI, 1.06-3.07) (**Table 2**). In the higher-dose group, the adjusted HR for unexpected deaths was significantly increased (HR, 3.51; 95% CI, 1.54-7.96), with 45 excess deaths per 100 000 person-years (range, 10-125 per 100 000 person-years). In contrast, the risk of death from injury or suicide was not increased (HR, 1.03; 95% CI, 0.53-2.01). Patients in the lower-dose group had no significantly increased risk of total mortality (HR, 1.43; 95% CI, 0.62-3.30; $P = .41$).

When more detailed causes of death were examined (Table 2), the higher-dose group had an increased risk of unexpected deaths other than from unintentional drug overdose (HR, 3.50; 95% CI, 1.35-9.11), including increased risk for deaths due to cardiovascular or metabolic causes (HR, 4.29; 95% CI, 1.33-13.89). There was an increased risk of deaths due to unintentional drug overdose, but the difference was not significant (HR, 3.51; 95% CI, 0.99-12.43; $P = .052$). Deaths due to overdose in the control group were predominantly associated with opioids and illegal drugs, whereas those deaths in the higher-dose group more often involved nonopioid prescription medications (eTable 12 in the Supplement). There was no significantly increased risk of death from either injury (HR, 1.21; 95% CI, 0.54-2.73) or suicide (HR, 0.74; 95% CI, 0.26-2.15).

Sensitivity Analyses

The increased risk for unexpected death in the higher-dose group persisted in sensitivity analyses that restricted the study cohort (**Table 3**). These analyses changed the upper age limit to 21 years and the lower age limit to 12 years and excluded patients with bipolar disorder, previous mood stabilizer use, autism or Asperger syndrome, or intellectual disability.

The increased risk also persisted when key study definitions were altered (Table 3). These study definitions included time-dependent covariates for psychiatric and somatic hospitalizations, not allowing cohort reentry, considering patient as a random effect in the statistical analysis, censoring patients after 30 days without a prescription fill for the study medication class, restricting in-hospital deaths to within 1 day of admission, and not truncating the inverse probability of treatment weights.

A sensitivity analysis assessed the association of an unmeasured confounder (eTable 13 in the Supplement). To explain the risk of unexpected death in the higher-dose group, the confounder would have to increase risk by 5-fold, have a 75% prevalence in the higher-dose antipsychotic treatment group, and not be present in control patients.

Discussion

Among study children and youths without life-threatening somatic illness or psychosis who initiated antipsychotic therapy, those receiving doses higher than 50-mg chlorpromazine equivalents during follow-up had an 80% increased risk of death that was attributable to a 3.5-fold increased risk of

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Table 1. Characteristics of Children and Youths Who Were New Users of Antipsychotic or Control Medications Before Propensity Score Adjustment

