Antidepressants in Adult Suicides in New York City: 2001–2004

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Background: The U.S. Food and Drug Administration recently extended the Black Box warning on antidepressants regarding pediatric suicidality to include young adults. The decision was guided by results from meta-analyses of 372 randomized controlled clinical trials of antidepressants for adults. Nearly all suicidality in those trials was nonfatal suicide attempts and ideation. Here, we consider whether antidepressants are linked with adult suicide deaths.

Method: Subjects in this medical examiner surveillance study included all suicides, 18 years and older, in New York City from 2001–2004. Postmortem blood was analyzed for the presence of antidepressants.

Results: There were 1419 adult suicides in New York City during the study period. Antidepressants were detected at autopsy in 23.1% of the suicides who met criteria for toxicology analyses. Antidepressants were least prevalent in suicides aged 18–24 years (13.9%).

Conclusions: Antidepressants were detected in less than one-quarter of adult suicides in New York City from 2001–2004. The majority of the suicides were not attributable to antidepressant use, and perhaps many could have been prevented with appropriate treatment. Although this study does not provide evidence for a link between antidepressant use and subsequent suicide, careful monitoring of patients receiving antidepressants remains critically important.

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Suicidal thoughts, attempts, and deaths represent a core feature of major depressive disorder. Yet, there has been concern whether the psychopharmacologic agents designed to treat these and other symptoms of depression, in fact, provoke suicidality. The U.S. Food and Drug Administration (FDA) has held at least 4 Psychopharmacologic Drugs Advisory Committee (PDAC) meetings regarding antidepressants and suicidality. The first of these, in 1991, was motivated, in part, by a case report.[1] Extensive FDA analyses were presented at 2 FDA committee meetings (February 2004 and September 2004) that examined suicidality in over 4400 child and adolescent participants in 24 randomized placebo-controlled clinical trials (RCTs) of antidepressants.[2,3] There were no suicide deaths in the pediatric trials. However, there was an elevation in pediatric suicidality, primarily suicidal ideation, among those randomly assigned to active medication relative to placebo controls. Given that only 4 of the 15 pediatric RCTs for depression showed a positive antidepressant treatment effect over placebo, the risk-benefit ratio was disturbing and had considerable influence on the final PDAC recommendations in favor of a Black Box warning that, in fact, was issued by the FDA.[4]

Most recently, on December 13, 2006, a meeting of the PDAC was convened to consider the risk of suicidality among adults who take antidepressants and whether extending the Black Box warning on antidepressants regarding pediatric suicidality to adults would be warranted. In these hearings, results of analyses were presented that examined 372 RCTs for adults that included nearly 100,000 participants.[5] The suicidality reported in the adult trials for psychiatric indications came from adverse event reports and was primarily suicidal ideation (N = 358, 70.3% of the suicidality), but also included suicide attempts (N = 133, 26.1%), other nonfatal suicidal behavior (N = 10, 2.0%), and suicide deaths (N = 8, 1.6%).[6] The safety analyses indicated that, relative to placebo, there was a nonsignificant elevation in risk of suicidality in the antidepressant group among those 18–24 years of age, whereas there was a significant protective effect of antidepressants in those 65 and older.

On May 2, 2007, the FDA issued a revised Black Box warning for all antidepressants that will now apply to

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patients under 25 years of age. Among other points, it states, "Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior"[7] The risks and benefits of imposing a Black Box warning have been considered in detail elsewhere.[8,9]

Here, we examine the extent to which this phenomenon applies to adult suicide deaths in the general population in New York City from 2001–2004. We sought to determine the proportion of suicides in New York City in which antidepressants were detected at autopsy.

