ORIGINAL ARTICLE

Suicidality in Pediatric Patients Treated With Antidepressant Drugs

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Context: There has been concern that widely used antidepressant agents might be associated with an increased risk of suicidal ideation and behavior (suicidality) in pediatric patients.

Objective: To investigate the relationship between antidepressant drugs and suicidality in pediatric patients participating in randomized, placebo-controlled trials.

Data Sources: Data were derived from 23 trials conducted in 9 drug company–supported programs evaluating the effectiveness of antidepressants in pediatric patients and 1 multicenter trial (the Treatment for Adolescents With Depression Study) that evaluated fluoxetine hydrochloride.

Study Selection: All placebo-controlled trials submitted to the Food and Drug Administration were eligible for inclusion. Evaluable data were derived from 4582 patients in 24 trials. Sixteen trials studied patients with major depressive disorder, and the remaining 8 studied obsessive-compulsive disorder (n=4), generalized anxiety disorder (n=2), attention-deficit/hyperactivity disorder (n=1), and social anxiety disorder (n=1). Only 20 trials were included in the risk ratio analysis of suicidality because 4 trials had no events in the drug or placebo groups.

Data Extraction: Individual patient data were available for all the trials.

Data Synthesis: A meta-analysis was conducted to obtain overall suicidality risk estimates for each drug individually, for selective serotonin reuptake inhibitors in depression trials as a group, and for all evaluable trials combined. There were no completed suicides in any of these trials. The multicenter trial was the only individual trial to show a statistically significant risk ratio (4.62; 95% confidence interval [CI], 1.02-20.92). The overall risk ratio for selective serotonin reuptake inhibitors in depression trials was 1.66 (95% CI, 1.02-2.68) and for all drugs across all indications was 1.95 (95% CI, 1.28-2.98). The overall risk difference for all drugs across all indications was 0.02 (95% CI, 0.01-0.03).

Conclusion: Use of antidepressant drugs in pediatric patients is associated with a modestly increased risk of suicidality.

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THERE HAS BEEN CONCERN that widely used antidepressant drugs might be associated with an increased risk of suicidal ideation and behavior (suicidality) in pediatric patients. The first evidence from placebo-controlled trials suggesting such an association was provided in a June 2003 report to the Food and Drug Administration (FDA) by GlaxoSmithKline, the manufacturer of the drug paroxetine. That report suggested an increased risk of possible suicide-related adverse events (SREs) in paroxetine-treated pediatric patients, particularly those with major depressive disorder (MDD). This finding led the FDA to request that manufacturers of 8 other widely used antidepressants search for SREs in their antidepressant databases for pediatric studies using an approach similar to that used by GlaxoSmithKline.

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Based on summary data resulting from these searches, the FDA expanded its investigation of these pediatric suicidality adverse event data in 4 ways. First, the FDA expanded the search for potentially relevant adverse events beyond those identified initially by pharmaceutical companies to ensure completeness of case finding. Second, the FDA requested and received electronic patient-level data sets to permit exploration for confounding and effect modification that was not possible with the available summary data used for a preliminary analysis that showed an apparent increase in suicidality risk.[1] Third, the FDA

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Table 1. Variables for Individual Patients Included in the Data Sets Provided to the Sponsors of the Antidepressant Drugs

Demographic Variables	Trial-Related Variables	Disease-Related Variables	Drug-Related Variables	History of
Age	Trial location (North America vs non–North America)	Baseline depression severity score	Duration of treatment (exposure)	Suicide attempt
Sex	Trial setting (inpatient vs outpatient)	Suicidality score at baseline	Premature discontinuation	Suicide ideation
Race		Duration of illness before treatment	Erratic compliance	Psychiatric hospitalization
Body mass index				Substance abuse
				Hostility or aggressive behavior
				Irritability or agitation
				Insomnia

arranged for an independent and blinded classification of narrative case materials by suicidology experts external to the agency because there was a concern that many of the cases captured by the broad screening approaches may not have represented suicidality or may not have been categorized appropriately. Finally, the FDA obtained data on changes in suicide item scores from the depression rating scales used in these trials as an alternative approach to evaluating suicidality. The objective of this article is to provide the detailed methods and results of the FDA's exploration and analysis of the pediatric suicidality adverse event data and suicide item score data.

