A Pooled Analysis of Suicidality in Double-Blind, Placebo-Controlled Studies of Sertraline in Adults

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Objective: The analyses were conducted to identify possibly suicide-related adverse events in Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline in adult patients and evaluate the risk of suicidality with sertraline versus placebo.

Method: U.S. Food and Drug Administration (FDA)–defined search methodology was used to identify possibly suicide-related adverse events in short-term, all-duration/all-indication, and psychiatric studies of sertraline. Categorization of possibly suicide-related adverse events was based on the approach developed by the Columbia group for the FDA's analysis of pediatric suicide risk with antidepressants. The incidences of possibly suicide-related adverse events were calculated for individual classifications and for the predefined combined category of suicidality along with the sertraline versus placebo relative risks and corresponding 95% CI limits. Exact binomial CI limits were calculated for the individual treatment group incidences. Age group analyses were also performed using the age limits defined by the FDA.

Results: Ninety-nine suicidality events were identified among 19,923 sertraline- and placebo-treated subjects participating in 126 studies conducted between the mid-1980s and the mid-2000s. Four cases of completed suicides among 10,917 sertraline-treated subjects yielded an incidence of 0.04% (95% CI = 0.01 to 0.09) and 3 cases among 9,006 placebo treated subjects yielded an incidence of 0.03% (95% CI = 0.01 to 0.10). There were no statistically significant differences between sertraline and placebo in any of the individual categories or combined suicidality risk category across all performed analyses.

Conclusion: Results of short-term, all-duration, and psychiatric studies analyses, as well as age-group analyses, performed in accordance with the FDA-specified search strategy, show no significant increase in suicidality risk in adult sertraline- versus placebo-treated patients.

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Suicide is an inherent risk in many psychiatric disorders, including mood and anxiety disorders and schizophrenia.[1–8] The occurrence of suicidality in the context of treating patients with depression and other psychiatric illnesses has been a concern and a topic of debate for decades[9] that intensified in the 1990s[9,10] and became a focus of regulatory interest in 2003 and 2004.

In 2003, in response to continuing public concerns about the safety of selective serotonin reuptake inhibitors (SSRIs), United Kingdom's Committee on the Safety of Medicines raised questions regarding the possibility of an increased risk of suicidal behavior in children and adolescents during treatment with SSRIs (for review, see Laughren[9]). Following results of an analysis of pediatric trials (for review, see Laughren[9]) of paroxetine conducted by GlaxoSmithKline, which showed a statistically significant increase in suicidal behavior with paroxetine versus placebo, in 2004, the U.S. Food and Drug Administration (FDA) requested the manufacturers of all 9 antidepressant drugs tested in children and adolescents in the United States to perform a similar search of their databases.[11] The risk of suicidality was assessed in a combined analysis of short-term (4 to 16 weeks), placebo-controlled trials in children and adolescents with major depressive disorder (MDD), obsessive-compulsive disorder, or other psychiatric disorder, involving a total of 24 trials with over 4400 subjects.[12,13] An analysis of all suicide-related adverse events was performed using narrative summaries for each of the identified suicide-related events, serious adverse

events, accidental injuries, and accidental overdoses.[13] The narratives were blinded and independently classified by a group of 10 pediatric suicidology experts convened by Columbia University. Pooled categories of suicide attempt, preparatory actions toward imminent suicidal behavior, and suicidal ideation were used as the primary outcome "suicidal behavior or ideation." No suicides occurred in those trials, with the overall suicidal behavior or ideation risk estimate for all drugs across all indications of 1.95 (95% CI = 1.28 to 2.98). On the basis of this finding, i.e., a possible signal for an increased risk of suicidality in association with short-term antidepressant use in pediatric patients, the Psychopharmacologic Drugs Advisory Committee recommended in 2004 that the FDA add a "boxed" warning to antidepressant labeling and require a medication guide to alert patients, families, and caregivers to this risk (for review, see Laughren[9]).

In adults, meta-analyses published between 2001 and 2003 examined a potential relationship between suicide and antidepressant treatment in large sets of placebo-controlled antidepressant studies and concluded that the risk for completed suicide is the same with antidepressants as with placebo.[14,15] No increase in risk of suicide with antidepressants versus placebo was also found in an early reanalysis of the data by the FDA, later published in 2006.[16] However, 2 reviews of data from controlled trials of antidepressants[17,18] and 1 article reporting on a nested case-control study[19] provided equivocal results regarding increased risk for self-harm, suicide attempts, and completed suicide in adults treated with antidepressants.

In light of the ongoing controversy, in late 2004, the FDA requested data from all antidepressant manufacturers in the United States on possibly suicide-related adverse events in patients aged 18 years or older. The FDA's meta-analysis for suicidality[11] included the primary outcome "suicidal ideation or worse" (outcomes 1, 2, 3, or 4 above as per Posner et al.[20]), also called "suicidality" or "suicidal behavior and ideation." The principal secondary outcome variable was "preparatory actions or worse" (outcomes 1, 2, or 3 as per Posner et al.[20]), also called "suicidal behavior."

