

Paroxetine, Other Antidepressants, and Youth Suicide in New York City: 1993 Through 1998

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Background: Regulatory agencies in the United Kingdom and the United States have recently issued warnings about a possible link between suicidal ideation and attempts and the use of paroxetine in a pediatric patient population. The objective of this study was to determine the proportion of youth suicides that tested positive for paroxetine or other antidepressants in medical examiner toxicologic testing in New York City from 1993 through 1998, the first 6 years that paroxetine was available in the United States.

Method: Subjects in this medical examiner surveillance study were suicides less than 18 years of age. Serum toxicology was examined for paroxetine and other antidepressants.

Results: There were 66 suicides among persons under 18 years of age in the years 1993 through 1998. Toxicology was tested in 58 (87.9%) of the 66 suicides, and 54 (81.8%) had injury-death intervals of 3 days or less. None of the victims had paroxetine detected in their blood obtained at the time of autopsy. Imipramine was detected in 2 victims and fluoxetine in another 2.

Conclusion: Despite regulatory concerns, none of the autopsies of youth suicides in New York City detected paroxetine in the victims, although other antidepressants were detected in 4 victims. However, in the vast majority of the youth suicides, there was no evidence of antidepressant use immediately prior to death.

(*J Clin Psychiatry* 2004;65:915–918)

Received Jan. 21, 2004; accepted May 11, 2004. From the Department of Psychiatry (all authors) and the Dept. of Public Health (Drs. Leon and Tardiff), Weill Medical College of Cornell University, New York, N.Y.

Support for this work was provided by the National Institutes of Health grants MH60447 (Dr. Leon) and DA06534 (Dr. Tardiff).

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Paroxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) that was approved for the treatment of depression by the United Kingdom's Drug Licensing Authority in 1990 and then by the U.S. Food and Drug Administration (FDA) on December 29, 1992. In June 2003, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom's Drug Licensing Authority reported that, on the basis of preliminary analyses of placebo-controlled randomized clinical trials, "there is an increase in the rate of self-harm and potentially suicidal behavior in children and adolescents, when paroxetine is used for depression."¹ The agency stated that the benefits of paroxetine in those under 18 years of age do not outweigh these risks.² After further review, in December 2003, the MHRA issued a press release stating, "There is no, or insufficient, evidence from clinical trials that benefits outweigh the risks of side effects for sertraline (Lustral), citalopram (Cipramil), escitalopram (Cipralext) and fluvoxamine (Faverin). Fluoxetine, or Prozac, appears to have a positive balance of risks and benefits in the treatment of depressive illness in the under 18s."³

In June 2003, the FDA commenced review of a possible increased risk of suicidal ideation and attempts in children and adolescents being treated with paroxetine for major depressive disorder (MDD). Although the evaluation is ongoing at this time, the FDA has recommended that paroxetine not be used to treat depression in patients younger than 18 years.⁴ The agency initially based this recommendation on 3 randomized, placebo-controlled clinical trials (RCTs) of paroxetine for children with MDD, only 1 of which was published.⁵ The results of these trials reported no difference in efficacy between paroxetine and placebo in the treatment of MDD. More recent analyses⁴ of safety data from these RCTs suggest that although there were no fatalities in the trials, suicidal ideation and suicide attempts may have been more common in children receiving paroxetine than in those receiving placebo.⁴

In February 2, 2004, the FDA held a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee to consider the risks of antidepressants based on published and unpublished data from 15

RCTs for MDD in children and adolescents.⁶ These RCTs typically excluded persons with recent suicide attempts or current suicidal ideation at intake. Therefore, if suicidality developed during the trial, it could be assumed that such ideation emerged after participants had begun receiving an antidepressant. Based on data presented and other issues that were addressed at that meeting, the FDA issued a public health advisory on March 22, 2004, stating, "Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases."⁷

Although the FDA recommendation has to do with risk of suicidal ideation and attempts, we chose to look at completed suicide, which represents the most adverse outcome on the continuum of suicidality. The objective of the current report is to determine the proportion of suicides in New York City by people under the age of 18 years, who had paroxetine or other antidepressants detected at autopsy from 1993 through 1998, the initial 6-year period following the availability of paroxetine on the market in the United States.

METHOD

Study Sample

The Office of Chief Medical Examiner of New York City is responsible for investigating all deaths believed to be suicides, homicides, or accidents and instances of death unattended by a physician. Distinction between a suicide and an accident is based on investigation of the death scene (e.g., notes), statements from friends and family that bear upon risk factors for suicide, the decedent's medical and psychiatric history, and toxicologic data. Our research group has reviewed the details about each suicide that was certified by the Office of the Chief Medical Examiner of New York City from 1990 through 1998.⁸ For purposes of this report, analyses are limited to suicides under age 18 years, which took place from 1993 through 1998, the period during which paroxetine was first available in the United States. Victims had to have undergone systematic toxicologic analysis for antidepressant drugs. Paroxetine has an elimination half-life of approximately 21 hours⁹ and thus would most likely not be detected in deceased individuals who had lived more than 3 days after injury. Therefore, we noted the injury-death interval for all cases and did not include toxicologic results for those who survived more than 3 days.

Toxicology

Antidepressant drugs, including paroxetine, are screened by gas chromatography using a nitrogen phosphorous detector. The quantitation limit is 0.1 mg/L. All positive findings are confirmed by gas chromatography/mass spectrometry.