METHODS

DATA SOURCES

The data were derived from 23 placebo-controlled clinical trials conducted in 9 drug development programs of antidepressants in pediatric patients and in a placebo-controlled, multicenter trial funded by the National Institute of Mental Health (the Treatment for Adolescents With Depression Study [TADS]) that evaluated fluoxetine. Electronic patient-level data sets were provided for all 24 trials. Details of the TADS are published elsewhere.[2] The studied drugs included fluoxetine, sertraline hydrochloride, paroxetine, fluvoxamine maleate, citalopram hydrobromide, bupropion hydrochloride, venlafaxine hydrochloride (extended release), nefazodone hydrochloride, and mirtazapine. Only fluoxetine is approved by the FDA for use in pediatric MDD and obsessive-compulsive disorder. Fluvoxamine and sertraline are approved for use in pediatric obsessive-compulsive disorder.

ADVERSE EVENT DATA EXTRACTION

The Division of Neuropharmacological Drug Products asked manufacturers of the 9 antidepressant drugs to search their databases to identify adverse events that might potentially represent suicidal ideation or behavior, that is, possible SREs. The identification of potential SREs was to be performed by personnel blinded to treatment assignment to avoid bias. Potential SREs were identified by means of an electronic search of adverse event databases using the following search algorithm: any events that included the text strings *suic, overdos, attempt, cut, gas, hang, hung, jump, mutilat-, overdos-, self damag-, self harm, self inflict, self injur-, shoot, slash,* and *suic-*. Sponsors provided narrative summaries for each of the identified SREs and for adverse events identified as serious, accidental injuries, and accidental overdoses. The regulatory definition of a serious adverse event includes any adverse drug experience resulting in death, a life-threatening adverse drug experience, or inpatient hospitalization or prolongation of an existing hospitalization.

Because the adverse events captured using this approach varied substantially in the level of detail provided and in their nature, the Division of Neuropharmacological Drug Products arranged to have all potential SRE narratives independently and blindly classified into relevant categories by a group of 10 pediatric suicidology experts assembled by Columbia University to provide as much assurance as possible that SREs had been appropriately classified. The SRE narratives were classified into 5 categories: suicide attempt, preparatory actions toward imminent suicidal behavior, suicidal ideation, self-injury with intent unknown, and injury events with not enough information to determine whether they represented self-injury or other injury. The first 3 categories most clearly represented instances of suicidality and were identified a priori to be used as the primary outcome "suicidal behavior or ideation." These events are most easily interpreted from a clinical standpoint and are least likely to be susceptible to misclassification. The latter 2 categories represented the less certain cases and, together with the first 3 categories, were used as the secondary outcome "possible suicidal behavior or ideation." This expanded outcome was used as part of the sensitivity analysis. Many of the originally captured events were excluded because they were medical or psychiatric events that were not considered to represent suicidality, as were those that represented self-injury with nonsuicidal intent. A standardized data file structure was designed and provided to all sponsors to assist in their creation of electronic patient-level data sets containing the variables depicted in **Table 1**.

SUICIDE ITEM SCORE DATA

Another approach to evaluating suicidality was to examine suicide item scores for the depression scales used in the trials that included such measures. Seventeen of the 24 trials used 1 of the following 3 depression rating scales, each of which includes a suicide item: the Children's Depression Rating Scale–Revised, the Hamilton Depression Rating Scale, and the Montgomery Asberg Depression Rating Scale. "Worsening of suicidality" was defined as an increase relative to baseline at any time during the controlled phase of the trial of 1 point or more on item 3 of the Hamilton Depression Rating Scale or of 2 points or more on item 13 of the Children's Depression Rating Scale–Revised or item 10 of the Montgomery Asberg Depression Rating Scale, regardless of subsequent change. "Emergence of suicidality" was defined as the subset of patients with worsening of suicidality whose baseline suicide item scores suggested no or minimal suicidal ideation. As with worsening, emergence was defined to reflect the first time such worsening occurred, regardless of subsequent change.

DATA ANALYSIS

Data were analyzed using several statistical software packages (JMP version 4.0.4 and SAS version 8.2 for Windows; SAS In-

stitute Inc, Cary, NC, and STATA/SE version 8.2 for Windows; Stata Corp, College Station, Tex).