The final FDA analysis was based on data from 372 randomized, placebo-controlled trials of antidepressants, including sertraline, and was presented in 2006.[11,23] The pooled estimate for all patients ≥ 18 years in psychiatric clinical trials showed no treatment effect on suicidality (OR = 0.83, 95% CI = 0.69 to 1.00, p = .05) or suicidal behavior risk (OR = 1.10, 95% CI = 0.77 to 1.56, p = .60).[11] However, the analysis by age group in the same population showed an increased risk for suicidality (OR = 1.94, 95% CI = 1.37 to 2.74, p = .0002) and suicidal behavior (OR = 2.35, 95% CI = 1.35 to 4.09, p = .002) among patients < 25 years of age. The FDA concluded that for adults between the ages of 25 and 64 years, the net effect of antidepressants appeared to be neutral for suicidal behavior but possibly protective for suicidality, while in subjects aged 65 years and older, antidepressants appeared to reduce the risk for both suicidality and suicidal behavior.[11,23]

The sertraline studies submitted for FDA analysis were limited to short-term studies up to 17 weeks' duration. To obtain a comprehensive insight into possibly suicide-related adverse events regardless of duration of treatment with sertraline across different indications, Pfizer Inc. pursued an additional analysis on all-duration studies, utilizing the FDA-specified search strategy. The present analysis aimed to identify possibly suicide-related adverse events with sertraline or placebo in Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed studies of sertraline in adult patients and evaluate the risk of suicidality with sertraline versus placebo. Conclusions of the FDA investigation were based on an analysis of psychiatric indication studies and also included an age-group analysis.[11] We included analyses of both psychiatric and all-indication studies in our investigation, basing the sertraline versus placebo suicidality risk age group analysis on the age limits defined in the FDA Briefing Document.[11]

METHOD

Three analyses were performed in Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed adult studies of sertraline: the first, in response to the FDA request in 2004 (for details, see Stone and Jones[11]), was limited to short-term studies; the second removed the limitation of up to 17 weeks' duration; and the third included both short-term and all-duration studies in psychiatric indications only. Data from prematurely terminated studies were not included. The studies were conducted between the mid-1980s and mid-2000s.

For the short-term studies overall analysis, as per FDA's request,[11] the results are presented for sertraline versus placebo for all studies as well as separately for major depressive disorder (MDD) and non-MDD studies and includes both individual codes and combined outcome of suicidality (or suicidal ideation or worse; codes 1, 2, 3, or 4). The same analysis was performed for the expanded set of all-duration studies and all indications (with additional exposure-adjusted rate and age-group analyses) and on the set of psychiatric studies only. Twelve studies did not have duration of treatment data available and were therefore excluded from the exposure-adjusted rate analysis in the number of events (11 events; 9 with sertraline and 2 with placebo) and number of subjects treated.

Short-Term Studies Analysis

The initial FDA-defined criteria for inclusion of studies[11] identified Pfizer-sponsored, phases 2 through 4,

double-blind, placebo-controlled, short-term (up to 17 weeks duration), completed studies of sertraline. While the FDA recommended the exclusion of studies with < 20 subjects per treatment arm,[11] we included all available subjects in this analysis.

The search for studies with possibly suicide-related adverse events was limited to the double-blind phase of the treatment or within 1 day of stopping randomized treatment and was based on the following FDA-specified text strings[11] used in searches of all preferred and verbatim terms of adverse events, serious adverse events, or deaths: *accident**, *attempt*, *burn*, *cut*, *drown*, *gas*, *gun*, *hang*, *hung*, *immolat*, *injur**, *jump*, *monoxide*, *mutilate**, *overdos**, *self-damag**, *self-harm*, *self-inflict*, *self-injur**, *shoot*, *slash*, *suic**, *poison*, *asphyxiation*, *suffocation* and *firearm*.

All possibly suicide-related adverse events identified by this search strategy and not excluded as "false positives" (e.g., the text string *gas* was almost always associated with the adverse event flatulence or was part of the word *orgasm* in the adverse event delayed orgasm) had narrative summaries prepared in line with the FDA instructions, i.e., providing information regarding patient ID number, trial number, and treatment group; sex and age; diagnosis; dose at time of event (mg); recent dose change; history of suicidal thoughts/suicide attempt/self-harm; adverse event–preferred term; adverse event verbatim term; serious adverse event (yes/no); number of days on drug at the time of event; treatment discontinuation following event (yes/no); patient died—if yes, elaborate on cause of death; associated treatment-emergent adverse events; concurrent psychosocial stressors; psychiatric comorbidities; concomitant medication; and other pertinent information (e.g., family history of psychiatric disorders). The narratives were blinded to treatment assignment and details that might bias the assessment and classification.

