ORIGINAL ARTICLE

Relationship Between Antidepressant Medication Treatment and Suicide in Adolescents

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Context: A decade of increasing antidepressant medication treatment for adolescents and corresponding declines in suicide rates raise the possibility that antidepressants have helped prevent youth suicide.

Objective: To evaluate the relationship between regional changes in antidepressant medication treatment and suicide in adolescents from 1990 to 2000.

Design: Analysis of prescription data from the nation's largest pharmacy benefit management organization, national suicide mortality files, regional sociodemographic data from the 1990 and 2000 US Census, and regional data on physicians per capita.

Participants: Youth aged 10 to 19 years who filled a prescription for antidepressant medication and same-aged completed suicides from 588 three-digit ZIP code regions in the United States.

Main Outcome Measures: The relationship between regional change in antidepressant medication treatment and suicide rate stratified by sex, age group, regional median income, and regional racial composition.

Results: There was a significant adjusted negative relationship between regional change in antidepressant medication treatment and suicide during the study period. A 1% increase in adolescent use of antidepressants was associated with a decrease of 0.23 suicide per 100 000 adolescents per year ($\beta = -.023$, $t = -5.14$, $P < .001$). In stratified adjusted analyses, significant inverse relationships were present among males ($\beta = -.032$, $t = -3.81$, $P < .001$), youth aged 15 to 19 years ($\beta = -.029$, $t = -3.43$, $P < .001$), and regions with lower family median incomes ($\beta = -.023$, $t = -3.73$, $P < .001$).

Conclusions: An inverse relationship between regional change in use of antidepressants and suicide raises the possibility of a role for using antidepressant treatment in youth suicide prevention efforts, especially for males, older adolescents, and adolescents who reside in lower-income regions.

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OVER THE past several years, there has been a steady decline in suicide rates for adolescents in the United States.[1,2] Despite this trend, youth suicide remains an important public health concern. It is the third-leading cause of death among older adolescents aged 15 to 19 years and the fourth-leading cause among younger adolescents aged 10 to 14 years.[1]

Several factors have been considered as possible causes of the recent decline in adolescent suicide. These include a reduction in the use of drugs and alcohol,[3] a mandate for catalytic converters that lower automobile carbon monoxide emissions (used in self-asphyxiation),[4] the economic boom in the United States during the 1990s,[5] and the introduction of new firearms security regulations in several states.[6] A link between firearms in the home and suicide is supported by findings from epidemiological, case-control, and prospective studies.[7]

Recent increase in antidepressant medication treatment for adolescents in the United States[8-10] and in other industrialized countries[11-15] provides a possible complementary explanation for the recent decline in suicide by adolescents. Because most youth who commit suicide have a psychiatric disorder at the time of their death[16,17] and because the newer antidepressant medications are effective in treating adolescent major depression[18,19] and several anxiety disorders,[20-23] it is possible that the recent growth in antidepressant treatment has contributed to the decline in youth suicide. We explore this possibility by examining changes from 1990 to 2000 in rates of antidepressant

medication treatment and suicide by adolescents in a large number of US geographic regions.

METHODS

Four sources of data were used to examine regional variation in trends in the relationship between antidepressant medication treatment and suicide rates: (1) prescription data from a large pharmacy benefit management organization, (2) national suicide mortality files from the Centers for Disease Control and Prevention, (3) regional geographic characteristics from the US Census Bureau, and (4) information on the geographic distribution of physicians from the Area Resource File.[24]

ANTIDEPRESSANT RATES

Rates of antidepressant medication treatment for each 3-digit ZIP code region were calculated from data provided by AdvancePCS, Irving, Tex, the nation's largest pharmacy benefit service organization. AdvancePCS provided complete pharmacy data for approximately 340 000 adolescents for a 1-month period in 1989 and approximately 720 000 adolescents for a corresponding 1-month period in 2001. The datasets include the national drug code, patient age, patient sex, encrypted identification number, and the 3-digit ZIP code of the filling pharmacy for each prescription. Mail-order prescriptions were excluded from the analysis, because the filling "pharmacy" was unlikely to be within the geographic region of the patient.

Person-level antidepressant rates per 1000 patients receiving medication were calculated, stratified by sex and 2 age groups: 10 to 14 years and 15 to 19 years. A count of adolescents receiving medication in each group served as the denominator for antidepressant medication treatment rates. The mean number of adolescents receiving medication per region was 518 (1989) and 1086 (2000), and the median was 322 (1989) and 713 (2000).

SUICIDE RATES

Rates of suicide were calculated from the Centers for Disease Control and Prevention's Compressed Mortality Files.[25] These data provide underlying cause of death (4-digit *International Classification of Diseases, Ninth Revision* code) for all deaths occurring in the United States stratified by county of residence, sex, and age group, and population estimates from the US Census Bureau. Data were pooled to provide stable estimates of mortality due to suicide (*International Classification of Diseases, Ninth Revision*, codes 950.00-959.99) for the 2 time periods, 1985 to 1989 and 1995 to 1999. Suicide rates for each county were calculated by age group and sex.