EXPOSURE WINDOW

The adverse events assessed were those that occurred during the double-blind acute treatment period or within 1 day of the end of this period. For patients who left the study before reaching the planned end of the double-blind phase of any study, only events that occurred before discontinuation or on the day after the last dose of assigned treatment were included in the analysis. Events that occurred after the double-blind period were excluded to avoid the uncontrollable confounding resulting from the wide array of treatment scenarios that occurred after the end of any given trial. For example, patients may have continued taking study medication, changed to another active medication, been abruptly withdrawn from treatment, been tapered off study medication, or been given placebo. Events that occurred before randomization were also excluded.

EXAMINING AND HANDLING MISSING DATA FOR EXPLANATORY VARIABLES

Variables that were completely reported in all the trials were age, sex, race, setting of trial, location of trial, and baseline severity score. Variables that were missing from many trials were duration of illness before randomization (10 trials) and history of psychiatric hospitalization (21 trials), substance abuse (9 trials), and hostility or aggressive behavior (8 trials).

Any variable that had missing information for more than 10% of patients in a given trial was not considered further. For binary variables (eg, history of insomnia), when a trial was missing information on 10% or fewer patients, the missing data were replaced with "zero" (which translates, for example, to no history of insomnia). For continuous variables with missing data in 10% or fewer patients, data were imputed using the average value of that variable in the particular trial where the data were missing.

STRATIFIED ANALYSIS

Stratified analysis of the primary outcome was performed to identify potential interactions (effect modification) between the effect of exposure to drug and the effect of other pertinent variables. Investigating such effect modifications was difficult because of the inherent lack of statistical power in this situation where few events were observed during the trials. The approach used was to investigate whether there was a "consistent" change in the signal, that is, the effect associated with exposure to drug compared with placebo, in most trials when patients were stratified by the variables of interest. For this investigation, variables that are well known to affect the risk of suicidality were used, namely, age, sex, and history of suicide attempt or ideation. Results showed no consistent evidence suggesting that these variables affected the risk for the primary outcome because most trials had events occurring in all of the examined strata; the details of these analyses are not included in this article.

INVESTIGATING CONFOUNDING

The crude associations of continuous and categorical explanatory variables with the exposure (drug vs placebo) and the primary outcome were evaluated using the Mantel-Haenszel χ^2 test (or the Fisher exact test if ≥25% of the cells had expected counts <5) or the t test (or the Wilcoxon rank sum test for sample sizes of <30), as appropriate. Variables that were associated with the exposure and the primary outcome at $P \leq .10$ were considered further in the modeling stage as potential confounders.

A few variables showed evidence of an imbalance between the drug and the placebo groups in some trials, reaching the traditional level for statistical significance ($P \leq .05$), suggesting that randomization largely succeeded in creating treatment groups with reasonably similar clinical profiles with respect to the distribution of baseline variables. This evidence of similar distribution of measured variables was reassuring considering that some trials were missing information on some of these variables; that is, it would be reasonable to assume that these variables also would not exhibit major imbalances in those trials. Because none of the imbalances identified were found to meaningfully change the primary outcome risk estimates for any of the drugs, the crude estimates for suicidality risk were used in the meta-analysis. The details of investigating confounding are not given in this article.

DECISION TO FOCUS ON RISK RATIOS

Average exposure times for the drug and placebo groups were compared for each trial, and most trials had no meaningful difference. Thus, the unit of analysis within trials was persons rather than person-time, and the analyses generated risk ratios (RRs) rather than rate ratios. An alternative approach would have been to focus on time to event, and such analyses were explored. However, these were short-term trials. In addition, there were so few events that the confidence intervals (CIs) on the hazard curves were very wide and overlapping. Furthermore, the events were distributed across the several weeks of the trials, that is, they did not cluster at the start of therapy as might have been anticipated. For these reasons, results of analyses based on person-time and those focusing on time to event are not included in this article.

META-ANALYSES OF ADVERSE EVENT DATA AND SUICIDE ITEM SCORES[3]

Modeling Approach

Data were pooled to generate an overall estimate of various drug effects. To accomplish this pooling, an overall weighted estimate of treatment effects from individual trials was calculated. The fixed-effects approach was used as the primary analytical approach, using the Mantel-Haenszel method, for RR and risk difference (RD).[4] This approach was selected because the test for heterogeneity was not significant. However, it is possible that some of the residual heterogeneity between trials was missed owing to lack of statistical power to detect its existence. Therefore, the results of the random-effects model (using the method of DerSimonian and Laird)[5] are also shown for the overall estimates for comparison purposes as part of a sensitivity analysis.