The FDA also specified a categorization system for the possibly suicide-related adverse events based on the approach developed by the Columbia group for the pediatric suicidality narratives[20]: completed suicide (code 1); suicide attempt (code 2); preparatory acts toward imminent suicidal behavior (code 3); suicidal ideation (code 4); self-injurious behavior, intent unknown (code 5); not enough information (fatal) (code 6); self-injurious behavior, no suicidal intent (code 7); other—accident, psychiatric, medical (code 8); and not enough information (nonfatal) (code 9). The blinded narratives were reviewed and events classified using the above classification independently by 2 board-certified psychiatrists, employed by Pfizer. In situations in which the psychiatrists arrived at different classifications for the same case, the 2 psychiatrists reviewed the case together to see if there could be a consensus. If this was not possible, a third psychiatrist would be called in to settle on a final classification.

All-Duration/All-Indication Studies Analysis

The expanded all-duration study analysis was based on Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed adult studies of sertraline, regardless of treatment duration and including all indications. The search for possibly suicide-related adverse events was based on the same FDA-specified text strings and review of serious adverse events and deaths used in the initial short-term study analysis, but the event capture window was extended through 30 days after stopping double-blind treatment, thus including the 30-day Pfizer standard adverse event follow-up period.

For the possibly suicide-related adverse events identified from the text strings, the case report forms were obtained and reviewed. Specially developed data forms were populated with all the relevant information, and any relevant pages in the case report forms were flagged. In cases in which the case report form was not obtainable, data summaries were obtained from the database, with as much information as possible. All of the serious adverse events had detailed reports in English already generated per standard study procedures. The data forms and other sources of information were blinded to treatment assignment and forwarded for independent evaluation and classification by 2 board-certified psychiatrists. Categorization of the newly-identified possibly suicide-related adverse events previously not included in the short-term studies analysis was done using the same Columbia group approach.[20]

Psychiatric Studies Analysis

This analysis was performed on Pfizer-sponsored, phases 2 through 4, placebo-controlled, completed all-duration adult studies of sertraline in psychiatric indications only by using the same methodology as in the all-indication short-term and all-duration studies analysis.

Statistical Analysis

In all analyses, the incidences of possibly suicide-related adverse events for codes 1 through 4 were calculated for each individual classification as well as for the predefined combined category (i.e., suicidality) for the sertraline and placebo groups along with the sertraline versus placebo relative risks and corresponding 95% CI limits. Exact binomial CI limits were calculated for the individual treatment-group incidences. For the relative risk, CIs that exclude the value of 1 indicated a statistically significant difference between the incidences in the sertraline and placebo treatment groups. An exploratory exposure-adjusted rate analysis performed on the all-duration studies used calculations on the basis of person-years, i.e., sum of treatment duration of all subjects, where duration = (last dose date – first dose date + 1)/365.25. In contrast to the FDA analysis, studies with no events were included in these analyses, allowing for increased

precision of point estimates. Analyses were performed using SAS Version 8.2 and 9.1 (SAS Institute Inc., Cary, N.C.).

In the relapse prevention studies (i.e., randomized withdrawal studies with subjects initially treated with sertraline followed by a double-blind treatment with either sertraline or placebo and then evaluated for the risk of withdrawal reactions), the double-blind phase was used except for 1 study in which both phases were included in the search.

As a sensitivity analysis, risk differences between sertraline and placebo were estimated using a Mantel-Haenszel approach,[23] which is a generalization to risk differences of the Mantel-Haenszel odds ratio (OR) method. A common risk difference (sertraline minus placebo) across studies was estimated using a weighted average method in which the weight was a function of the number of patients in each individual trial. Ninety-five percent CIs for the common risk differences were obtained using a normal approximation to the binomial distribution. In order to avoid individual trial variances being equal to 0, a 0.5 continuity correction was applied to empty cells for trials in which either treatment arm had no events. In addition, a separate analysis was performed using exact methods for estimating a common OR (sertraline/placebo) across studies. This approach makes use of studies in which at least 1 event occurred in either treatment arm; studies with no events are not included. The exact methods were applied with the software StatXact 5 for SAS, using the PROC STRATIFY procedure. Homogeneity of ORs was verified by a Zelen's test, which is the exact equivalent of the Breslow-Day asymptotic test. "Mid-p adjusted" 95% exact CIs were calculated for the common OR.

RESULTS

In all cases, the 2 psychiatrists independently or through consensus arrived at the same classification for each of the blinded narratives reviewed.

Short-Term Studies Analysis

An overview of short-term studies per indication is presented in Table 1. A total of 48 subjects with suicidality was identified among 12,041 sertraline-treated or placebo-treated subjects. One case of completed suicide was reported in a placebo-treated subject participating in a non-MDD study (1/5480 [0.02%]; 95% CI = 0.00 to 0.10) (Table 2).

The MDD studies included 19 studies with 2171 sertraline- and 1686 placebo-treated subjects. The absolute number of suicidality events was low across both treatment groups, without any completed suicides occurring in these studies (Table 2).

