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# Suicide Risk and Symptom Reduction in Patients Assigned to Placebo in Duloxetine and Escitalopram Clinical Trials: Analysis of the FDA Summary Basis of Approval Reports

**ARIF KHAN, MD**

Northwest Clinical Research Center, Bellevue, WA and Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

**KELLY SCHWARTZ, MS**

Northwest Clinical Research Center, Bellevue, WA, USA

***Background.*** *We assessed suicide and suicide attempt risk as well as symptom reduction among 3,282 depressed patients participating in duloxetine and escitalopram clinical trials assigned to either an antidepressant or placebo.*
***Methods.*** *We reviewed the FDA Summary Basis of Approval reports for data regarding safety and efficacy for duloxetine and escitalopram. Furthermore, we compared suicide risk among antidepressant clinical trials in this study with our two previous analyses on seven antidepressant clinical trials.*
***Results.*** *Suicide and suicide attempt risk varied considerably among the three analyses, showing up to ten fold differences. Interestingly, the variability exists across the three reports, rather than between treatments (antidepressants versus placebo).*
***Conclusions.*** *These findings suggest caution in generalizing suicide risk even from a relatively large number of participants and thus, firm conclusions can only be drawn if the number of participants is overwhelmingly large (approximately two million patients). We also noted similar magnitude of response to placebo and antidepressants among the three studies.*

**Keywords** Depression, Antidepressants, Symptom reduction, Suicide, Clinical drug studies

## *INTRODUCTION*

Since the early 1990s, concern that some antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), may increase suicidal behavior has grown considerably (1–5). So much so that the FDA has placed black box warnings on antidepressants including fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, bupropion, venlafaxine, nefazadone, and mirtazapine (see http://www.fda.gov/cder/drug/antidepressants/default.htm). However, the implementation of the warning box is based on limited research data associating SSRI use with increased suicidal behavior (1).

In two earlier publications (6,7), we reported that depressed patients assigned to placebo in antidepressant clinical trials do not have a greater risk for suicide or suicide attempt than patients assigned to an active treatment. Among 19,639 participating patients, the annual suicide and attempted suicide rates in the 2000 report were 0.4% and 2.7% with placebo, 0.7% and 3.4% with active comparators, and 0.8% and 2.8% with investigational antidepressants, respectively. In the 2001 reports, 23,201 patients had annual rates of suicide and attempted suicide of 0.5% and 6.7% with placebo, 0.9% with active comparator (attempted suicide rates not available), and 0.6% and 6.3% with investigational drugs.

Address correspondence to Arif Khan, MD, 1900 116th Ave NE Bellevue, WA 98004. E-mail: akhan@nwcrc.net

We also noted that patients receiving placebo experience a substantial reduction of depressive symptoms, although not of the same magnitude experienced by patients assigned to an active treatment. These findings challenged some assumptions regarding ethical considerations governing the use of placebo in clinical trials (8–13). Although the two earlier reports analyzed data on over 42,000 patients, replication of these former studies is warranted given the continued debate over the use of placebo in antidepressant clinical trials.

Additionally, variability may exist between these two studies and the current study. Although we reported no difference in suicide and suicide attempt rates between patients assigned to placebo and patients treated with an antidepressant, the rates may differ across studies. In the current study, we evaluate potential differences between the three studies.

Since our earlier reviews, two new antidepressants (duloxetine and escitalopram) have been introduced to the United States market. We review the Review and Evaluation of Clinical Data in the Summary Basis of Approval (SBA) reports from the Food and Drug Administration (FDA) for these newer antidepressants. The SBA reports provide a unique overview of clinical trials evolved in the evaluation of a new antidepressant. The SBA reports detail pivotal studies and include information regarding the number of failed trials, effect sizes, baseline rating scale scores, and scores at the final visit for not only the investigational antidepressant, but for the active comparator and placebo as well. The SBA reports regarding suicide and suicide attempts is based on serious adverse events (SAEs) documented by investigators, compiled by sponsors, and then submitted to the FDA.

We assessed the rates of suicide, suicide attempts, and the reduction of depressive symptoms among patients treated with an antidepressant or placebo. For depressive symptom reduction, we examined the data from those trials the FDA considered pivotal, well-designed, and controlled.