	%[a]		
		Antipsychotic Treatment	
Characteristic	Control Treatment	≤50 mg	>50 mg
New users, No.	189 361	28 377	30 120
Prescriptions during follow-up, No.	1 745 206	232 981	414 741
Age at prescription fill, mean (SD), y	12.0 (5.1)	11.7 (4.4)	14.5 (4.8)
Female sex	43.4	32.3	39.2
White race/ethnicity	72.3	60.8	60.6
Disability-related Medicaid enrollment	11.3	25.8	29.7
Standard metropolitan statistical area	55.8	57.7	61.4
Psychiatric conditions in past year			
ADHD, conduct disorder, or impulsivity	71.4	76.3	64.1
Major depression	6.0	8.7	14.7
Other mood disorder	18.6	25.8	34.6
Bipolar disorder	2.7	11.1	21.9
Anxiety, including panic disorder	13.2	15.2	19.5
Mild or moderate intellectual disability	0.9	2.8	4.2
Autism or Asperger syndrome	1.4	6.4	6.2
Alcohol or drug abuse	2.5	3.1	7.8
Suicidal tendencies or ideation	1.6	4.3	8.0
Self-harm	1.2	1.9	3.8
Psychiatric inpatient stay	2.5	7.7	15.0
Learning disability	5.6	7.0	5.3
Sleep disorder	5.5	6.0	7.2
Other psychiatric diagnosis[b]	5.3	7.8	10.1
Psychoactive medications in past 90 d			
ADHD medication: psychostimulant, SNRI, or α2-agonist	66.2	61.0	45.1
Study antidepressant: SSRI, SNRI, or mirtazapine	26.9	24.8	30.2
Mood stabilizer[c]	6.6	13.3	25.0
Cyclic antidepressant	2.6	5.4	3.8
Trazodone	3.9	5.0	8.2
Benzodiazepine or selective benzodiazepine receptor agonist	4.7	3.8	9.8
Anticonvulsants, occasional use as mood stabilizers[d]	1.8	2.5	5.9
Opioid	11.4	8.7	14.4
Cardiovascular conditions in past year			
Arrhythmia	1.2	1.4	1.9
Diabetes[e]	1.9	1.6	2.7
Cardiovascular diagnosis			
Other major[f]	3.5	3.4	3.5
Other	2.7	2.3	4.0
Smoker	4.3	3.0	8.1
Obesity	3.5	2.3	4.0
Cardiovascular medication			
Major[g]	1.2	1.0	1.3
Other	3.1	2.3	5.0
Other conditions or medical care in past year			
Seizure disorder or convulsions[h]	2.9	5.1	6.0
Migraine or other neuropathic pain	7.1	5.6	9.6

(continued)

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Table 1. Characteristics of Children and Youths Who Were New Users of Antipsychotic or Control Medications Before Propensity Score Adjustment (continued)

Characteristic	%[a]		
		Antipsychotic Treatment	
	Control Treatment	≤50 mg	>50 mg
Asthma[i]	28.1	23.8	25.1
Pneumonia	3.1	2.3	2.6
Sleep apnea	1.2	0.7	0.9
Somatic inpatient stay	9.0	6.5	10.1
Pregnancy	4.8	1.7	4.3
Emergency department injury visit	25.3	26.6	30.5
Previous adverse drug reaction	1.8	2.8	4.3
≤2 Outpatient visits	63.9	41.6	43.7

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Weighted according to the number of prescriptions written during follow-up. Age, calendar year, and psychoactive medication use were determined as of the date of each prescription fill; values of the other variables were fixed at the beginning of follow-up.

[b] Includes antisocial and other personality disorders, dissociative disorder, eating disorder, sexual dysfunction, organic psychoses, and other psychiatric diagnoses.

[c] Lithium and anticonvulsant mood stabilizers (carbamazepine, divalproex sodium, lamotrigine, oxcarbazepine, valproate sodium, and valproic acid).

[d] Gabapentin, pregabalin, lacosamide, levetiracetam, tiagabine, topiramate, and zonisamide.

[e] Diagnosis of diabetes or prescription for insulin.

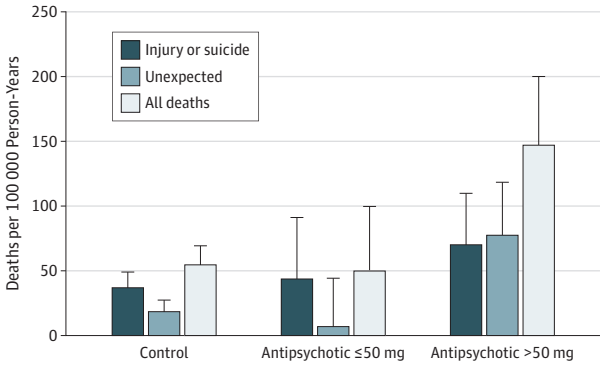
[f] Angina, revascularization, myocardial infarction or other coronary heart disease, valve disease, heart failure, cerebrovascular disease, peripheral vascular disease, malignant hypertension, and congenital cardiac anomaly.