To calculate the RR in trials with zero events, in one of the trial arms, the meta-analysis procedure automatically corrects for this "zero cell" problem by adding 0.5 to each of the 4 cells (so-called continuity correction) before proceeding with the analysis. This correction was not needed for the RD analysis. Because 4 trials did not have events in any of their groups, only 20 trials were used for the RR calculation, whereas all 24 trials were used for the RD calculation.

Sensitivity Analysis

Two approaches were used for the sensitivity analysis. For the adverse event outcomes and the suicide item scores, the ro-

bustness of results of the meta-analysis modeling approach was examined by comparing the results of the fixed-effects model with those of the random-effects model. In addition, for adverse event outcomes, the robustness of results of event ascertainment was examined by comparing the results of the primary and secondary outcomes.

RESULTS

CLINICAL TRIALS

Data from 4582 patients were available from the 24 pediatric trials of 9 antidepressant drugs. Most of the trials were conducted in the late 1990s, and trial durations ranged from 4 to 16 weeks. The indications studied included MDD (16 trials), obsessive-compulsive disorder (4 trials), generalized anxiety disorder (2 trials), social anxiety disorder (1 trial), and attention-deficit/hyperactivity disorder (1 trial).

DISPOSITION OF ADVERSE EVENTS

A total of 427 potential SRE narratives were accumulated for all the trials (other than the TADS). There were no completed suicides in any of the trials. A total of 260 events were not pertinent to the analysis because they were classified as other psychiatric or medical events not related to suicidality, and they were excluded from any further analysis. The broad approach to capturing any possibe SREs explains the large number of events that were eventually excluded from the analysis after expert classification.

A total of 167 events were considered for the analysis. Eleven events were classified as self-injury with nonsuicidal intent and were excluded from further analyses. Of the remaining 156 SREs, 47 occurred in 21 patients who had more than 1 event. For those patients, the most severe event was used in the analysis, according to the following ranking of the Columbia University classification: suicide attempt > preparatory actions toward imminent suicidal behavior > suicidal ideation > self-injurious behavior with intent unknown > events with not enough information. This selection process resulted in 130 unique patients with an SRE. Twenty-one events that occurred outside the exposure window were not included in the analysis. Therefore, 109 SREs were pertinent to the analysis in addition to 11 events recorded in the TADS.

For this analysis, SREs were grouped as 2 outcomes: the primary outcome suicidal behavior or ideation (n=89) and the secondary outcome possible suicidal behavior or ideation (n=120). The number and percentage of patients with both outcomes are provided by drug, trial, and treatment in **Table 2**.

META-ANALYSIS OF THE PRIMARY OUTCOME FOR ADVERSE EVENT OUTCOMES

Four of the 24 trials did not have any events: 75 (bupropion [attention-deficit/hyperactivity disorder]), CN104-141 and CN104-187 (nefazodone [MDD]), and 396 (venlafaxine [extended release] [generalized anxiety disorder]). Ten trials had no events in 1 of the