## *METHODS*

Under the Freedom of Information Act (14), we accessed public domain FDA clinical trial data for duloxetine and escitalopram through the FDA's website, www.fda.gov. We extracted pertinent information for each drug relating to safety and efficacy from the Review and Evaluation of Clinical Data section in the SBA reports.

The FDA reports ten pivotal trials for these two newer antidepressants. Out of 3,282 patients, 44.6% of patients received a new antidepressant, 19.6% received an established antidepressant, and 35.8% received placebo. Four out of the six duloxetine trials compared duloxetine to an active comparator (fluoxetine or paroxetine). Three out of four escitalopram trials compared escitalopram to citalopram.

To assess safety, we reviewed all available data on the incidence of suicide and suicide attempts for the new antidepressants, active comparators, and placebo. The data presented in Table 1 encompasses both pivotal and non-pivotal studies. For a subset of the patients (based on available data), we estimated the incidence of suicide and suicide attempts using patient exposure years, defined as the cumulative time subjects are exposed to either the new antidepressant, active comparator, or placebo. The suicide risk is calculated at 100,000 per year. To obtain risk, we divided the number of suicides and suicide attempts by the total exposure time. PEY analysis allows us to assess risk based on exposure to a particular treatment (active drug versus placebo) rather than simply evaluating risk based on gross numbers.

We utilized chi-square analysis to determine the presence of statistical differences in the frequencies of suicide and suicide attempts in the escitalopram clinical trials among the three treatment groups (new antidepressant, active comparator, and placebo). Due to the limited data on suicides and suicide attempts in the duloxetine clinical trials, we could not conduct any meaningful analysis.

**Table 1** Incidence of Suicides and Suicide Attempts Among 7,588 Patients in Worldwide Phase I – Phase III Safety Trials of Two New Antidepressants

| | Suicides | | | Suicide Attempts | | |
|---|---|---|---|---|---|---|
| New Antidepressant and Study Group | Number of Patient Exposure Years[a] | N | %[b] | Number of Patient Exposure Years | N | %[b] |
| Duloxetine | | | | | | |
| New Antidepressant (N = 3490) | —[c] | 2 | —[c] | —[c] | 7 | —[c] |
| Established Antidepressant (N = NR) | —[c] | —[c] | —[c] | —[c] | —[c] | —[c] |
| Placebo (N = NR) | —[c] | —[c] | —[c] | —[c] | —[c] | —[c] |
| Escitalopram | | | | | | |
| New Antidepressant (N = 2552) | 645 | 11 | 1.7 | 645 | 4 | 0.6 |
| Established Antidepressant (N = 347) | 65 | 2 | 3.1 | 65 | 0 | 0.0 |
| Placebo (N =1199) | 83 | 2 | 2.4 | 83 | 0 | 0.0 |

[a]Cumulative time that patients were exposed to active drug or placebo while in a research program.
[b]Rates per patient exposure years are determined by number of suicides divided by number of patient exposure years in each treatment cell.
[c]Data not available.
NR equates to scores or numbers not reported in the SBA reports.

To assess efficacy, we analyzed the data from randomized, placebo-controlled clinical trials reviewed by the FDA in support of the drug's indication. We examined the magnitude of symptom reduction with both the antidepressants and placebo by recording the mean total scores on the Hamilton Depression Rating Scale (HAM-D) (15) or the Montgomery-Asberg Depression Rating Scale (MADRS) (16) at baseline and the mean change in total rating scale scores using the last observation carried forward technique (LOCF). With LOCF, patients terminating prematurely from a trial are assumed to experience no further improvement and the last measured HAM-D or MADRS scores are considered the final scores.

In order to assess differences across studies, we analyzed differences in suicide and suicide attempt rates based on PEY data using chi-square analyses (Table 3). We then tabulated the total number of suicide and suicide attempts in all three studies for patients assigned to an investigational antidepressant, an established antidepressant, or placebo. We then utilized chi-square analysis to determine differences in suicide risks among the three treatment groups.

## *RESULTS*

Table 1 lists available information for all patients participating in clinical trials evaluating duloxetine and escitalopram. During the escitalopram clinical trials, 11 patients receiving escitalopram committed suicide and the FDA reports 4 suicide attempts. In the active comparator group, 2 committed suicide and no reports of the patients attempting suicide. Two committed suicide in the placebo treated group, while no patients reportedly attempted suicide while assigned to placebo.