The non-MDD studies included 56 studies with 4390 sertraline- and 3794 placebo-treated subjects. The absolute number of suicidality events was also low, with the above-mentioned 1 case of completed suicide in a placebo-treated subject participating in a study assessing the effects of sertraline on negative symptoms of schizophrenia (Table 2).

Table 1. Overview of Pfizer-Sponsored, Phases 2 Through 4, Completed, Placebo-Controlled, Short-Term Studies of Sertraline in Adults Included in the Analysis

Indication	No. of Studies	Sertraline, N	Placebo, N
Psychiatric indications			
MDD	19	2171	1686
Bipolar disorder/MDD	3	68	65
Panic disorder	12	1000	789
Obsessive-compulsive disorder	6	541	380
Substance abuse (alcohol, cocaine)	3	111	108
Posttraumatic stress disorder	4	374	376
Generalized anxiety disorder	1	262	190
Atypical depression	1	89	92
Dysthymia/dysthymia MDD	3	325	316
Premenstrual dysphoric disorder	2	257	249
Generalized social phobia	1	209	199
Bulimia nervosa	1	107	54
Seasonal affective disorder/recurrent MDD	1	93	94
Neurasthenia	2	144	135
Negative symptoms of schizophrenia	1	86	86
Nonpsychiatric indications			
Obesity	6	352	359
Smoking cessation	3	96	95
Sexual function	3	177	115
Sleep in healthy volunteers	1	22	22
Fibromyalgia	1	55	48
Nonulcer dyspepsia	1	22	22
Total	75	6561	5480

Abbreviation: MDD = major depressive disorder.

In these analyses, there were no statistically significant differences in risk between sertraline and placebo in any of the individual categories or the combined suicidality risk category.

All-Duration/All-Indication Studies Analysis

A total of 99 subjects with suicidality events was identified in 19,923 sertraline- and placebo-treated subjects. Four cases of completed suicides among 10,917 sertraline-treated subjects yielded an incidence of 0.04% (95% CI = 0.01 to 0.09), and 3 cases among 9006 placebo-treated subjects yielded an incidence of 0.03% (95% CI = 0.01 to 0.10). There were no statistically significant differences between sertraline and placebo in the all-subjects analysis or age group analysis for any of the individual or suicidality-combined code categories (Table 3). The results of an exploratory exposure-adjusted rate analysis, based on 2897 person-years of treatment with sertraline and 2306 person-years with placebo, concur with the results for suicidality (codes 1–4) in the all-duration study analysis (relative rate, 0.85; 95% CI = 0.56 to 1.29).

Table 2. Incidences of Possibly Suicide-Related Adverse Events in MDD and Non-MDD Studies and Corresponding 95% CIs in Pfizer-Sponsored, Phases 2 Through 4, Completed, Placebo-Controlled, Short-Term Studies of Sertraline in Adults[a]

	Sertraline		Placebo		Sertraline vs Placebo	
Variable	n (%)	95% CI[b]	n (%)	95% CI[b]	Relative Risk	95% CI[b]
MDD and non-MDD studies combined						
No. of subjects treated	6561		5480			
Code[c]						
1	0 (0.00)	0.00 to 0.00	1 (0.02)	0.00 to 0.10	…	…
2	5 (0.08)	0.02 to 0.18	7 (0.13)	0.05 to 0.26	0.60	0.19 to 1.88
3	1 (0.02)	0.00 to 0.08	1 (0.02)	0.00 to 0.10	0.84	0.05 to 13.35
4	13 (0.20)	0.11 to 0.34	20 (0.36)	0.22 to 0.56	0.54	0.27 to 1.09
Suicidality (codes 1–4)[d]	19 (0.29)	0.17 to 0.45	29 (0.53)	0.35 to 0.76	0.55	0.31 to 0.97
MDD studies						
No. of subjects treated	2171		1686			
Code[c]						
1	0 (0.00)	0.00 to 0.00	0 (0.00)	0.00 to 0.00	…	…
2	2 (0.09)	0.01 to 0.33	3 (0.18)	0.04 to 0.52	0.52	0.09 to 3.09
3	1 (0.05)	0.00 to 0.26	1 (0.06)	0.00 to 0.33	0.78	0.05 to 12.41
4	2 (0.09)	0.01 to 0.33	4 (0.24)	0.06 to 0.61	0.39	0.07 to 2.12
Suicidality (codes 1–4)[d]	5 (0.23)	0.07 to 0.54	8 (0.47)	0.21 to 0.93	0.49	0.16 to 1.48
Non-MDD studies						
No. of subjects treated	4390		3794			
Code[c]						
1	0 (0.00)	0.00 to 0.00	1 (0.03)	0.00 to 0.15	…	…
2	3 (0.07)	0.01 to 0.20	4 (0.11)	0.03 to 0.27	0.65	0.15 to 2.89
3	0 (0.00)	0.00 to 0.00	0 (0.00)	0.00 to 0.00	…	…
4	11 (0.25)	0.13 to 0.45	16 (0.42)	0.24 to 0.68	0.59	0.28 to 1.28
Suicidality (codes 1–4)[d]	14 (0.32)	0.17 to 0.53	21 (0.55)	0.34 to 0.84	0.58	0.29 to 1.13

[a]All *n*'s represent number of subjects having an event.
[b]Exact binomial CI limits are used for treatment-group percentages.
[c]Code 1 = completed suicide, code 2 = suicide attempt, code 3 = preparatory acts toward imminent suicidal behavior, and code 4 = suicidal ideation.
[d]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al.[20]), also called suicidal ideation or worse or suicidal behavior and ideation.[11]
Abbreviation: MDD = major depressive disorder.