Table 2. Primary and Secondary Outcomes by Drug, Trial, and Treatment

Drug and Trial No.	Treatment Group	Patients, No.	Outcomes, No. (%)	
			Primary (n = 89)*	Secondary (n = 120)†
Bupropion				
75	Drug	72	0	0
	Placebo	37	0	1 (2.7)
Citalopram				
94404	Drug	124	9 (7.3)	14 (11.3)
	Placebo	120	5 (4.2)	6 (5.0)
CIT-MD-18	Drug	93	1 (1.1)	1 (1.1)
	Placebo	85	2 (2.4)	2 (2.4)
Fluoxetine				
HCCJ	Drug	21	0	1 (4.8)
	Placebo	19	1 (5.3)	1 (5.3)
HCJE	Drug	109	6 (5.5)	8 (7.3)
	Placebo	110	6 (5.4)	6 (5.4)
HCJW	Drug	71	1 (1.4)	2 (2.8)
	Placebo	32	0	1 (3.1)
X065	Drug	48	2 (4.2)	2 (4.2)
	Placebo	48	2 (4.2)	2 (4.2)
TADS	Drug	109	9 (8.3)	9 (8.3)
	Placebo	112	2 (1.8)	2 (1.8)
Fluvoxamine				
RH-114-02-01	Drug	57	2 (3.5)	2 (3.5)
	Placebo	63	0	0
Nefazodone				
CN104-141	Drug	95	0	1 (1.0)
	Placebo	95	0	0
CN104-187	Drug	184	0	0
	Placebo	94	0	0
Paroxetine				
329	Drug	93	4 (4.3)	7 (7.5)
	Placebo	88	1 (1.1)	1 (1.1)
	Active control	95	2 (2.1)	3 (3.2)
377	Drug	180	6 (3.3)	7 (3.9)
	Placebo	95	2 (2.1)	3 (3.2)
676	Drug	165	3 (1.8)	5 (3.0)
	Placebo	156	0	0
701	Drug	104	2 (1.9)	3 (2.9)
	Placebo	102	1 (1.0)	1 (1.0)
704	Drug	99	1 (1.0)	2 (2.0)
	Placebo	107	0	0
Mirtazapine				
003-045	Drug	170	1 (0.6)	2 (1.2)
	Placebo	89	0	1 (1.1)
Sertraline				
90CE21-0498	Drug	92	0	0
	Placebo	95	1 (1.0)	1 (1.0)
A0501001	Drug	97	3 (3.1)	4 (4.1)
	Placebo	91	0	0
A0501017	Drug	92	2 (2.2)	2 (2.2)
	Placebo	93	2 (2.2)	2 (2.2)
Venlafaxine (extended release)				
382	Drug	80	3 (3.8)	5 (6.2)
	Placebo	85	0	1 (1.2)
394	Drug	102	5 (4.9)	7 (6.9)
	Placebo	94	0	0
396	Drug	80	0	0
	Placebo	84	0	0
397	Drug	77	1 (1.3)	1 (1.3)
	Placebo	79	1 (1.3)	1 (1.3)

Abbreviation: TADS, Treatment for Adolescents With Depression Study.
*The primary outcome is suicidal behavior or ideation.
†The secondary outcome is suicidal behavior or ideation plus self-injurious behavior with intent unknown and events with not enough information ("worst-case scenario").