[g] Anticoagulant, antiarrhythmic, digoxin, loop diuretic, nitrate, other antianginal, peripheral vasodilator, and platelet inhibitor.

[h] Diagnosis of convulsion or seizure disorder, or prescription for anticonvulsant.

[i] Diagnosis of asthma or prescription for inhaled corticosteroid, bronchodilator, or β-agonist.

Figure. Unadjusted Incidence of Study Deaths According to Cause of Death and Study Medication



There were 123 005 person-years for the control group with 45 deaths due to injury or suicide and 22 unexpected deaths, 16 159 person-years for the group receiving 50 mg or less of antipsychotic treatment with 7 deaths due to injury or suicide and 1 unexpected death, and 27 354 person-years for the group receiving more than 50 mg of antipsychotic treatment with 19 deaths due to injury or suicide and 21 unexpected deaths. Bars indicate upper 95% confidence limits.

unexpected deaths. In contrast, the risk of deaths from injuries or suicides was not increased. The elevated risk persisted for unexpected deaths not due to overdose, with a 4.3-fold increased risk of death from cardiovascular or metabolic causes. No significantly increased risk was associated with antipsychotic doses of 50 mg or lower, although there were few deaths in this group and the 95% CIs were wide.

Unexpected death was an important study end point because, absent adverse medication events, such deaths should rarely occur in a young population without serious somatic illness. Although previous definitions of unexpected death in children and youths have excluded unintentional drug overdoses,[56] we included these deaths because the clinical circumstances often are similar to those of deaths due to cardiovascular causes (eg, unexplained death during sleep), and it can be difficult to distinguish the mechanisms post mortem.[61,62] Furthermore, antipsychotics are potent central nervous system depressants[54,55] that can impair respiration[25-30] and thus could increase risk of fatal inadvertent overdose with other medications. Our analysis that did not consider overdoses as unexpected deaths showed increased risk of comparable magnitude to that of the primary analysis.

For every 100 000 person-years of follow-up, the higher-dose group had 45 excess unexpected deaths, which exceeded the 44 deaths per 100 000 person-years from unintentional injuries other than overdoses in this group, a major focus of public health campaigns for children and youths.[63,64] If the association observed were causal, improving the safety of antipsychotic medication prescribing for the more than 1 million young persons who receive antipsychotics annually in the United States[4] would be of high priority.

The study findings seem to reinforce existing guidelines for improving the outcomes of antipsychotic therapy in children and youths.[5,65] These guidelines include restriction to indications for which there is good evidence of efficacy, adequate trial of alternatives including psychosocial interventions when possible, cardiometabolic assessment before treatment and monitoring after treatment, and limiting therapy to the lowest dose and shortest duration possible.

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Table 2. Causes of Death Among Patients Receiving Control Treatment and Those Receiving Antipsychotic Treatment With a Dose Higher Than 50-mg Chlorpromazine Equivalents[a]

Cause of Death	Patients Receiving Control Treatment		Patients Receiving Antipsychotic Treatment >50 mg		Adjusted (95% CI)[b]		
	Deaths	Rate, per 100 000 Person-Years	Deaths	Rate, per 100 000 Person-Years	Hazard Ratio	Rate Difference, per 100 000 Person-Years	No. Needed to Harm
All	67	54.5	40.0	146.2	1.80 (1.06-3.07)	43.8 (3.3 to 112.6)	2283 (888 to 30 097)
Unexpected	22	17.9	21	76.8	3.51 (1.54 to 7.96)	44.9 (9.7 to 124.7)	2229 (802 to 10 288)
Nonoverdose[c]	11	8.9	11	40.2	3.50 (1.35 to 9.11)	22.3 (3.1 to 72.2)	4487 (1386 to 32 287)
Cardiovascular or metabolic	6	4.9	7	25.6	4.29 (1.33 to 13.89)	16.1 (1.6 to 63.2)	6196 (1583 to 62 410)
Other[d]	5	4.1	4	14.6	2.59 (0.50 to 13.49)	6.5 (−2.1 to 51.2)	15 349 (1952 to ∞)
Unintentional drug overdose	11	8.9	10	36.6	3.51 (0.99 to 12.43)	22.3 (−0.1 to 101.7)	4482 (983 to ∞)
Injury or suicide	45	36.6	19	69.5	1.03 (0.53 to 2.01)	1.0 (−17.3 to 36.9)	97 580 (2708 to ∞)
Injury	33	26.8	12	43.9	1.21 (0.54 to 2.73)	5.6 (−12.4 to 46.4)	17 768 (2156 to ∞)
Suicide	12	9.8	7	25.6	0.74 (0.26 to 2.15)	−2.5 (−7.3 to 11.3)	NA

