Antidepressants and Suicide Attempts in Children

WHAT'S KNOWN ON THIS SUBJECT: Warnings of increased risk for suicidality have been placed on antidepressant medications. Because antidepressants differ in their characteristics, including effects on neurotransmitters, it is possible that the risk of suicidal behavior for individual medications may differ.

WHAT THIS STUDY ADDS: In a cohort of 36 842 children with review of medical records for confirmation of suicide attempts, we found no difference for risk of suicide attempts among individual medications compared with fluoxetine, the currently recommended antidepressant for treatment of depression.

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abstract

OBJECTIVES: Recent data showing possible increased risk for suicidal behavior among children and adolescents treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) antidepressants have created significant concern among patients, families, and providers, including concerns about the risk of individual antidepressants. This study was designed to compare the risk for medically treated suicide attempts among new users of sertraline, paroxetine, citalopram, escitalopram, and venlafaxine to risk for new users of fluoxetine.

METHODS: A retrospective cohort study included 36 842 children aged 6 to 18 years enrolled in Tennessee Medicaid between 1995 and 2006 who were new users of 1 of the antidepressant medications of interest (defined as filling no prescriptions for antidepressants in the preceding 365 days). Medically treated suicide attempts were identified from Medicaid files and vital records and confirmed with medical record review.

RESULTS: Four hundred nineteen cohort members had a medically treated suicide attempt with explicit or inferred attempt to die confirmed through medical record review, including 4 who completed suicide. The rate of confirmed suicide attempts for the study drugs ranged from 24.0 per 1000 person-years to 29.1 per 1000 person-years. The adjusted rate of suicide attempts did not differ significantly among current users of SSRI and SNRI antidepressants compared with current users of fluoxetine. Users of multiple antidepressants concomitantly had increased risk for suicide attempt.

CONCLUSIONS: In this population-based study of children recently initiating an antidepressant, there was no evidence that risk of suicide attempts differed for commonly prescribed SSRI and SNRI antidepressants. *Pediatrics* 2014;133:204–210

Major depressive disorder (MDD) is a common condition in children and adolescents[1,2] and has significant negative impacts on children's development, functioning, and risk for suicide.[2–5] Antidepressant medications are often used to treat childhood depression, but concerns about possible increased risk for suicidal behavior among children and adolescents treated with antidepressants led to warnings from the US Food and Drug Administration (FDA) and the UK Medicine Healthcare Products Regulatory Agency.[6–9]

Regulatory warnings for suicide risk in children and adolescents treated with antidepressants do not distinguish individual antidepressants, but data from clinical trials suggested that the risk might differ for individual drugs, particularly for newer selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[9,10] Individual drug characteristics, such as neurotransmitter selectivity or elimination half-life, could differentially influence the neurobiological processes of suicide, including impulsivity and hopelessness.[11–13] For example, the SNRI drug venlafaxine has both serotonergic and noradrenergic effects, whereas SSRIs have more selective serotonergic effects.[12,13] Understanding more about the potential risks for suicides related to individual antidepressants would provide important information for patients, families, and providers to guide treatment decisions.

Thus, we conducted an observational study with a cohort of children who were new users of individual SSRI and SNRI antidepressants and conducted medical record review for all suicide attempts identified from Medicaid claims and vital records. We compared the risk for medically treated suicide attempts for sertraline, paroxetine, citalopram, escitalopram, and venlafaxine to fluoxetine, the currently FDA-recommended antidepressant for treatment of depression in children and adolescents.

METHODS

Design and Data Sources

We assembled a retrospective cohort of children, aged 6 to 18 years, enrolled in Tennessee Medicaid from 1995 to 2006. Tennessee Medicaid files linked with state death certificates and statewide hospital discharge data provided an efficient source for identifying the cohort, determining periods of probable exposure to medications, and ascertaining end points. The Medicaid data included enrollment records, outpatient and inpatient claims, and records of filled prescriptions (including dispensing date, drug name, dose, quantity, and days of supply), which have been shown to have concordance of ≥90% with patient self-report of medication use.[14–17]