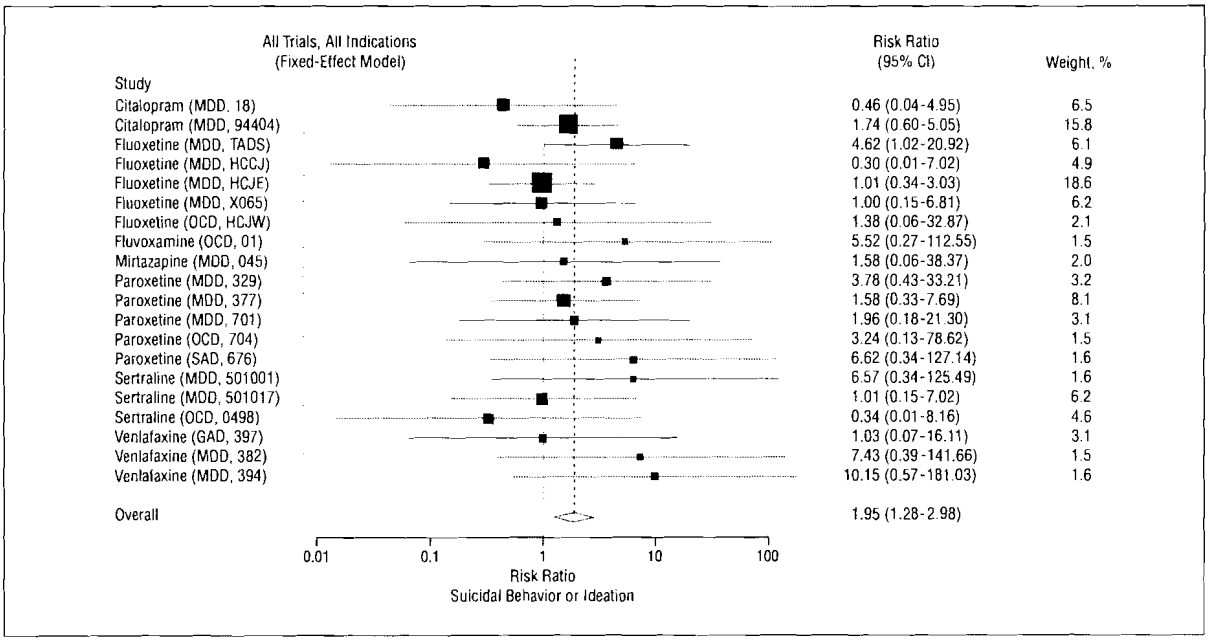

Figure. Risk ratios for the 20 evaluable trials of all drugs across all indications. CI indicates confidence interval; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SAD, social anxiety disorder. Percentage weight takes into consideration the sample size and the number of events in each trial. Vertical solid line represents the value 1; vertical dashed line, overall risk ratio.

treatment groups: HCCJ and HCJW (fluoxetine), RH-114-02-01 (fluvoxamine), 676 and 704 (paroxetine), 003-045 (mirtazapine), A0501001 and 90CE21-0498 (sertraline), and 382 and 394 (venlafaxine [extended release]). The incidence of the primary outcome across trials varied from 0% to 8%.

The results for each of the 20 trials with events are shown in the **Figure**, revealing the variation between the risk estimates of trials even within the same drug development program and the same indication. Only the TADS showed a statistically significant excess of suicidality (suicidal ideation and behavior) in the drug-treated group. However, 8 other trials had an RR of 2 or more. The Figure also provides an overall RR for suicidality for all the trials and indications of 1.95 (95% CI, 1.28-2.98). Separate analyses for suicidal ideation and behavior for all the trials and indications yielded similar results, that is, the RR for suicidal ideation was 1.74 (95% CI, 1.06-2.86) and the RR for suicidal behavior was 1.90 (95% CI, 1.00-3.63). The overall RR for suicidality for selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) in depression trials was 1.66 (95% CI, 1.02-2.68), which is not shown in the Figure.

To understand the observed discrepancies between the risk estimates of trials, the attributes of the trial designs were examined. The examined attributes focused on inclusion and exclusion criteria that would affect the likelihood of recruiting high-risk patients. None was found to consistently explain the observed differences in the risk estimates between trials within or between development programs. **Table 3** summarizes the pooled overall RR estimates of the primary outcome by drug. The pooled overall estimates varied by drug, and venlafaxine (extended release) is the only drug that did not include "1" in the 95% CI of its risk estimate.

SENSITIVITY ANALYSIS FOR ADVERSE EVENT OUTCOMES

No substantive difference was observed in the overall risk estimates between the fixed-effects (RR, 1.95; 95% CI, 1.28-2.98) and random-effects (RR, 1.75; 95% CI, 1.11-2.76) methods. In addition, no substantive difference was observed in the overall risk estimates between the primary (RR, 1.95; 95% CI, 1.28-2.98) and secondary (RR, 2.19; 95% CI, 1.50-3.19) outcomes.

THE RD FOR ADVERSE EVENT OUTCOMES

This analysis estimates the absolute increase in the risk of the event of interest due to treatment, which was calculated as the difference between the risk in the drug group and the risk in the placebo group. The overall RD for the primary outcome was 0.01 (95% CI, 0.01-0.02) and for the secondary outcome was 0.02 (95% CI, 0.01-0.03). This can be interpreted as indicating that when considering 100 treated patients, we might expect 1 to 3 patients to have an increase in suicidality beyond the risk that occurs with depression itself owing to short-term treatment with an antidepressant.

SUICIDE ITEM SCORE FINDINGS

Few of the 17 individual trials for which suicide item score data were available had a finding suggestive of either excess worsening or emergence of suicidality for drug compared with placebo. Meta-analyses for all 17 trials also revealed no signal for excess suicidality for drug, that is,

the RR for worsening of suicidality was 0.92 (95% CI, 0.76-1.11) and for emergence of suicidality was 0.93 (95% CI, 0.75-1.15).