For the escitalopram clinical trials, the overall incidence of suicide based on patient exposure years was 1,892/100,000 per year (15/793). Among the 2,552 patients receiving the new antidepressant, the incidence of suicide rate was 1,705/100,000 per year (11/645); patients receiving an established antidepressant had an incidence of suicide of 3,077/100,000 per year (2/65); among patients receiving placebo, the incidence of suicide was 2,410/100,000 per year (2/83). The differences in suicides between drug treatment groups (new antidepressant, established antidepressant, and placebo) did not reach statistical significance, $\chi^2 = 0.7$, df = 2, p = 0.0705.

The overall incidence of suicide attempts based on patient exposure years was 504/100,000 per year (4/793) among patients participating in the escitalopram clinical trials. Escitalopram treated patients had a suicide attempt rate of 620/100,000 per year (4/645). The FDA did not report any occurrence of suicide attempts for patients receiving either the active comparator (0/65) or placebo (0/83) during these trials. Differences in reported suicide attempts did not approach statistical significance, $\chi^2 = 0.917$, df = 2, p = 0.6322.

Among the 3,490 patients receiving duloxetine, two committed suicide and seven patients attempted suicide. The SBA reports did not disclose information regarding the suicide and suicide attempts among patients receiving an active comparator or placebo during the duloxetine trials, nor did the reports contain patient exposure years. Therefore, we could not conduct any analyses.

Table 2 delineates the mean baseline HAM-D or MADRS scores, as well as the mean change in total rating scale scores at LOCF. Among the 744 patients receiving a new antidepressant in the duloxetine trials, the mean change in HAM-D scores was 38.7%; among the 240 patients receiving an active comparator, 34.0%; and among the 583 patients receiving placebo, 29.1%. In the escitalopram clinical trials, the 720 receiving a new antidepressant, the mean change in MADRS scores was 47.6%; among the 403 patients receiving an established antidepressant, 46.5%; and among the 592 patients receiving placebo, 39.1%.

Also depicted in Table 2 are the patient study completion rates for all three treatment groups. Out of the 10 studies, five favored the new antidepressant, 4 studies favored placebo, and 1 study produced equivalent completion rates for both the placebo group and new antidepressant group.

Table 3 lists the suicide and suicide attempt rates based on available PEY data in each treatment condition for the three studies. In regards to suicide, significant differences exist between patients receiving an investigational medication in the 2001 report (9/1509.3) and patients receiving escitalopram (11/645), $\chi^2 = 5.904$, df = 1, p = 0.015. The 2000 and the 2001 reports did not have differential suicide rates for patients assigned to an investigational medication. We did not note any other significant differences in suicide risks between the placebo groups in the three studies or the active comparator groups.

We observe several significant differences in suicide attempts using PEY data between the three studies. Patients assigned to placebo participating in the clinical trials reported in the 2001 publication (131/192.7) had a significantly higher risk rate than patients receiving placebo in the 2000 publication (15/556), $\chi^2 = 5.914$, df = 1, p = 0.015. Further, patients assigned to placebo in the escitalopram clinical trials (0/83) had a significantly lower suicide attempt rate compared to the 2000 report and 2001 report, $\chi^2 = 9.613$, df = 2, p = 0.008. The suicide attempt rate was significantly higher among patients assigned to an investigational antidepressant in the 2001 report (95/1509.3) compared to those patients treated with an investigational antidepressant in the 2000 report (90/3206) and this report (4/645), $\chi^2 = 50.801$, df = 2, p = 0.000. The suicide attempt rates did not differ in patients assigned to an active comparator in the 2000 report and the current study.

## *DISCUSSION*

We aimed to determine the relative risk of suicide and suicide attempts for patients treated with placebo during clinical trials evaluating duloxetine and escitalopram. We also examined the amount of symptom reduction experienced by depressed patients assigned to placebo during these clinical trials.