Study Population

To assemble the cohort, we identified new users of fluoxetine, sertraline, paroxetine, citalopram, escitalopram, or venlafaxine, defined as those who filled no prescriptions for an antidepressant during the preceding 365 days. Restricting the cohort to new users allowed the study to identify end points that may occur early in treatment.[18] Fluvoxamine, another SSRI antidepressant marketed during the study period, was not included because it is primarily used for different indications, and there was limited use in the Tennessee Medicaid population (*n* = 261 new users). Cohort members had continuous Medicaid enrollment during the 365 days before the first prescription and had no evidence of major mental illness other than MDD (defined as filling prescriptions for lithium, antipsychotics, mood stabilizing anticonvulsants in the absence of a seizure diagnosis, or claims with a diagnosis of bipolar disorder, psychosis, or schizophrenia including ≥1 inpatient or 2 outpatient claims). We also excluded the small number of

children with life-threatening illness in the 365 days before the first prescription (<1%) because these children may have an atypical risk of suicidality. Children were followed until the earliest of the last study day, their 19th birthday, death, loss of enrollment of ≥7 days (typically ≤10%), development of an exclusion illness, no filling of antidepressant prescriptions for 180 consecutive days, or a suicide attempt. Once children left the cohort, they were allowed to reenter if they met eligibility requirements again.

Antidepressant Use

Every person-day during study follow-up was classified according to use of 1 of the study antidepressants. Current use of an antidepressant was defined as the period between the prescription start date and the end of the days of supply (including up to a 7-day carry-over period from previous prescriptions). Follow-up days with current use of ≥2 antidepressants concomitantly were included in a separate exposure category for multiple antidepressants. We also recorded person time after current use ended but focused on current use for this study to capture the potential acute effects of study medications on the study end point.

Study End Points

Medically treated suicide attempts were defined as self-harm associated with a stated or inferred intent to die. Suicide deaths were defined as self-harm associated with death. Potential end points were identified from computerized records for inpatient, emergency department, and outpatient encounters and included *International Classification of Diseases* (9th and 10th revisions) codes used in previous population-based studies of suicide epidemiology.[19,20] Because we planned to review medical records for all end points, the algorithm to identify cases

was intentionally broad and included injuries that might reasonably be related to self-harm (eg, all claims for falls from a height, gunshot wounds), as we have previously described.[21] Medical records, including emergency medical services reports, emergency department records, mental health evaluations, as well as records from medical and psychiatric hospitalizations were reviewed to confirm that the attempt was related to self-harm with an explicit or inferred intent to die, by using the Columbia Suicidality Classification Scale.[22] For all deaths in the cohort, we reviewed autopsy and toxicology reports. The principal investigator (WOC) and a second investigator (STC) reviewed all cases (agreement of 100% on case status for a 10% random sample of cases). Cases the primary adjudicators considered to be equivocal (8%) were reviewed by a larger group, which included the 2 adjudicators and a child (DCF) and adult (RCS) psychiatrist. Of the equivocal cases, the larger group was able to determine outcome status for all but 2.4%.

We identified 1480 episodes of potential suicidal behavior from medical claims data and vital records. Of these, 1285 (86.8%) had records available for adjudication. In cases in which we were unable to obtain medical records or had insufficient information for adjudication (13.2% of cases), we determined the case status using a computer case definition, derived from cases with completed adjudication, which had a positive predictive value of 85%. Using these methods, we identified 419 end points, including 415 confirmed attempts and 4 completed suicides.

Analysis

The analysis estimated the relative risks for current use of sertraline, paroxetine, citalopram, escitalopram, and venlafaxine compared with current use of fluoxetine by using generalized estimating equation regression models with Poisson distribution.[23,24] These regression models were weighted by the inverse of the probability of treatment to adequately adjust for potential confounding. The Poisson distribution was used as it is suitable for rare events.[23] Generalized estimating equation models accounted for dependency among repeated hospitalizations.[24] Propensity scores were computed as the probability of being in each antidepressant category on the first day of study follow-up.[25] Baseline variables used in creating the propensity score included sociodemographic characteristics (age, gender, race, ethnicity, urban/rural residence, enrollment because of disability, and calendar year and month at study entry) as well as information on medical care encounters in the previous 365 days consistent with psychiatric disorders, asthma, diabetes, seizures, and thyroid disease, as well as medications used to treat these conditions, visits associated with psychiatric diagnoses in inpatient, outpatient, and emergency department settings, and previous suicide attempts. Inverse probability of treatment weighting based on the propensity scores was used to adjust for differences between the antidepressant exposure groups.[26] Inverse propensity score weights were trimmed at the 99th percentile to prevent bias from including overly influential points.[27] To demonstrate the adequacy of the propensity score models in achieving covariate balance, we compared the mean of each propensity score before and after inverse probability of treatment weighting (Supplemental Table 3).