METHOD

Study Sample

The data are from a medical examiner surveillance study of suicides in New York City. The New York City Office of Chief Medical Examiner investigates all deaths believed to be homicides, suicides, or accidents. Other instances of death that were not attended by a physician are also investigated. In an effort to classify the manner of death, Medical Examiner personnel review the circumstances and the setting of the fatality, including statements from family and friends, evidence gathered from the death scene, the decedent's psychiatric and other medical history, and toxicologic data. This is particularly useful in distinguishing between a suicide and an accident.[10,11]

Our research group reviewed the medical files of each suicide that was certified by the New York City Office of Chief Medical Examiner from 2001 through 2004 with funding from the National Institute on Drug Abuse (R01DA06534, principal investigator: Kenneth Tardiff, M.D.). We have reported the results of toxicologic analyses of a variety of classes of psychotropics in suicides in adults in the early 1990s in New York City[12] and, more recently, antidepressants in youth suicide in New York City.[13,14] In the current report, we include suicides that occurred from 2001–2004 in New York City among those 18 years of age and older. We required that the decedent had undergone systematic toxicologic analysis for antidepressant drugs. Furthermore, the injury-death interval is recorded for all cases. Those who survived the suicide injury for more than 3 days before dying were not included in the toxicologic results presented below. This time frame took into account the elimination half-life of the various antidepressants.[15]

Toxicology

Antidepressants were screened with gas chromatography using a nitrogen phosphorous detector. Gas chromatography/mass spectrometry was used to confirm each positive finding. Antidepressants are reported as detected regardless of whether the parent compound or the metabolite was detected at autopsy.

Study Variables

In addition to the postmortem blood toxicology results, method of suicide and demographic characteristics were examined.

Data Analyses

The primary data analyses are limited to descriptive statistics, in which the focus is the proportion of suicides with antidepressants detected at autopsy, and the 95% confidence interval. In an effort to mirror the stratified results presented in the December 13, 2006, FDA PDAC meeting, the proportion of suicides with antidepressants detected is also presented by age group. In addition, χ^2 tests and Mann-Whitney tests, each with 2-tailed α levels of .05, compared characteristics of the suicides with toxicology available and an injury-death interval of 72 hours or less to those of suicides that did not meet these inclusion criteria.

RESULTS

There were 1419 suicides of persons 18 years and older in New York City during the 4-year study period, ranging from 327 to 372 per year (Table 1). Nearly three-quarters of the suicides were men (74.1%). The distribution of suicides across ethnic groups was somewhat disproportional to their representation in the general population of New York City, with whites (52.5% of suicides) overrepresented and Hispanics (18.7%), African Americans (17.3%), and Asians and other ethnic groups (11.5%) underrepresented. The ages ranged from 18 to 97 (mean = 46.1, median = 43, SD = 19.0) years. The most common methods of suicide were jumping (30.4%), hanging (27.8%), firearms (16.6%), and drug overdoses (9.1%).

Toxicologic analyses were completed on 1340 (94.4%) of the 1419 suicides. However, 182 (13.6%) of those with toxicology test results were excluded from subsequent analyses because their injury-death interval exceeded 72 hours. This was done in order to reduce the likelihood of reporting false-negative results. Thus, 1158 suicides (81.6% of 1419 suicides) are included in our examination of presence of antidepressants at the time of death. The elderly, whites, and those from Brooklyn were somewhat less likely to have toxicology available (Table 1).

Antidepressants were detected at the time of autopsy in 267 of the suicides, representing 23.1% (267/1158; 95% confidence interval [CI] = 20.6% to 25.5%) of those with toxicology results and injury-death intervals of 72 hours or less. Prevalence of antidepressants in the suicides was comparable across the 4 study years, as indicated by the overlapping confidence intervals: 20.4% in 2001 (95%