**Table 2** Mean Total Baseline HAM-D or MADRS Scores, Mean Change in Total HAM-D or MADRS Scores, and Effect Size of Mean Change in Total HAM-D or MADRS Scores for 8-Week Clinical Trials[a]

| Investigational Drug Protocol No. | Placebo | Investigational Drug | Effect Size | Active Comparator | Effect Size |
|---|---|---|---|---|---|
| Duloxetine hydrochloride | | | | | |
| HMAQa[f,g] | 20.6/–6.6 (70 [66]) | 19.6/–8.3 (70 [66]); 40–120mg | 0.20 | 19.2/–6.6 (33 [64]); 20mg[b] | 0.002 |
| HMAQb[f,g] | 20.4/–6.8 (75 [59]) | 19.9/–6.8 (82 [70]); 40–120mg | 0.01 | 21.4/–7.0 (37 [62]); 20mg[b] | 0.04 |
| HMATb[e,g] | 17.2/–4.2 (88 [61]) | 18.6/–7.2 (84 [70]); 40mg | 0.42 | 17.7/–6.1 (84 [64]); 20mg[c] | 0.26 |
| | | 18.1/–7.7 (86 [64]); 80mg | 0.51 | NA | NA |
| HMATa[f,g] | 17.8/–4.3 (89 [70]) | 17.5/–5.4 (90 [72]); 40mg | 0.16 | 18.0/–6.2 (86 [72]); 20mg[c] | 0.28 |
| | | 17.4/–5.5 (81 [75]); 80mg | 0.19 | NA | NA |
| HMBHa[e,g] | 21.1/–5.2 (122 [71]) | 21.5/–9.3 (123 [65]); 60mg | 0.58 | NA | NA |
| HMBHb[e,g] | 20.5/–7.2 (139 [65]) | 20.3/–8.9 (128 [61]); 60mg | 0.23 | NA | NA |
| Escitalopram oxalate | | | | | |
| MD-01[e,h] | 29.5/–9.4 (122 [75]) | 28.0/–12.8 (119 [80]); 10mg | 0.38 | 29.2/–12.0 (125 [74]); 40mg[d] | 0.26 |
| | | 28.9/–13.9 (125 [75]); 20mg | 0.49 | NA | NA |
| MD-02[f,h] | 28.8/–11.2 (127 [83]) | 28.7/–12.9 (125 [77]); 10–20mg | 0.17 | 28.3/–13.0 (123 [81]); 20–40mg[d] | 0.18 |
| 99001[e,h] | 28.7/–12.0 (189 [85]) | 29.2/–14.9 (191 [84]); 10mg | ..... | NA | NA |
| 99003[e,h] | 28.7/–12.5 (154 [90]) | 29.2/–14.2 (160 [95]); 10–20mg | 0.18 | 29.0/–15.3 (155 [94]); 20–40mg[d] | 0.31 |

[a]Data for placebo-treated patients are given as baseline rating score/mean change in rating score at last observation (number of patients [percentage of completers]). Data for investigational drug and active comparator treated patients are given as baseline rating score/mean change in rating score at last observation (number of patients [percentage of completers]); dose of drug. Scores are rounded to the nearest tenth.
[b]Active comparator is Fluoxetine.
[c]Active comparator is Paroxetine.
[d]Active comparator is Citalopram.
[e]The FDA considered this a positive trial.
[f]The FDA considered this a failed trial.
[g]HAM-D scores presented.
[h]MADRS scores presented.

**Table 3** Suicide and Suicide Attempt Rates Across Three Studies

| | 2000[a] | | 2001[b] | | Current | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | PEY Rate | N | PEY Rate | N | PEY Rate | N | PEY Rate |
| Suicide | | | | | | | | |
| Placebo | 3,079 | 360/100,000 | 976 | 518/100,000 | 1,199 | 2,410/100,000 | 5,254 | 601/100,000 |
| Investigational medication | 12,879 | 842/100,000 | 4,873 | 596/100,000 | 347 | 1,705/100,000 | 18,099 | 877/100,000 |
| Active comparator | 3,681 | 686/100,000 | 1,198 | 948/100,000 | 2,552 | 3,077/100,000 | 7,431 | 896/100,000 |
| Suicide attempts | | | | | | | | |
| Placebo | 3,079 | 2,698/100,000 | 976 | 6,736/100,000 | 1,199 | 620/100,000 | 5,254 | 3,365/100,000 |
| Investigational medication | 12,879 | 2,807/100,000 | 4,873 | 6,296/100,000 | 347 | 0/100,000 | 18,099 | 3,526/100,000 |
| Active comparator | 3,681 | 3,429/100,000 | 1,198 | NA | 2,552 | 0/100,000 | 7,431 | 2,488/100,000 |

[a]Khan A, Warner HA, Brown WA: Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the Food and Drug Administration database. Arch Gen Psychiatry 2000; 57:311–317.
[b]Khan A, Khan SR, Leventhal RM, Brown WA: Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: A replication analyses of the Food and Drug Administration database. Int J Neuropsychopharmacol 2001; 4:113–118.