In our primary models, we adjusted for medication-specific propensity score and several time-dependent covariates (age, calendar year and month, mental health diagnoses, and use of psychotropic medications). Additional analyses were stratified by gender, age, and presence of a suicide attempt before study entry. We performed all analyses with SAS 9.1 (SAS Institute, Cary, NC) and R 3.0 (www.r-project.org).

Human Subjects Protection

The study was approved by the institutional review board at Vanderbilt University, the Tennessee Department of Health, and the TennCare Bureau.

RESULTS

Study Population

The cohort included 36 842 children who were new users of study antidepressants during the study period (Table 1). The mean age of new users of the drugs of interest was 14.0 years; 59.3% were female; 15.9% were African American; and 30.2% resided in urban settings. In the year preceding cohort entry, just less than one-half (47.4%) of the cohort members had a diagnosis of MDD, and approximately one-fourth had a diagnosis of attention-deficit/hyperactivity disorder. Other common psychiatric conditions among cohort members included conduct disorder and anxiety. Approximately 10% of the cohort members had asthma, 2% to 3% had seizures, and 1.6% had diabetes. Before entering the cohort, 10.0% had been hospitalized in a psychiatric facility, and 2.9% had a medically treated suicide attempt.

The study drug exposure groups were comparable in terms of demographic characteristics, although venlafaxine and escitalopram users were somewhat older than fluoxetine users, and a smaller proportion of venlafaxine users lived in urban settings (Table 1). The exposure groups were also comparable in the proportion with depression and attention-deficit/hyperactivity disorder diagnoses, but a smaller proportion of fluoxetine users had anxiety diagnoses compared with the other study drugs. A higher proportion of venlafaxine users also filled prescriptions

TABLE 1 Demographic and Clinical Characteristics at Baseline of Children and Adolescents in Tennessee Medicaid Who Were New Users of Antidepressant Medications During the Study Period