Abbreviation: NA, not applicable.

[a] In the control group, there were 123 005 person-years; in the antipsychotic treatment group, 27 354 person-years.

[b] Reference category is control medications. Hazard ratios adjusted for all study covariates (eTable 9 in Supplement 1) by inverse probability of treatment (propensity score)-weighted proportional hazards regression model. Rate difference per 100 000 person-years, estimated as I_O(hazard ratio − 1), where I_O is the unadjusted rate for the controls; CIs were calculated analogously. Number needed to harm was calculated as 1/rate difference. If the 95% CI for the rate difference includes zero, the upper confidence limit for the number needed to harm is ∞. If the rate difference is negative, indicating a beneficial association, the number needed to harm is undefined.

[c] Consistent with the National Institutes of Health and Centers for Disease Control and Prevention definition of unexpected death.[56]

[d] Control group: 2 deaths from neurologic causes and 1 death each from preeclampsia, volume depletion, and mental and behavioral disorders due to use of alcohol. Antipsychotics group: 2 deaths from respiratory causes and 2 deaths from neurologic causes. Because there were fewer than 10 total deaths, adjusted hazard ratio CIs may be too narrow.

Table 3. Sensitivity Analyses for Patients Who Received Antipsychotics With Doses Higher Than 50 mg Chlorpromazine Equivalents During Follow-up

Variable	Unexpected Deaths		Deaths Due to Injury or Suicide	
	No.	Hazard Ratio (95% CI)[a]	No.	Hazard Ratio (95% CI)[a]
Primary analysis	43	3.51 (1.54-7.96)	64	1.03 (0.53-2.01)
Cohort				
Age at prescription fill ≤21 y	27	4.04 (1.39-11.71)	45	1.19 (0.54-2.63)
Age at prescription fill ≥12 y	39	3.00 (1.27-7.07)	55	0.98 (0.48-2.00)
No bipolar disorder	39	3.12 (1.30-7.53)	55	1.07 (0.51-2.25)
No previous mood stabilizer[b]	37	3.35 (1.36-8.24)	54	1.02 (0.47-2.20)
No autism or Asperger syndrome	40	3.26 (1.39-7.66)	62	0.98 (0.49-1.95)
No intellectual disability	40	3.27 (1.40-7.68)	63	1.00 (0.50-1.98)
Key study definitions				
Psychiatric and somatic time-dependent hospitalizations	43	3.33 (1.43-7.76)	64	1.03 (0.52-2.02)
Patients not allowed cohort reentry	29	4.87 (1.63-14.54)	46	1.08 (0.44-2.69)
Patient considered as random effect in statistical analysis	43	3.51 (1.54-7.96)	64	1.03 (0.53-2.01)
Censor if >30 d without prescription fill for the study medication	31	3.92 (1.55-9.91)	40	1.26 (0.55-2.88)
Censor after first calendar year after cohort entry	33	4.42 (1.74-11.23)	45	0.88 (0.37-2.14)
No in-hospital deaths >1 d after admission	40	3.21 (1.35-7.62)	58	0.91 (0.46-1.79)
Inverse probability of treatment weights not truncated	43	3.04 (1.26-7.36)	64	0.93 (0.48-1.80)

[a] Reference category is control medications. Hazard ratios adjusted for all study covariates (eTable 9 in Supplement 1) by inverse probability of treatment (propensity score) weighted proportional hazards regression model.