Psychiatric Studies Analysis

In the psychiatric studies analyses, there were no statistically significant differences in risk between sertraline and placebo in any of the individual categories or the combined suicidality category. In all psychiatric short-term studies, there were 18 subjects with suicidality events among 5863 sertraline-treated subjects and 27 among 4845 placebo-treated subjects, yielding a relative risk of 0.55 (95% CI = 0.30 to 1.00). The respective values for MDD studies were identical to the values reported for all short-term MDD studies (Table 2). In the non-MDD psychiatric studies, there were 13 subjects with suicidality events among 3692 sertraline-treated subjects and 19 among 3159 placebo-treated subjects, yielding a relative risk of 0.59 (95% CI = 0.29 to 1.18).

The relative risk for suicidality in all-duration psychiatric studies was 0.96 (95% CI = 0.64 to 1.44), based on suicidality events in 51 of 8804 sertraline-treated subjects and in 43 of 7134 placebo-treated subjects. In the all-duration psychiatric studies age group analyses, the relative risks were 0.60 (95% CI = 0.16 to 2.23) in the group 25 years or younger (4 suicidality events in 614 sertraline-treated subjects and 5 in 458 placebo-treated subjects); 0.88 (95% CI = 0.55 to 1.39) in the group aged 25 to 64 years (34 subjects with suicidality events in 6806 sertraline-treated subjects and 33 in 5587 placebo-treated subjects); and 1.32 (95% CI = 0.32 to 5.52) in the group 65 years or older (5 subjects with suicidality events in 830 sertraline-treated subjects and 3 in 641 placebo-treated subjects).

Sensitivity Analysis

The results for the Mantel-Haenszel test differences for short-term MDD and non-MDD combined studies as well as for all-duration psychiatric studies are shown in Table 4. All CIs included the value of 0, which indicates that sertraline and placebo are not significantly different with respect to the risk of suicidality. For the common OR exact methods in all instances in which the common OR was estimable, the CIs included the value of 1, again indicating there are no statistically significant differences between sertraline and placebo.

DISCUSSION

The results of all of our analyses are consistent in showing no significant difference in suicidality in patients treated with sertraline versus those treated with placebo. These results are also in harmony with the FDA findings in their psychiatric studies analysis, in which sertraline,

Table 3. Incidences of Possibly Suicide-Related Adverse Events in All Subjects and by Age Group and Corresponding 95% CIs in Pfizer-Sponsored, Phases 2 Through 4, Completed, Placebo-Controlled, All-Duration/All-Indication Studies of Sertraline in Adults[a]

	Sertraline[b]		Placebo[b]		Sertraline vs Placebo[b]	
Variable	n (%)	95% CI[c]	n (%)	95% CI[c]	Relative Risk	95% CI[c]
All subjects						
No. of subjects treated	10,917		9006			
Code[d]						
1	4 (0.04)	0.01 to 0.09	3 (0.03)	0.01 to 0.10	1.10	0.25 to 4.91
2	21 (0.19)	0.12 to 0.29	11 (0.12)	0.06 to 0.22	1.57	0.76 to 3.27
3	2 (0.02)	0.00 to 0.07	2 (0.02)	0.00 to 0.08	0.83	0.12 to 5.86
4	27 (0.25)	0.16 to 0.36	29 (0.32)	0.22 to 0.46	0.77	0.46 to 1.30
Suicidality (codes 1–4)[e]	54 (0.49)	0.37 to 0.64	45 (0.50)	0.36 to 0.67	0.99	0.67 to 1.47
Subjects aged < 25 y[f]						
No. of subjects treated	718		540			
Code[d]						
1	0 (0.00)	0.00 to 0.00	0 (0.00)	0.00 to 0.00	…	…
2	3 (0.42)	0.09 to 1.22	3 (0.56)	0.11 to 1.61	0.75	0.15 to 3.71
3	0 (0.00)	0.00 to 0.00	0 (0.00)	0.00 to 0.00	…	…
4	1 (0.14)	0.00 to 0.77	2 (0.37)	0.04 to 1.33	0.38	0.03 to 4.14
Suicidality (codes 1–4)[e]	4 (0.56)	0.15 to 1.42	5 (0.93)	0.30 to 2.15	0.60	0.16 to 2.23
Subjects aged 25–64 y[f]						
No. of subjects treated	8236		6822			
Code[d]						
1	1 (0.01)	0.00 to 0.07	3 (0.04)	0.00 to 0.13	0.28	0.03 to 2.65
2	12 (0.15)	0.08 to 0.25	7 (0.10)	0.04 to 0.21	1.42	0.56 to 3.60
3	1 (0.01)	0.00 to 0.07	2 (0.03)	0.00 to 0.11	0.41	0.04 to 4.57
4	23 (0.28)	0.18 to 0.42	23 (0.34)	0.21 to 0.51	0.83	0.47 to 1.48
Suicidality (codes 1–4)[e]	37 (0.45)	0.32 to 0.62	35 (0.51)	0.36 to 0.71	0.88	0.55 to 1.39
Subjects aged ≥ 65 y[f]						
No. of subjects treated	1037		823			
Code[d]						
1	2 (0.19)	0.02 to 0.69	0 (0.00)	0.00 to 0.00	…	…
2	2 (0.19)	0.02 to 0.69	0 (0.00)	0.00 to 0.00	…	…
3	0 (0.00)	0.00 to 0.00	0 (0.00)	0.00 to 0.00	…	…
4	1 (0.10)	0.00 to 0.54	3 (0.36)	0.08 to 1.06	0.26	0.03 to 2.54
Suicidality (codes 1–4)[e]	5 (0.48)	0.16 to 1.12	3 (0.36)	0.08 to 1.06	1.32	0.32 to 5.52