Characteristic	Fluoxetine	Sertraline	Paroxetine	Citalopram	Escitalopram	Venlafaxine	Multiple SSRIs
N persons	7967	10 495	8769	3302	2791	1684	1834
Calendar year of study entry, t0	2001.0	2002.5	2001.0	2002.7	2004.1	2002.3	2001.5
Demographics at study entry							
Age, y, mean (SD)	13.8 (3.2)	13.7 (3.3)	14.0 (3.2)	14.1 (3.3)	14.9 (2.8)	14.8 (3.1)	14.7 (2.8)
Female gender, %	60.1	57.5	57.5	60.0	64.4	62.2	62.9
African American race, %	15.8	16.8	15.5	16.6	16.0	10.0	17.2
Hispanic ethnicity, %	0.8	1.0	0.7	0.7	0.9	0.6	0.7
Urban residence, %	32.5	31.4	30.9	26.1	27.5	20.0	30.9
Disability, %	13.8	12.1	12.6	11.8	11.3	8.6	11.2
Psychiatric conditions, past year, %							
MDD	48.2	46.0	46.2	50.1	45.8	44.3	58.5
ADHD	24.8	27.4	25.8	26.6	19.8	21.4	19.8
Conduct disorder	18.0	17.9	18.5	18.3	13.8	14.0	21.2
Anxiety	14.0	19.6	23.2	17.3	17.9	20.1	19.4
Alcohol/drug dependence and abuse	7.3	7.3	7.9	9.2	10.0	10.1	14.6
Adjustment reaction	5.2	3.9	5.8	4.7	3.0	3.4	8.7
Mental retardation	4.4	4.3	4.0	4.3	3.3	2.1	2.5
Other psychiatric	4.4	5.5	4.8	5.4	4.2	3.6	9.1
Eating disorder	2.3	1.9	2.3	2.2	2.1	1.9	2.8
Psychiatric meds, past year, %							
ADHD medications[a]	14.6	13.8	11.7	11.7	11.6	9.1	5.6
Other ADHD medications[b]	4.7	4.2	4.1	4.0	2.7	2.4	2.9
Anxiolytics[c]	3.4	3.7	4.4	3.9	5.2	6.5	3.9
Other conditions, past year, %							
Asthma	9.1	10.4	9.5	9.0	9.7	9.7	10.8
Pain	3.3	4.3	4.5	3.7	5.6	6.4	1.9
Seizures	3.1	2.7	2.6	3.4	2.8	2.3	2.0
Headache	2.5	3.6	3.5	3.4	4.5	4.0	2.4
Fatigue and malaise	2.1	2.2	2.6	2.5	3.5	4.1	1.6
Diabetes	1.8	1.3	1.5	1.8	2.1	1.8	1.3
Premenstrual syndrome	1.7	0.8	0.8	0.6	0.9	0.7	0.3
Thyroid disease	1.2	1.2	1.2	0.9	1.1	1.5	0.7
Enuresis	0.4	0.4	0.4	0.2	0.2	0.2	0.4
Tobacco use disorder	0.3	0.5	0.5	0.2	0.8	0.4	0.1
Insomnia	0.1	0.1	0.1	0.0	0.1	0.1	0.3
Use of health care, past y, %							
Psychiatric hospitalization	11.9	7.3	10.2	10.6	8.3	6.0	22.3
Nonpsychiatric hospitalization	11.4	11.5	10.9	11.6	13.3	12.6	13.7
Previous suicide attempt	3.2	2.4	2.3	3.6	2.9	2.0	6.7
Treated injury	27.3	27.6	28.8	29.5	26.9	29.2	34.3

ADHD, attention-deficit/hyperactivity disorder.
[a] Medications included amphetamines, methylphenidate, and atomoxetine.
[b] Included clonidine and guanfacine.
[c] Included benzodiazepines, chloral hydrate, ramelteon, and buspirone.

for anxiolytics in the year preceding cohort entry. Venlafaxine users were also somewhat less likely to have a psychiatric hospitalization than users of other antidepressants, but approximately the same proportion had nonpsychiatric hospitalizations. The groups were comparable in terms of the proportion with previous suicide attempts (2.0%–3.6%). Cohort members who used multiple antidepressants concomitantly had higher rates of previous psychiatric hospitalizations and more frequent suicide attempts before study entry than fluoxetine users.

Study End Points

Four hundred nineteen cohort members had a medically treated suicide attempt with explicit or inferred attempt to die confirmed through medical record review, including 4 cohort members who completed suicide. Cohort members with medically treated suicide attempts had a mean age of 15.4 years at the time of the attempt. The rate of confirmed suicide attempts for current users of the study drugs ranged from 24.0 per 1000 person-years to 29.1 per 1000 person-years (Table 2). For current users of sertraline, paroxetine, citalopram, escitalopram, and venlafaxine, the adjusted rate of suicide attempts did not differ significantly from that for current users of fluoxetine (Table 2). Children who used multiple antidepressants

concomitantly had higher risk for medically treated suicide attempts (adjusted relative risk 1.70, 95% confidence interval 1.10–2.62) than did fluoxetine users.

Alternative Analyses

We performed several alternative analyses to test the robustness of study findings (Fig 1). We performed analyses stratified by gender and found no statistically significant difference in the risk for medically treated suicide attempts for either gender for any of the study drugs. In other analyses, we compared the risk among the individual antidepressants when we restricted the cohort to children of age 13 to 18 years and when we restricted the cohort to children who had no history of a suicide attempt in the year preceding cohort entry. Finally, we conducted an analysis restricting the cohort to the final 6 years of the study period to assess the effect of temporal changes in antidepressant prescribing. In these additional analyses, we found no statistically significant differences when current users of the study drugs were compared with current users of fluoxetine (Fig 1).