COMMENT

There has been a long-standing concern that antidepressant drugs might actually induce suicidality early in treatment. A textbook of psychiatry published more than 40 years ago, in referring to observations of depressed patients during initial treatment with tricyclic antidepressants, noted that, "With beginning convalescence, the risk of suicide once more becomes serious as retardation fades."[6(p231)] Although this concern has been part of medical lore for many decades, it has remained a belief rather than an established fact. The debate on this question regarding adult depression intensified in 1990 with the publication of an article[7] describing a series of 6 adult patients with depression who, in the view of the researchers, became suicidal as a result of being treated with fluoxetine. This article and the ensuing discussion led the manufacturer of the drug to conduct a pooled analysis[8] of their controlled trials data to explore for the emergence of suicidality; the analysis revealed no signal of increased suicidality associated with the use of fluoxetine.

During the next decade, additional data on suicidality in adult patients were accumulating as additional antidepressant agents became available for use. A meta-analysis[9] encompassing data on attempted and completed suicides from 45 placebo-controlled trials involving 7 new antidepressant drugs in a population of almost 20 000 depressed adult patients did not find a significant difference between those assigned to drug vs placebo in rates of attempted or completed suicide. Storosum and colleagues,[10] from the Medicines Evaluation Board of the Netherlands, performed an analysis of attempted suicides from adult antidepressant drug data available to them and reached the same conclusion. The FDA has also explored this question, focusing on completed suicides in 234 randomized controlled trials of MDD involving 20 antidepressant drugs. Based on our initial analyses of these data, we reached a similar conclusion, that is, there does not seem to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD.[11]

In the early 1990s, there was also concern about possible antidepressant drug–induced suicidality in pediatric patients based on uncontrolled clinical observations.[12] When this concern reemerged in the middle of 2003 based on data from randomized clinical trials, summaries of selected data analyses performed by individual pharmaceutical companies for various antidepressant drug trials in pediatric patients were made available on the Medicines and Healthcare Products Regulatory Agency Web site (http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON019494&ssSourceNodeId=242&ssTargetNodeId=221). However, the FDA's meta-analysis of suicidality adverse events from individual patient data from 24 placebo-controlled antidepressant drug trials in pediatric patients is the first effort to systematically quantify the risk of antidepressant drug–induced suicidality in younger patients. It is important, however, to recognize the limitations of this analysis:

Table 3. Summary of the Overall Risk Estimates of the Primary Outcome by Drug Across All Indications and in MDD Trials

Drug	Risk Ratio (95% CI)	
	MDD Trials	All Trials, All Indications
Citalopram	1.37 (0.53-3.50)	1.37 (0.53-3.50)
Fluvoxamine	No MDD trials	5.52 (0.27-112.55)
Paroxetine	2.15 (0.71-6.52)	2.65 (1.00-7.02)
Fluoxetine	1.53 (0.74-3.16)	1.52 (0.75-3.09)
Sertraline	2.16 (0.48-9.62)	1.48 (0.42-5.24)
Venlafaxine (extended release)	8.84 (1.12-69.51)	4.97 (1.09-22.72)
Mirtazapine	1.58 (0.06-38.37)	1.58 (0.06-38.37)
Nefazodone	No events	No events
Bupropion	No MDD trials	No events

Abbreviations: CI, confidence interval; MDD, major depressive disorder.

1. As with any post hoc analysis in which multiple outcomes and many subanalyses increase the level of uncertainty in the findings, caution is warranted in the interpretation of the findings.

2. The present analyses focused on short-term data (4-16 weeks); thus, the risk of suicidality beyond 16 weeks is unknown.

3. This study cannot provide valid comparisons of the 9 drugs studied. Pooling data across drugs within a class, as has been done herein, is unavoidable when there are few events for each drug. Use of pooling, however, requires that one assume that the rate of suicidality is similar across this class of drugs. Among the different development programs included in this analysis, some had smaller databases than others and thus a smaller opportunity to observe suicidality events. There are also possible unmeasurable and uncontrollable differences in the level of ascertainment of events and completeness of narrative summaries provided between various trials and various sponsors. Thus, the observed differences in risk among drugs have many possible explanations, including true differences among the drugs, inadequately powered studies, and differences among trials in ascertainment and reporting of adverse events.

4. The observed rates of suicidality might not reflect actual rates among patients in the general population because patients who volunteer to participate in randomized clinical trials might not be representative of patients overall.

5. Most trials included in this analysis involved flexible dosing, limiting the FDA's ability to explore for a dose effect.