[a]All *n*'s represent number of subjects having an event.
[b]Studies 89CE21-0457, N-0254, N-0255, N-0256, N-0325, N-0355, N-0359, STL-CR-90-002, STL-JP-93-603, STL-JP-94-601, STL-JP-94-603, and STL-JP-94-604 did not have data available and are excluded from this table.
[c]Exact binomial CI limits are used for treatment group percentages.
[d]Code 1 = completed suicide, code 2 = suicide attempt, code 3 = preparatory acts toward imminent suicidal behavior, and code 4 = suicidal ideation.
[e]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al.[20]), also called suicidal ideation or worse or suicidal behavior and ideation.[11]
[f]One relapse-prevention study may contain data from both phases.

compared to other SSRIs, was associated with a low OR for suicidality risk (sertraline, OR = 0.51 vs. range of ORs for other SSRIs: fluoxetine, 0.71 to escitalopram, 2.44).[11]

These results are different from those obtained in a previously published meta-analysis by Gunnell et al.[18] looking into suicide, nonfatal self-harm, and suicidal thoughts data. In contrast to our analysis, Gunnell and colleagues' results show 4 cases of suicide in 7169 sertraline-treated patients and no cases among 5106 placebo-treated patients, yielding an OR of 6.42 (95% CI = 0.35 to 119.20). The Gunnell et al.[18] analysis was based on randomized, placebo-controlled trials of SSRIs in adults submitted by pharmaceutical companies to the safety review by the U.K. Medicines and Healthcare products Regulatory Agency. It differed in many respects from both the FDA analysis and our analysis. It was based on summed-up endpoint data provided by the sponsors for the medication- and placebo-treated groups across all trials and for all indications. Because no predefined inclusion criteria for studies were used (see below), the sertraline data set in the Gunnell et al. analysis comprised 156 trials across all indications, with 7169 sertraline- and 5106 placebo-treated subjects, compared with 126 trials with 8804 sertraline- and 7134 placebo-treated subjects included in our analysis of studies, also across all indications.

On the basis of their results of 4 completed suicides among sertraline and no cases among placebo, Gunnell et al.[18] calculated an OR of 6.42, with a very broad corresponding 95% CI of 0.35 to 119.20. By contrast, in our analysis, there were 4 cases of completed suicide among the sertraline group but also 3 cases among the placebo-treated subjects, yielding a relative risk of 1.10 with a

Table 4. Psychiatric Studies Sensitivity Analyses: Incidences of Possibly Suicide-Related Adverse Events and Corresponding 95% CIs in Pfizer-Sponsored, Phases 2 Through 4, Completed, Placebo-Controlled Studies of Sertraline[a]

	Sertraline		Placebo		Sertraline vs Placebo	
Variable	n (%)	95% CI[b]	n (%)	95% CI[b]	Relative Risk	95% CI[b]
Short-term psychiatric studies[c]						
No. of subjects treated	5863		4845			
Code[d]						
1	0 (0.00)	0.00 to 0.06	1 (0.02)	0.00 to 0.11	–0.001	–0.004 to 0.002
2	4 (0.07)	0.02 to 0.17	7 (0.14)	0.06 to 0.30	–0.001	–0.004 to 0.002
3	1 (0.02)	0.00 to 0.09	1 (0.02)	0.00 to 0.11	–0.001	–0.004 to 0.002
4	13 (0.22)	0.12 to 0.38	18 (0.37)	0.22 to 0.59	–0.002	–0.005 to 0.002
Suicidality (codes 1–4)[e]	18 (0.31)	0.18 to 0.48	27 (0.56)	0.37 to 0.81	–0.002	–0.006 to 0.001
All-duration psychiatric studies[f]						
No. of subjects treated	8804		7134			
Code[d]						
1	4 (0.05)	0.01 to 0.12	3 (0.04)	0.01 to 0.12	–0.001	–0.003 to 0.002
2	20 (0.23)	0.14 to 0.35	11 (0.15)	0.08 to 0.28	–0.000	–0.003 to 0.003
3	2 (0.02)	0.00 to 0.08	2 (0.03)	0.00 to 0.10	–0.001	–0.003 to 0.002
4	25 (0.28)	0.18 to 0.42	27 (0.38)	0.25 to 0.55	–0.001	–0.004 to 0.002
Suicidality (codes 1–4)[e]	51 (0.58)	0.43 to 0.76	43 (0.60)	0.44 to 0.81	–0.000	–0.003 to 0.003