DISCUSSION

In this large cohort of 36 842 children who were new users of SSRI and SNRI antidepressant medications, we found no evidence that the use of paroxetine, sertraline, citalopram, escitalopram, or venlafaxine was associated with a greater risk of medically treated suicide attempts than fluoxetine. In analyses stratified by gender, older age, absence of a suicide attempt before initiating antidepressants, and data from the most recent years of the study period, there was also no evidence of increased risk for any of the study drugs relative to fluoxetine.

This study addresses many limitations of previous research in this area. The study included a large cohort with racial, ethnic, and sociodemographic diversity, allowing for comparisons of outcomes among individual drugs rather than classes of drugs. Restricting the cohort to adolescents who had not used antidepressants in the previous year (ie, new users) allowed the study to avoid underascertainment of outcomes occurring early in treatment and the inability to control for risk factors for suicide that may be altered by study drugs.[18] We performed medical record review for all potential suicide attempts and applied a validated algorithm for suicidality.[22] Applying these rigorous definitions, the rate of medically treated suicide attempts for SSRI and SNRI users (24–29/1000 person years) was comparable to that

described by Schneeweiss et al using data from Canada and in the US FDA's descriptions of suicidality and antidepressants (20–40/1000).[28,29] We controlled for several important covariates, including measures of use of mental health services, by calculating a propensity score at baseline for all cohort members and by using inverse propensity score weighting in multivariate models.
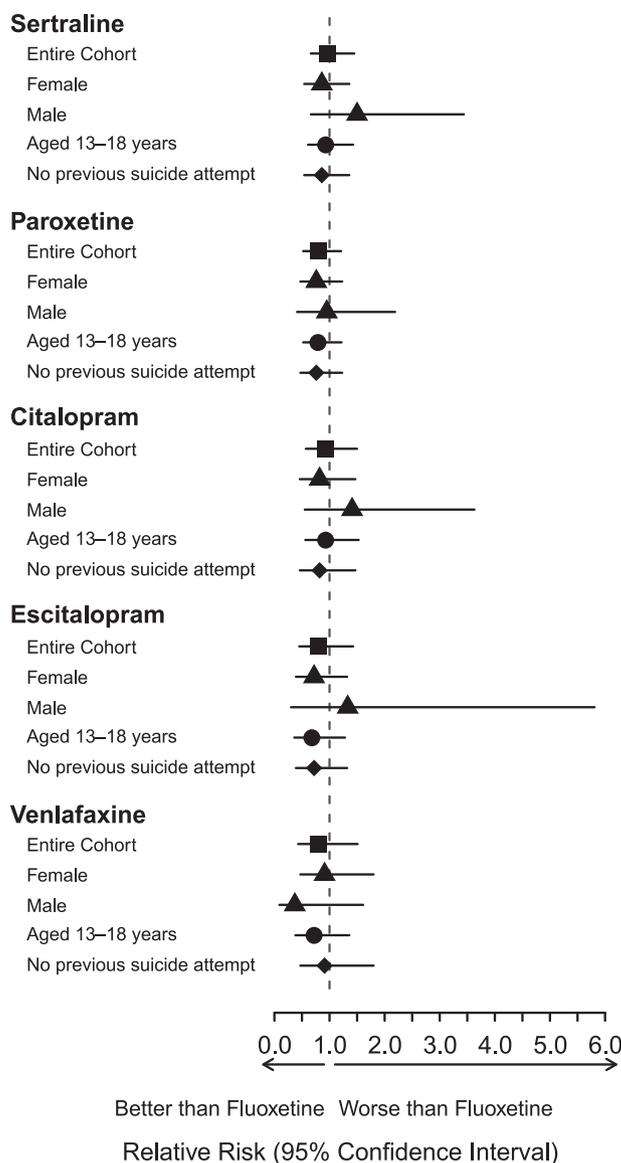
Previous analyses of clinical trials data suggested that there may be differences in the risk of suicidality among antidepressants, including particular evidence of increased risk for venlafaxine.[8] We found no evidence of increased risk for venlafaxine or any of the other drugs studied, although the point estimate for venlafaxine was higher than that for fluoxetine. Our study findings suggest that we can rule out potential absolute excess risk of 13 per 1000 person years for venlafaxine compared with fluoxetine. Given the purported role of increased levels of anxiety in suicide risk related to antidepressants,[6,7] it is interesting to note that a higher proportion of venlafaxine users had comorbid anxiety diagnoses, and a greater proportion filled prescriptions for anxiolytics in the year preceding study entry. We found increased risk for suicidal behavior for study participants who had overlapping use of multiple antidepressants, which likely reflects the increased severity of depression for these individuals rather than a drug effect.[30]