County-level suicide rates were converted to 3-digit ZIP code region rates using a ZIP code–to–county correspondence file.[26] A population-based weighted suicide rate was computed when more than one county fell within a ZIP code region.

GEOGRAPHICAL CHARACTERISTICS

Data from the US Census Bureau and Area Resource File[24] were used to characterize each 3-digit ZIP code region in 1990 and 2000. Specifically, median household income and percentage white population were extracted from census Summary Tape File 3B,[27] and the number of psychiatrists, child psychiatrists, and pediatricians per capita for each region in 1990 and 2000 were extracted from the Area Resource File.[24] These variables were used in the analysis to control for and stratify by regional sociodemographic characteristics.

STATISTICAL ANALYSIS

For ease of interpretation, we refer to the earlier time point as 1990 and the more recent point as 2000 for all comparisons. Only ZIP code regions containing at least 100 total prescriptions (N = 588) are included in the analyses. The included regions contain 86.6% of the total US population. Compared with excluded regions (n = 324), included regions were more populous (mean population: 372 166 vs 104 133) and had a slightly lower percentage white population (80.9% vs 83.3%), a higher family median income ($41 600 vs $36 600), and lower suicide death rate per 100 000 adolescents (6.0 vs 7.0) in 2000.

We first computed overall rates and 95% confidence intervals of antidepressant medication treatment and suicide for 1990 and 2000 and for the change in rates between the 2 time points. Adjusted linear regression models were then used to assess the association between antidepressant medication treatment (independent variable) and suicide (dependent variable) accounting for regional racial composition, median income, and physicians per capita for each year and change over time, as appropriate. Similar analyses are presented stratified by sex, age group, median regional income, and racial composition. Two-tailed, unpaired t tests were used for comparisons. The Cook's D statistic was used to remove extreme outliers ($D > 0.4$) from the regression analyses. No more than 1 ZIP code region was removed from any model. Separate models examined suicide by firearms and by all other causes of suicide. A further post hoc analysis examined change in tricyclic antidepressant medication treatment in relation to suicide.

RESULTS

ANTIDEPRESSANT MEDICATION TREATMENT AND SUICIDE

In 1990 and in 2000, there was a significant positive relationship between regional antidepressant medication treatment and suicide, indicating that regions with high rates of antidepressant medication treatment also tend to have high suicide rates. Significant associations were observed for most sex, age, race, and income strata (**Table**).

TIME TRENDS

A significant negative relationship was observed between 1990 and 2000 for changes in the regional rates of overall antidepressant medication treatment and changes in the regional suicide rates after adjusting for change in percentage white population, median income, and number of physicians per capita (Table). A significant negative adjusted trend association was observed in stratified analyses of male children; children aged 15 to 19 years; and in lower-income regions. The strength of the relationship between change in use of antidepressants and change in suicide rate was similar in firearms ($\beta = -.012$, $t = 3.56$, $P < .001$) and nonfirearms ($\beta = -.010$, $t = 4.38$, $P < .001$) suicide.

The rate of adolescents filling prescriptions for tricyclic antidepressant medications was low in 1990 (1.2%) and 2000 (0.8%). In a post hoc analysis limited to regions with 1 or more antidepressant prescription, change in all types of antidepressant prescriptions was negatively related to change in suicide rate ($\beta = -.016$, $t = 3.19$,

Association Between Regional Antidepressant Medication Treatment and Suicide Rate in 588 Children Aged 10 to 19 Years*

Variable	Antidepressant Rate per 1000 Medication Users			Suicide Rate per 100 000 Population†			Adjusted β (*P* Value)		
	1990	2000	Change	1990	2000	Change	1990	2000	Change
Total	11.54	73.15	61.61	6.51	6.00	−0.51	.050 (t = 4.67, P<.001)	.014 (t = 4.28, P<.001)	−.023 (t = 5.14, P<.001)
Sex									
Male	12.02	74.49	62.47	10.26	9.11	−1.15	.081 (t = 4.36, P<.001)	.026 (t = 4.02, P<.001)	−.032 (t = 3.81, P<.001)
Female	10.54	72.16	61.62	2.45	2.08	−0.37	.028 (t = 3.54, P<.001)	.006 (t = 3.28, P = .001)	−.005 (t = 1.42, P = .16)
Age, y									
10–14	10.00	60.96	50.96	1.46	1.72	0.26	.019 (t = 3.07, P = .002)	.006 (t = 2.46, P = .01)	.000 (t = 0.09, P = .92)
15–19	12.62	83.68	71.06	10.94	9.80	−1.14	.112 (t = 5.54, P<.001)	.031 (t = 4.56, P<.001)	−.029 (t = 3.43, P<.001)
White population									
Low	11.06	67.31	56.25	6.06	5.77	−0.29	.055 (t = 3.74, P<.001)	.017 (t = 4.51, P<.001)	−.016 (t = 3.50, P<.001)
High	12.02	78.98	66.96	6.97	6.24	−0.73	.048 (t = 3.15, P = .002)	.010 (t = 1.67, P = .12)	−.026 (t = 3.12, P = .002)
Median income									
Low	10.89	67.66	56.77	6.57	6.62	0.05	.024 (t = 1.37, P = .17)	.016 (t = 3.60, P<.001)	−.023 (t = 3.73, P<.001)
High	12.19	78.63	66.44	6.45	5.39	−1.06	.068 (t = 5.44, P<.001)	.011 (t = 2.13, P = .03)	−.010 (t = 1.73, P = .08)