[a]All *n*'s represent number of subjects having an event.
[b]Exact binomial CI limits are used for treatment group percentages.
[c]One classification 2 event (subject 4401 from non-MDD study A0501060) was removed (open-label sertraline).
[d]Code 1 = completed suicide, code 2 = suicide attempt, code 3 = preparatory acts toward imminent suicidal behavior, and code 4 = suicidal ideation.
[e]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al.,[20] also called suicidal ideation or worse or suicidal behavior and ideation).[11]
[f]Six open-label sertraline subjects were excluded from the denominator (subjects 1231 and 831 from protocol 320; subjects 541, 602, and 1071 from protocol 93CE21-0631; and subject 4401 from protocol A0501060). One relapse-prevention study, may contain data from both phases.

corresponding 95% CI of 0.25 to 4.91 and an OR of 1.10 with a 95% CI of 0.25 to 4.92. Of the 3 placebo completed suicides included in our analysis but not in Gunnell and colleague's,[18] 1 case may not have had any other available data, apart from the available serious adverse event report at that time, necessary for inclusion into the Gunnell et al.[18] analysis, while, in the other 2 cases, the suicide occurred ≥ 7 days after stopping treatment, rendering both of them ineligible for inclusion in the Gunnell et al.[18] analysis. The Gunnell et al.[18] analysis differed in other important ways as well. The authors did not have access to the study or patient-level data allowing individual classification of each event identified by the predefined search strategy. Different outcome variables were used than in the FDA and our analyses (i.e., suicide, nonfatal self-harm, and suicidal thoughts data vs. suicidality and suicidal behavior). The study and subject numbers differed substantially from our analysis: although the Gunnell et al.[18] analysis comprised 19% more sertraline trials, it actually had 34% fewer sertraline- and 43% fewer placebo-treated subjects.

Two other previously mentioned meta-analyses by Fergusson et al.[17] and Martinez et al.[19] compared the risks associated with different antidepressant classes but not with individual antidepressants and therefore cannot be compared with our results.

As per the FDA briefing document,[11] the short-term studies analysis included 5821 sertraline- and 5589 placebo-treated patients (i.e., a total of 11,410 subjects), while, in our short-term studies analysis, the totals are somewhat different in that there were 6561 sertraline- and 5480 placebo-treated subjects (i.e., a total of 12,041). The inclusion criteria for the 2 analyses were the same, except for the inclusion of all studies irrespective of the number of subjects per study arm into our analysis. However, on the basis of information contained in the FDA briefing document in the public domain,[11,23] the relatively small difference in total number of subjects included into our versus the FDA short-term study analyses remains unexplained. Nevertheless, despite the difference in the sample sizes described above, both our and the FDA short-term studies analyses obtained the same overall result, demonstrating lack of statistically significant differences in suicidality risk between sertraline and placebo.

The FDA age group analysis results for the sertraline short-term psychiatric studies are consistent with our analysis of age group results for the sertraline psychiatric studies, demonstrating low risk with sertraline for suicidality across all age groups, both < 25 and ≥ 25 years. In the age group < 25 years, the FDA sertraline study analysis of suicidality yielded an OR of 0.99 (95% CI = 0.34 to 2.87) and in the ≥ 25 years group, an OR of 0.62 (95% CI = 0.33 to 1.18),[11] both in favor of sertraline.

Furthermore, among all antidepressants studied by the FDA, in the age group < 25 years, sertraline was associated with a low OR for suicidal behavior and ideation risk (sertraline, OR = 0.84 vs. OR range: fluoxetine, 1.51–fluvoxamine, 4.53).[11] These results in subjects aged < 25 years also concur with a previously reported positive benefit-to-risk ratio for suicidality with sertraline

treatment in adolescents with MDD.[24] In addition, data from a large Veterans Affairs database of 226,866 veterans with a diagnosis of depression demonstrated that SSRIs have a protective effect against suicide attempts across all age groups in this population.[25] This is in agreement with the trend for sertraline in age groups 18 to 24 and 25 to 65 years obtained in our age-group analyses but is at odds with the FDA analysis, which found suicidality positively associated with treatment with antidepressant drugs in subjects < 25 years of age (OR = 1.94, 95% CI = 1.37 to 2.74, p = .0002).[11]