Table 1. Characteristics of Suicides in New York City: 2001–2004

	Total (N = 1419)		Toxicology Available (N = 1158; 81.6%)		Toxicology Unavailable (N = 261; 18.4%)[a]				
Characteristic	N	%	N	%	N	%	χ^2	df	p Value[b]
Gender									
Male	1052	74.1	864	74.6	188	72.0	0.740	1	.390
Female	367	25.9	294	25.4	73	28.0			
Race/ethnicity									
White	745	52.5	565	48.8	180	69.0	58.356	3	< .001
African American	245	17.3	230	19.9	15	5.7			
Hispanic	266	18.7	240	20.7	26	10.0			
Other	163	11.5	123	10.6	40	15.3			
Borough of death									
Manhattan	490	34.5	411	35.5	79	30.3	18.756	4	< .001
Bronx	208	14.7	180	15.5	28	10.7			
Brooklyn	324	22.8	239	20.6	85	32.6			
Queens	321	22.6	264	22.8	57	21.8			
Staten Island	76	5.4	64	5.5	12	4.6			
Year of death									
2001	327	23.0	265	22.9	62	23.8	3.519	3	.318
2002	364	25.7	288	24.9	76	29.1			
2003	372	26.2	314	27.1	58	22.2			
2004	356	25.1	291	25.1	65	24.9			
Suicide method									
Jumping	431	30.4	343	29.6	88	33.7	18.300	6	.006
Hanging	395	27.8	324	28.0	71	27.2			
Firearm	235	16.6	208	18.0	27	10.3			
Drug overdose	129	9.1	107	9.2	22	8.4			
Train	92	6.5	77	6.6	15	5.7			
Cutting/piercing	56	3.9	38	3.3	18	6.9			
Other	81	5.7	61	5.3	20	7.7			
Age									
18–24 y	189	13.3	173	14.9	16	6.1	…	…	< .001[c]
25–34 y	285	20.1	246	21.2	39	14.9			
35–44 y	271	19.1	243	21.0	28	10.7			
45–54 y	244	17.2	194	16.8	50	19.2			
55–64 y	174	12.3	139	12.0	35	13.4			
65+ y	256	18.0	163	14.1	93	35.6			

[a]Either toxicology results were not available or the injury-death interval exceeded 72 hours.
[b]Compares those with and without toxicology results available.
[c]Derived from Mann-Whitney test.

Table 2. Antidepressants in Suicides in New York City From 2001–2004: Stratified by Age Group

		Antidepressants Detected	
Age	N	N	%
18–24 y	173	24	13.9
25–34 y	246	46	18.7
35–44 y	243	64	26.3
45–54 y	194	54	27.8
55–64 y	139	42	30.2
65+ y	163	37	22.7
Total (all ages)	1158	267	23.1

CI = 15.5% to 25.2%), 23.6% in 2002 (95% CI = 18.7% to 28.5%), 26.8% in 2003 (95% CI = 21.9% to 31.6%), 21.0% in 2004 (95% CI = 16.3% to 25.6%). In analyses that were stratified by age (Table 2), antidepressants were least prevalent among suicides aged 18–24 (13.9%).

The most common antidepressants to be detected among these suicides were sertraline (N = 67; 5.8% of 1158 suicides), citalopram (N = 63; 5.4%), bupropion (N = 46; 4.0%), paroxetine (N = 29; 2.5%), nortriptyline (N = 29; 2.5%), venlafaxine (N = 25; 2.2%), and fluoxetine (N = 22; 1.9%). (It should be noted that nortriptyline was present either as a parent drug or as a metabolite of amitriptyline.) Sixty-two of the suicidal drug overdoses (57.9%; 62/107 with toxicology available, Table 1) had an antidepressant detected.

DISCUSSION

Antidepressants were detected in 23.1% of the adult suicides in New York City from 2001–2004. This is higher than the approximately 11% reported in Sweden,[16] as well as the prevalences found in a postmortem study of suicides in New York City prior to the introduction of most of the newer antidepressants (16.3% from 1990–1992[12]) and in 2 postmortem studies of pediatric suicides in New York City (7.4% from 1993–1998[13] and 2.8% in 1999–2002[14]). Nevertheless, despite the wide availability of antidepressants, over three-quarters of adult suicides had not taken psychopharmacologic antidepressant treatment within 3 days of their deaths. Eighty-six percent of

those aged 18–24 had not taken psychopharmacologic antidepressant treatment.

We believe that the prevalence may comprise 6 groups of suicides. Among those with antidepressants detected, there are 3 groups:

1. Inadequate pharmacologic intervention: Those who were taking antidepressants, but in whom the dose or duration of use was insufficient to result in an adequate treatment.
2. Pharmacologic treatment failures: Those who received what is generally considered to be an adequate dose and duration of antidepressant treatment, but had not responded.
3. Side effects: Those who experienced antidepressant side effects or antidepressant withdrawal phenomena that contributed to their suicide.