The study has some limitations. By focusing on suicide attempts resulting in death or medical treatment, we potentially missed less serious attempts or suicidal thoughts. We chose to focus on treated attempts and completed suicides because we considered these to be more serious given that they resulted in greater use of medical care and represented a greater likelihood of medical or psychiatric morbidity than

TABLE 2 Risk for Suicide Attempts Among Children Who Were Current Users of Individual Antidepressants Compared With Children and Adolescents Who Were Current Users of Fluoxetine

	Person-Years of Current Use	Events	Rate/1000 Person-Years	Adjusted RR (95% Confidence Interval)[a]
Fluoxetine	3070	76	24.8	1
Sertraline	4208	104	24.7	0.97 (0.66–1.45)
Paroxetine	2956	71	24.0	0.80 (0.52–1.21)
Citalopram	1271	37	29.1	0.92 (0.57–1.50)
Escitalopram	1066	27	25.3	0.80 (0.45–1.43)
Venlafaxine	721	21	29.1	0.80 (0.43–1.51)
Multiple SSRIs only	1354	83	61.3	1.70 (1.10–2.62)

[a] Relative risks (RRs) were estimated with generalized estimate equation regression models with Poisson distribution and were weighted by the inverse of a propensity score for each medication, age, calendar year, psychiatric conditions (use of psychotropic medications and diagnoses for serious psychiatric disorders), and utilization of health care (psychiatric and medical hospitalizations, and unintentional injuries). Inverse propensity score weights were trimmed at the 99th percentile due to a few large, influential weights.

Sertraline

Entire Cohort
Female
Male
Aged 13–18 years
No previous suicide attempt

Paroxetine

Entire Cohort
Female
Male
Aged 13–18 years
No previous suicide attempt

Citalopram

Entire Cohort
Female
Male
Aged 13–18 years
No previous suicide attempt

Escitalopram

Entire Cohort
Female
Male
Aged 13–18 years
No previous suicide attempt

Venlafaxine

Entire Cohort
Female
Male
Aged 13–18 years
No previous suicide attempt

0.0 1.0 2.0 3.0 4.0 5.0 6.0

Better than Fluoxetine   Worse than Fluoxetine

Relative Risk (95% Confidence Interval)

FIGURE 1
Alternative analyses, risk for suicide attempt among children and adolescents who were current users of individual antidepressants compared with children and adolescents who were current users of fluoxetine.

nontreated events.[4] It is also possible that use of individual study drugs was guided by a child's mental illness severity, resulting in confounding by indication. We included several measures of mental health services use in propensity scores and time varying covariates in our analyses to mitigate the role of such confounding. We were unable to study the specific risk for completed suicides because of the small number of these events in our cohort. Finally, it is possible that children and adolescents in the Medicaid program may differ from other children because of increased exposure to poverty and other life stressors. Although this may be true, Medicaid provides insurance for a large proportion of children in Tennessee and the United States.[31] These children are typically underrepresented in clinical trials and thus represent an important population for study.

The study was not designed to identify risk for suicide attempts for antidepressant users compared with nonusers. Analyses of clinical trials data by the FDA and others suggested potential differences among individual antidepressants,[7,32] although power to detect differences among individual medications was limited in the FDA's analyses. Thus, we chose to focus the current study on the important question of individual medication risk. Additional work is needed to further characterize the relationship between antidepressant use and suicidal behaviors.

CONCLUSIONS

We found no evidence of increased risk for SSRI or SNRI antidepressants compared with fluoxetine for new users of antidepressants in the Tennessee Medicaid population. Use of any of the individual drugs studied would not be expected to increase risk for serious suicide attempts compared with the others.

ACKNOWLEDGMENTS

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