Table 1. Description of Suicides Under 18 Years of Age in New York City: 1993–1998 (N = 66)^a

Variable	N	%
Sex		
Male	50	75.8
Female	16	24.2
Ethnicity		
White	23	34.8
African American	22	33.3
Hispanic	19	28.8
Other	2	3.0
Borough of death		
Queens	17	25.8
Brooklyn	16	24.2
Bronx	15	22.7
Manhattan	13	19.7
Staten Island	5	7.6
Year of death		
1993	11	16.7
1994	14	21.2
1995	11	16.7
1996	10	15.2
1997	12	18.2
1998	8	12.1
Suicide method		
Firearms	25	37.9
Hanging	18	27.3
Jumping	11	16.7
Drug overdose	6	9.1
Trains	3	4.5
Drowning	2	3.0
Other	1	1.5

^aDeaths certified as suicide by the Office of Chief Medical Examiner of New York City.

Study Variables

Demographic characteristics, method of suicide, and serum toxicology were examined. To determine whether these results were biased misclassifications of some suicides as accidents, toxicology results were also examined in all accidental deaths under 18 years of age.

Data Analyses

The proportion of suicides and accidents with paroxetine or other antidepressants detected at autopsy was calculated.

RESULTS

Suicides

There were 66 suicides among New York City residents less than 18 years of age from 1993 through 1998. The population under 18 years of age in New York City was estimated to be 1,816,632 during those years.¹⁰ The ages of the deceased ranged from 10 to 17 years (mean = 15.5, SD = 1.8). Seven of the suicides were less than 13 years of age. About 75% were males. The ethnicity of the suicides was nearly evenly split among African Americans, Hispanics, and whites. The most common methods of suicide were firearms and hanging (Table 1). Toxicology was tested in 58 (87.9%) of the 66 suicides,

and 54 (81.8%) had injury-death intervals of 3 days or less. Paroxetine was not detected in any of them. Imipramine was detected in 2 of them and fluoxetine was detected in another 2.

Accidents

Five hundred thirty-five New York City residents less than 18 years of age were victims of fatal accidents from 1993 through 1998, as certified by the Office of the Chief Medical Examiner of New York City. Overall, the accident victims were younger (mean = 8.1, median = 7.0, SD = 6.0 years of age) than the suicides. Only 40% of these youths were over 10 years of age. Males were over-represented (61.7%), as were African Americans (44.5%) and Hispanics (31.8%). Pedestrian fatalities were most common (22.1%). Toxicology was tested in 457 (85.4%) of these accidental deaths, and 407 (89.1%) of those with toxicology tests had injury-death intervals of 3 days or less. Amitriptyline was detected in 2 of the accidental deaths and fluoxetine in 1 other. Paroxetine was not detected in any of them.

DISCUSSION

The objective of this study was to determine the presence of paroxetine and other antidepressants in suicides less than 18 years of age in New York City from 1993 through 1998. Paroxetine was detected in none of the youth suicides.

This finding is consistent with the FDA Advisory⁴ that clearly states that there were no reports of completed suicide among the participants in the RCTs of paroxetine for children or adolescents with MDD. However, the entry criteria for the RCTs typically exclude those with active suicidality. In contrast, our analyses focused exclusively on suicides.

Although the initial report¹¹ on a series of 6 cases described an association between fluoxetine and suicidality in adults, subsequent empirical studies have not shown an elevated risk of suicidality in those taking SSRIs.¹²⁻¹⁶ One RCT with suicidal adults found that paroxetine was actually associated with a reduction in suicidal behavior relative to placebo.¹⁷ We are unaware of any such studies in children or adolescents.

We acknowledge that toxicology was unavailable or the injury-death interval exceeded 3 days for 12 (18.2%) of the 66 suicides, and thus presence or absence of paroxetine could not be established for these cases, which is a limitation of the results. We did, however, attempt to determine whether perhaps our analyses underestimated the role of paroxetine due to misclassification of suicides as accidents. As with suicides, paroxetine was not detected in any of the youths involved in fatal accidents.

Furthermore, we were unable to determine the number of New York City youths who used antidepressants during

the years of our study. This limitation precludes precise statements about the suicide risk associated with each antidepressant that was available at the time. There have, however, been several reports on trends in antidepressant use in the United States that can provide a benchmark. For instance, based on national prescription data, it was estimated that 1.0% of children and adolescents used antidepressants in 1996,¹⁸ and 1.6%¹⁹ used them in 1998. The estimates of antidepressant use among youths enrolled in Medicaid programs were about 1.8% in 1994²⁰ and 2.0% in 1996.²¹ These studies include ages 18 years and younger, whereas our study, in an effort to correspond to the initial FDA warning,⁴ was limited to those under 18 years of age. The extent to which these national estimates apply to antidepressant use among New York City youth is unclear. We acknowledge that without the denominator, the absolute risk cannot be calculated.

Our results do not address the question of whether paroxetine is associated with nonlethal suicide attempts and suicidal ideation. However, this study found that paroxetine apparently did not contribute to suicide among children and adolescents in New York City during the first 6 years that it was available in the United States. In fact, paroxetine may have prevented some youth suicides, but we do not know how many depressed suicidal youths in New York City were treated with it during those years. Further studies of youth with depression treated with paroxetine, including those with suicidal ideation and a history of suicide attempts, are needed to clarify whether paroxetine is associated with increased suicidal ideation and attempts compared with placebo and other types of antidepressants.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil), sertraline (Zoloft).

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