6. Although excluding patients outside the exposure window reduces the probability of including patients who might have had the event of interest because of discontinuation rather than as a consequence of administration of the drug, this is also a limitation. The analy-

sis does not address the possibility that suicidality might be a result of discontinuing antidepressant drug therapy.

Despite the limitations, the observed signal of risk for suicidality represents a consistent finding across trials, with many showing RRs of 2 or more. Moreover, the finding of no completed suicides among the approximately 4600 patients in the 24 trials evaluated does not provide much reassurance regarding a small increase in the risk of suicide because this sample is not large enough to detect such an effect.

The finding of lack of concordance in the signal for suicidality reported as an adverse event outcome and as ascertained with the suicide item in the depression rating scales is somewhat troubling. A possible explanation for this discrepancy is the fact that the depression rating scales were administered at set times and may not have adequately captured suicidality events that occurred between scheduled visits. Note that the suicidality signal as determined by adverse event reporting was consistent whether focusing on suicidal ideation or on behavior.

Although the finding of drug-induced suicidality based on adverse event reporting in pediatric patients during short-term treatment with antidepressant drugs seems to be robust, an overall interpretation of this finding and its implications for clinical practice are less clear. Furthermore, there exist alternative explanations for this finding. First, the apparent increased risk of drug-induced suicidality may actually represent a greater likelihood of reporting of suicidality events by patients rather than an increased rate of the events themselves. Suicidal ideation and attempts are often characterized as secretive in pediatric patients. Several antidepressant agents have been found to be effective in treating social anxiety, resulting in increased verbalization and communication with others. Thus, it is possible that antidepressant drug therapy leads to differentially greater reporting of suicidal thoughts and behaviors in pediatric patients compared with those receiving placebo. It is also possible that patients assigned to active drug therapy in these trials may have had other adverse events that drew clinical attention to them and resulted in better ascertainment for suicidality.

Finally, there are other pertinent data that seem inconsistent with a role for antidepressant drugs in inducing suicidality in pediatric patients. The absolute rate of adolescent suicide in the United States has declined in recent years; for example, the rate of suicide in males aged 15 to 19 years decreased from 17.6 per 100 000 person-years in 1992 to 12.2 per 100 000 person-years in 2002 (representing a 31% reduction in suicide risk).[13] There are ecologic data suggesting that increasing prescriptions for antidepressant drugs in adolescents are associated with a decrease in adolescent suicide.[14] In addition, 2 recent suicide autopsy studies[15,16] have failed to find evidence of antidepressant drug use in most adolescent victims, even in those who had been prescribed antidepressants before their deaths.

The FDA presented the results of its analysis of the pediatric suicidality data to a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee on September 13 and 14, 2004.[17] The committees agreed with the FDA's conclusion that the data suggested a risk of antidepressant drug–induced suicidality in the pediatric population and that this risk was best understood as applying to all antidepressant agents. They recommended that the FDA modify antidepressant drug labeling to include a boxed warning regarding this risk and mandate a medication guide for all antidepressant drugs to alert patients and their families and caregivers to this risk. A medication guide is a type of patient labeling that provides the same risk information included in the package insert but in a form that can be more easily understood by patients (http://www.fda.gov/cder/drug/antidepressants/MG_template.pdf). The FDA has now implemented these suggested changes.

Although there remain differences of opinion in the clinical community about the strength of this signal for antidepressant drug–induced suicidality in pediatric patients and the implications for clinical practice,[18,19] it is important to be clear that the FDA has not contraindicated any of the antidepressant drugs for pediatric use. Instead, the new labeling warns of the risk of suicidality and encourages prescribers to balance this risk with clinical need. The FDA recognizes that depression and other psychiatric disorders in pediatric patients can have significant consequences if not appropriately treated. The new warning language recognizes this need but advises close monitoring of patients as a way of managing the risk of suicidality.

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Announcement

Clinical Trials Registration Required. In concert with the International Committee of Medical Journal Editors, *Archives of General Psychiatry* will require, as a condition of consideration for publication, registration of clinical trials in a public trials registry (such as http://ClinicalTrials.gov or http://controlled-trials.com). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after March 1, 2006. For trials that began enrollment before this date, registration will be required by June 1, 2006. The trial registration number should be supplied at the time of submission.

For details about this new policy see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005(2005;293:2927-2929) issues of *JAMA*.