[b] None in the interval [t_O − 90 d, t_O − 1 d], which is consistent with the definition of psychiatric medication definitions for the propensity score.

Limitations

The primary limitation of this study is the potential for uncontrolled confounding by differences between antipsychotic users and controls. Because the number of deaths during follow-up was relatively small, the analysis relied on statistical adjustment for an extensive set of covariates to control for the substantially greater psychiatric comorbidities among antipsychotic users. Furthermore, study data (1) did not

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include important patient characteristics, such as body mass index, family history, or undiagnosed cardiovascular abnormalities; (2) were subject to underdiagnosis of risk factors; and (3) lacked information necessary to refine the end point definitions through psychological autopsies.

Several findings indicated that the study results were not attributable to confounding. The propensity score–based weighting balanced the distribution of measured comorbidities among the study groups. There was no increase in the adjusted risk for suicides, which should reflect unmeasured differences in serious psychiatric comorbidity. Sensitivity analyses that decreased comorbidity differences by restricting the cohort had essentially similar findings. Further studies are needed that compare antipsychotic users and controls within more narrow comorbidity ranges or in analyses that include richer clinical data.

The significantly elevated risk of death due to cardiovascular or metabolic disease is important because this end point should be less subject to unmeasured confounding and the finding is consistent with known antipsychotic adverse effects in children and youths. The prevalence of cardiovascular conditions was low and did not differ among the study groups. In younger populations, the corrected QT interval increases during antipsychotic treatment,[9] and there are at least 10 published case reports of antipsychotic-related, acquired long QT syndrome, including torsade de pointes.[10-19] Most antipsychotics cause rapid and substantial weight gain[66,67] and are associated with increased risk of diabetes,[20,21] including diabetic ketoacidosis.[22,68] Because the number of deaths due to cardiovascular or metabolic causes was small, this finding needs to be replicated in larger populations.

As in previous studies,[3,20,50] the primary analysis included children and youths from ages 5 through 24 years. However, there is substantial diagnostic heterogeneity within this broad age range. Sensitivity analyses that set the upper age bound at 21 years, consistent with the US Food and Drug Administration's definition of adolescents,[51] and the lower bound at 12 years, had similar findings. To better guide practice, data for more narrowly defined age groups are needed.

Sample size was insufficient to assess the association of individual antipsychotic, dose, and potential drug-drug interactions. Both adverse cardiovascular and metabolic events may differ for individual drugs.[69-72] The study analysis dichotomized the broad antipsychotic dose range at the median. Although there was no significantly increased risk of death among patients in the lower-dose group, there were 8 deaths in this group, and thus, it could not be directly compared with the higher-dose group. Additional information is needed regarding the relative safety of higher doses within the higher than 50-mg group, as well as for commonly coprescribed medications, including benzodiazepines, opioids, and antidepressants, that may be associated with a synergistic increase in the risk of death.

The single-state Medicaid cohort may limit the study's generalizability. However, the Medicaid population is important because this program provides health insurance coverage for an estimated 39% of US children,[73] among whom the prevalence of antipsychotic use is elevated.[74] Generalizability was further limited by the exclusion of patients with psychoses, neurologic indications for antipsychotics, major chronic diseases, or other severe conditions.

Conclusions

Children and youths beginning antipsychotic therapy who received doses higher than 50-mg chlorpromazine equivalents had a 3.5-fold increased risk of unexpected deaths but no increased risk for deaths from injuries or suicides. This finding suggests that the increased unexpected death risk was associated with the use of antipsychotics. These results appear to reinforce recommendations for careful prescribing and monitoring of antipsychotic regimens for children and youths and the need for larger antipsychotic safety studies in this population.

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