*Antidepressant medication treatment and suicide data are mean rates per 3-digit ZIP code region. Adjusted β values control for percentage white population, median income, and number of per capita physicians (pediatricians, child psychiatrists, and psychiatrists) by ZIP code region in 2000.
†Population based on row category.

P=.002), but change in the rate of tricyclic antidepressant medication treatment was not related to the change in suicide rate (β=−.010, t=0.53, P=.60).

COMMENT

In cross-sectional analyses, increased regional antidepressant medication treatment is linked to higher suicide rates. Although this relationship may reflect antidepressant-triggered suicide,[28] clinical and forensic studies cast doubt on this interpretation.[29-31] Communities with high rates of suicide (and presumably high rates of severe psychiatric illnesses) may simply tend to use more antidepressant medications than communities with low rates of suicide.

In accord with most studies of European countries,[11,12,15,32,33] an increase in antidepressant medication treatment was inversely related to the rate of suicide. In our study, a 1% increase in adolescent use of antidepressants was associated with a decrease of 0.23 suicide per 100 000 adolescents per year. This inverse time trend was not observed for tricyclic antidepressants. In contrast to the positive findings from clinical trials of treating adolescent depression with selective serotonin reuptake inhibitors, the findings with tricyclic antidepressants have been disappointing.[34] Compared with tricyclic antidepressants, selective serotonin reuptake inhibitors are associated with greater medication adherence[35,36] and are less dangerous when taken in overdose.[37]

A relationship between antidepressant medication treatment and suicide is exceedingly difficult to study with clinical experimental methods. Pooled analyses of depressed adult patients from clinical trials reveal statistically similar rates of suicide in participants receiving placebo and antidepressants.[38,39] Although such findings raise uncertainty regarding whether antidepressant medications can reduce suicide risk, the exclusion of individuals with a serious risk of suicide, short follow-up periods, high subject attrition, and the small number of suicides in clinical trials complicate interpretation of these findings.[40,41]

In the current study, significant inverse trends in antidepressant medication treatment and suicide rates were evident for older adolescents and males but not younger adolescents and females. Compared with younger adolescents who commit suicide, older adolescents who commit suicide are more likely to have a diagnosable disorder,[42,43] including depression,[17,43] and so these patients may be more likely to benefit from antidepressants. Previous research also indicates that compared with females, males are at lower risk of suicide attempts but at much greater risk of suicide.[44] With the availability of more effective antidepressant treatments for young people, gender differences in the case fatality rate may have created more clinical opportunities to lower the risk of suicide in males than females. In this regard, it may be worth exploring whether selective serotonin reuptake inhibitor–mediated suppression of impulsive aggressive behavior[45] reduces suicidal behavior in high-risk males.[46,47]

An inverse time trend was evident for adolescents residing in lower-income regions but not higher-income regions. Lower-income communities may have higher base rates of psychiatric disorder[48] and a greater unmet need for mental health services.[49] Increasing mental health treatment in these communities may selectively reach a proportionately larger number of youth at high risk for suicide.

We are unable to control for several potentially important risk factors (eg, substance use and firearms access) and protective factors (eg, psychotherapy and catalytic converters) that might confound the observed time trend relationships. A more rigorous test of the hypothesis that antidepressant medication treatment has contributed to declining youth suicide would involve simultaneous examination of these important factors.

The current study has several other limitations. Sampling adolescents receiving antidepressant medication rather than the general population may distort relation-

ships between rates of antidepressant medication treatment and suicide rates. Regional variation in the proportion of the population in the pharmacy database may introduce further measurement error. However, the pharmacy database is quite large, covering 75 million members in 2000. An absence of diagnostic data prevents analysis by clinical indication of the antidepressant medications. Further research is also needed to determine whether the findings are specific to antidepressants or whether similar correlations exist for other psychotropic medications or their interaction with antidepressants. Most important, the findings are open to ecologic challenge because they relate regional rather than individual characteristics.

The relationship between suicide and mental status is not simple, and merely expanding access to antidepressant medications is unlikely to ensure the abolition or even a continued rapid decline in adolescent suicide rates. Nevertheless, the current findings are consistent with suicide risk reduction policies that seek to improve the identification and psychopharmacological treatment of young people with major depression and other antidepressant-responsive psychiatric disorders.

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Correction

Error in Reference. In the letter titled "Standardized Mortality Ratio in Bulimia Nervosa," in the August issue of the ARCHIVES (2003;60:851), Keel et al, listed as reference 9, should have been listed as the first reference instead of Halmi et al.