Among those who had toxicologic testing and in whom antidepressants were not detected, there are 3 additional groups:

4. Untreated or nonadherent: Those who were undiagnosed and therefore never received pharmacologic treatment *or* had stopped taking antidepressants recently.
5. Nonpharmacologic treatment failures: Those who received nonpharmacologic treatments for depression (e.g., psychotherapy, electroconvulsive therapy, alternative medicine) but had not responded.
6. Antidepressant withdrawal: Those who had recently stopped taking antidepressants and were experiencing withdrawal phenomena that contributed to their suicide.

Our toxicology results do not allow us to distinguish the relative size of these 6 groups. However, the literature suggests that the groups of most concern regarding deleterious effects of antidepressants (pharmacologic treatment failures and antidepressant withdrawal) are likely to be small. For instance, a significant proportion of persons with depression, the principal mental illness linked to suicide, go undiagnosed and untreated.[17,18] Thus, among those who are antidepressant-negative, we suspect that the untreated or nonadherent comprise the largest group. The literature also suggests that among those who are treated, the dosage or duration of treatment is often inadequate.[17–22] Moreover, an increasing body of literature recognizes that a substantial proportion of individuals with depression are treatment refractory.[23–26] We suspect that among suicides with an antidepressant detected, those with inadequate pharmacologic intervention and those with pharmacologic treatment failures constitute the largest proportion.

One way to place the risk of suicidality attributable to antidepressants in perspective is to consider the trade-off between the risks and benefits associated with treated and untreated depression. The clinician will have to assess whether it is better to leave a serious depression untreated, which has a lifetime suicide rate of approximately 15%, ranging from 5% to 26%,[27] or proceed with antidepressant treatment, which has a much lower risk of mortality and morbidity. For instance, the small risk of adult suicidality during treatment with an antidepressant that was reported in the December 2006 FDA hearings, 0.69% in short-term RCTs for depression, largely involved ideation and nonlethal attempts, not death.[5] Moreover, a follow-up study of a cohort of suicide attempters in Finland found that use of antidepressants was associated with an increased risk of attempted suicide, but a decreased risk of completed suicide.[28] Several recent ecological studies have suggested that an increase in antidepressant sales corresponded to decreased suicide rates.[29–32] The clinician must therefore weigh these risks on a case-by-case basis. Careful monitoring of patients receiving antidepressants is critically important, as has been described by the FDA.[7,33]

We acknowledge that the current study examines only one part of the complex relationship between antidepressants and suicidality, albeit the most tragic. There are several limitations to the study design. First, and foremost, this postmortem study cannot estimate the number of suicides that were prevented by the use of antidepressants. Those patients, fortunately, are not part of this postmortem study. Second, and clearly related, we do not have access to sales data required to provide an estimate of the number of adult patients who took antidepressants in New York City during the 4-year study period. Third, our results cannot be generalized to nonfatal suicidal ideation and attempts, which are the adverse events that primarily served as the basis for the FDA's recent Black Box warning.[7] Nevertheless, our mortality results are not in conflict with those presented in the recent FDA meetings. Fourth, it is conceivable that there were false-negative results, particularly for suicides whose autopsies were conducted more than 3 days after death. However, over 80% met the inclusion criteria, which are based on the elimination half-life of most antidepressants. A longer threshold for injury-death interval would quite likely artificially lessen the antidepressant rates, whereas a shorter threshold would quite likely amplify rates. We sought a balance using a 3-day limit. Finally, some suicides might have been misclassified as accidental deaths. However, the New York City Office of Chief Medical Examiner conducts an extensive evaluation of each case and uses all available evidence to classify the cause of death.[10,11] It is unlikely that misclassification could have been so widespread that it substantially influenced our finding.

In conclusion, antidepressants were detected in 23.1% of the adult suicides in New York City from 2001–2004.

The results indicate that the majority of the suicides did not result from antidepressant use and perhaps could have been prevented with appropriate treatment. The study underscores the need for expanded public health awareness about identification of and treatments for depression and other psychiatric disorders.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), fluoxetine (Prozac and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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