The classification system of suicidality and suicidal behavior-related events developed by Posner et al.,[20] used by the FDA and in our analysis, has received some criticism,[26,27] in particular the fact that it is based on spontaneously reported adverse events and with varying quality of reporting.[20,28] It has also been proposed that this classification system may actually measure the impact of medication on the threshold for spontaneous reporting between the treatments instead of actual suicidal ideation.[28] The alternative scalar approach based on group mean reductions from baseline in the Hamilton Rating Scale for Depression (HAM-D) suicidality item or the Montgomery-Asberg Depression Rating Scale (MADRS) suicidal thoughts item[29,30] has also been criticized. Patients who are typically without active suicidality at baseline are selected into antidepressant studies, thus yielding low baseline item scores. Treatment-emergent suicidality is usually analyzed for patients with baseline HAM-D suicidality item scores of < 3 and is defined as an increase in score of ≥ 3 at any point during the study. The effect of antidepressants is assessed from a perspective of an increase or decrease from baseline in mean group scores.[31–33] Different domains are assessed by the HAM-D suicidality versus MADRS suicidal ideation items, and retrospective classification using this method is limited to those trials in which these instruments were employed.

Although both the HAM-D/MADRS method and the Columbia system provide information on suicidality in clinical trials, it appears that the Columbia classification system developed by Posner et al.[20] currently may provide a better means of retrospective identification of treatment-emergent suicidality and suicidal behavior. It is based on a systematic search and categorization of events occurring during the study and does not rely on the presence of specific preincluded scales and thus has broad applicability across different types of studies.

Inclusion of all-duration studies in our analysis could be of concern as the suicidality risk may be highest at the beginning of antidepressant treatment.[11] The evidence from large-scale epidemiologic studies suggests that in clinical populations the risk of suicide attempt is actually highest during the month before medication was initiated, decreasing with the time in treatment.[34] By extending analyses to the nonacute treatment phase, the suicidality risk could possibly be "diluted." For this reason, we present results based not only on the "all-duration" population but also on the sample of subjects from short-term and psychiatric studies (both further divided into MDD and non-MDD studies), therefore capturing the populations with the indications that may be associated with the highest risk. The all-duration analysis was complementary and performed to provide a full insight into sertraline data.

With respect to excluding studies with no events for analysis, the methods used in the FDA analysis that exclude studies with no events result in several biases that diminish the ability to assess whether treatment differences exist. Studies with no events are, in fact, quite informative in a descriptive manner. Statistically, the lack of precision (i.e., very wide CIs) generated by the reported methods severely limits the confidence of the resulting point estimates. Methods that exclude the majority of clinical trial data based on lack of events result in diminished precision of point estimates and, more importantly, an exaggeration of risk that is introduced by ascertainment bias. In addition, excluding studies with no events will tend to inflate the risk estimate for active treatments. Clinically, the lack of events within the clinical trials is informative, as many of the disease states studied involved populations at increased risk for suicide and related behaviors. Exclusion of studies with no events in either placebo or primary active drug arms may also be problematic because the absence of events may provide some information based on the background rate of events independent of drug effect.[11] For these reasons, studies with no events were included in our analyses.

Recently, there was a wealth of published data on the impact of antidepressant labeling changes in pediatric[35–37] and adult subjects[38–42] subsequent to the FDA analyses. However, the focus of our analyses in this study is assessment of the suicidality risk with sertraline versus placebo. To our knowledge, at the time of preparation of this article, there were only 2 similar publications comparing suicidality risk between a specific antidepressant drug and placebo. Fluoxetine was compared to placebo in subjects with MDD[43] or non-MDD disorders.[44] Both analyses, using slightly different methodology compared to ours, concluded that fluoxetine treatment in adults with MDD or non-MDD disorders did not appear to be associated with the risk of treatment-emergent suicidality. Another study compared the antiepileptic lamotrigine and placebo across a range of indications, including a separate analysis for all psychiatric disorders and bipolar disorder.[45] The results showing no increase in suicidality risk were comparable to the other similar studies, including ours.

In conclusion, results of our analyses on short-term, all-duration and psychiatric studies, based on Pfizer-sponsored, phases 2 through 4, placebo-controlled,

completed studies of sertraline in adults and performed in accordance with the FDA-specified search strategy, show no significant increase in suicidality risk in sertraline- versus placebo-treated patients. An important limitation of these types of analyses, ours as well as those performed by the FDA[11] and Gunnell et al.,[18] is that they are based on data from participants in clinical trials in which active suicidality is a standard exclusion criterion and not data from patients in everyday clinical practice. In order to gain a better understanding of this critically important issue, further research is needed that prospectively and systematically assesses emergence of suicidality and uses specifically designed tools such as the Columbia Suicide Severity Rating Scale.[46]

Drug names: escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lamotrigine (Lamictal and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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