When comparing the overall rates of suicide and suicide attempts from this current study to our earlier studies, we noticed the significantly higher rates in suicide for all three treatment groups (investigational antidepressant, active comparator, and placebo) in escitalopram trials (1,892/100,000 per year) compared to the Khan et al., 2000 report (757/100,000 per year) and the Khan et al., 2001 report (627/100,000), $\chi^2 = 11.527$, df = 2, p = 0.003. On the other hand, all three treatment groups in the escitalopram trials had a significantly lower risk of suicide attempts (504/100,000 per year) compared to the Khan et al., 2000 study (2,895/100,000 per year) and the Khan et al., 2001 study (6,746/100,000 per year), $\chi^2 = 34.41$, df = 2, p < 0.001.

This variability in suicide risk as measured by the frequency of suicides and suicide attempts among the three different analyses suggest caution in generalizing findings from individual samples of subjects. Paradoxically, completed suicide rates varied by eight fold among the three separate analyses (360/100,000/year to 2,410/100,000/year) among depressed patients assigned to placebo. Oddly enough, suicide risk attempt rates (showing ten fold variability) showed an opposite trend to completed suicides with placebo among the three separate analyses. Interestingly, suicide risk as measured by completed suicides and suicide attempts are more attuned to the series of trials, rather than the assigned treatment condition (placebo versus antidepressant).

These trends suggest extreme caution in interpreting results from small samples, as type I error is likely to occur. In other words, to overcome both type I and type II errors, sample sizes need to be considerably higher in the range of two million patients (2).

Unfortunately, the SBA reports for the duloxetine clinical trials contained minimal information regarding suicide and suicide attempt rates. It has been previously suggested that the FDA utilize CONSORT standards in reporting clinical trial data (17). The current lack of uniformity among the SBA reports limits the utility of such reports.

In regards to efficacy, placebo treated patients experienced a substantial reduction in depressive symptoms (29.1% change in HAM-D scores and 39.1% change in MADRS scores), although not to the same magnitude as patients assigned to an active compound (37.1% change in HAM-D and 47.2% change in MADRS scores). We noted similar results in our earlier reports. Interestingly, the baseline scores appear to be lower in these clinical trials compared to our earlier studies. Past reports (18,19) suggest that higher baseline scores are related to larger drug-placebo differences. The lower baseline rating scale scores in these trials may not have affected the outcomes—50% failure rate in the duloxetine trials and 25% failure rate in the escitalopram trials.

Several factors limited our analysis and conclusions. First, we had limited data regarding suicide and suicide attempts in the duloxetine clinical trials. The FDA also did not provide patient exposure years information for all three treatment groups. Second, the escitalopram reported MADRS scores while the duloxetine trials reported HAM-D scores. Therefore, we could not compare the changes in rating scale scores between the two drugs or provide an overall assessment.

Third, patients participating in antidepressant clinical trials are not representative of the general population of depressed patients. Patients who are actively suicidal or have comorbid psychiatric illnesses typically do not meet criteria to participate in antidepressant clinical trials.

Based on our results, we suggest that placebo use be continued among new antidepressant evaluation trials. This is based on the finding that suicide risk as measures by the frequency of suicides and suicide attempts being similar among depressed patients assigned to placebo compared to antidepressants. Furthermore, placebo treated depressed patients experience considerable symptom reduction. Patients assigned to placebo still receive some type of treatment. Even though the medication is pharmacologically inert, placebo treated patients receive many components of treatment similar to that of psychotherapies (20).

Contrary to expectations, we found that suicide risk varied considerably among the three different analyses we have conducted among depressed patients assigned to placebo and antidepressants. This finding suggests extreme caution in interpreting results from individual trials to represent risk for all depressed patients and treatment conditions.

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