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ARTICLE

Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: a replication analysis of the Food and Drug Administration Database

Arif Khan[1,2], Shirin R. Khan[1], Robyn M. Leventhal[1] and Walter A. Brown[3]

[1] *The Northwest Clinical Research Center, Bellevue, WA, USA*
[2] *The Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA*
[3] *The Department of Psychiatry, Brown University, Providence, RI, USA*

Abstract

The assumption that depressed patients who are assigned to placebo in antidepressant clinical trials are exposed to substantial morbidity and mortality has not been based on research data. Because of worldwide concern about placebo use and the implications of our earlier findings of no increased suicide risk in placebo-treated patients, we conducted a replication study in a new patient sample. We assessed suicide risk and symptom reduction among placebo-treated patients participating in antidepressant clinical trials for two recently approved antidepressants, venlafaxine ER and citalopram, which were unavailable during our previous study. Among 23 201 participant patients, 32 committed suicide and 172 attempted suicide. Rates of suicide and attempted suicide did not differ significantly among the placebo- and drug-treated groups. Based on patient exposure years, annual rates of suicide and attempted suicide were 0.5 and 6.7% with placebo, 0.9% with active comparator (rates for attempted suicide are unavailable), and 0.6 and 6.3% with investigational antidepressants. Symptom reduction was 47.9% with investigational drugs ($n = 1172$), 47.5% with active comparators ($n = 161$), and 35.5% with placebo ($n = 606$). These data may inform discussions about the use of placebo in antidepressant clinical trials.

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Key words: Placebo, suicide and antidepressant treatment, placebo problem, placebo-controlled trials, randomized controlled trial.

Introduction

In a recent report (Khan et al., 2000) we noted that depressed patients assigned to placebo in clinical trials are not at a greater risk for suicide or suicide attempts than patients assigned to an active treatment. Further, depressed patients assigned to placebo in clinical trials experience a substantial reduction of symptoms. These findings generated considerable controversy. They are counterintuitive and have implications for the design of clinical trials and the ethical considerations governing placebo use. Although our original study involved a large patient sample, replication is warranted given the pertinence of these findings to current debates over the use of placebo in antidepressant clinical trials.

Address for correspondence: Dr A. Khan, 1900 116th Ave NE no. 112, Bellevue, WA 98004, USA.
Tel.: (425) 453 0404 *Fax*: (425) 453-1033
E-mail: arif@accessone.com

Two new antidepressants have been introduced to the USA market since our earlier review. Given this opportunity to re-examine and replicate our earlier findings, we reviewed the Food and Drug Administration (FDA) database for these two antidepressants. We assessed rates of suicide, attempted suicide, and depressive symptom reduction.

Materials and methods

Under the Freedom of Information Act (US Congress, 1996), we obtained public domain data on FDA-reviewed studies for venlafaxine hydrochloride ER (Effexor XR) and citalopram hydrobromide (Celexa) by a specific request to the FDA (Freedom of Information Staff, Room 12A-16, 5600 Fishers Lane, Rockville, MD 20857). The data for venlafaxine hydrochloride were sent as a paper copy and citalopram hydrobromide on compact disc for a small fee.

Safety analysis, statistical analysis, efficacy analysis, subject inclusion and exclusion criteria, and study design

Table 1. Incidence of suicides and suicide attempts in worldwide phase I, II, and III investigational antidepressant clinical trials[a]

	Section A. Crude suicide and suicide attempt frequency		
Investigational drug	Patient randomization (*n*)	Suicides (*n*)	Suicide attempts (*n*)
Citalopram hydrobromide[c]			
Investigational drug	19666	27	129
Active comparator	1576	2	24
Placebo	792	2	12
Venlafaxine hydrochloride ER			
Investigational drug	705	1	4[d]
Active comparator	177	0	na
Placebo	285	0	3[d]
All patients in database per treatment group			
Investigational drug	20371	28	133
Active comparator	1753	2	24
Placebo	1077	2	15
Total patients in database	23201	32	172

	Section B. Suicide and suicide attempt frequency rates based on available PEY			
Investigational drug	Patient randomization (*n*)	PEY	Suicides (*n*) (%)[b]	Suicide attempts (*n*) (%)[b]
Citalopram hydrobromide[c]				
Investigational drug	4168	1347.7	8 (0.6)	91 (6.8)
Active comparator	1021	184.3	2 (1.1)	na
Placebo	691	150.3	1 (0.7)	10 (6.7)
Venlafaxine hydrochloride ER				
Investigational drug	705	161.6	1 (0.6)	4 (2.5)[d]
Active comparator	177	26.6	0 (0.0)	na
Placebo	285	42.4	0 (0.0)	3 (7.1)[d]
All patients with PEY per treatment group				
Investigational drug	4873	1509.3	9 (0.6)	95 (6.3)
Active comparator	1198	210.9	2 (0.9)	na
Placebo	976	192.7	1 (0.5)	13 (6.7)
Total patients with PEY	7047	1912.9	12 (0.6)	108 (6.3)

[a] PEY indicates patient exposure years, cumulative time that subjects were exposed to investigational antidepressant, active comparator, or placebo while in a research programme.
[b] Denominator is PEY. Rates per PEY are determined by number of suicides divided by PEY per treatment cell.
[c] Section A includes all data from all clinical trials. Section B includes only phase II/III trials that had available PEY.
[d] Includes suicide events; suicide attempts, intentional overdose, and suicide ideation.
na, Not available.

features are identical to those of our initial study (refer to Khan et al., 2000). Specifically, to assess safety, we reviewed all the available clinical data for incidence of suicides and suicide attempt. In addition to the frequency data, for a subset of patients we were able to estimate the incidence of suicide and suicide attempt based on patient exposure years (PEY; i.e. cumulative time that subjects were exposed to investigational antidepressant, active comparator, or placebo while in the research programme). To assess efficacy, we used the data from randomized, placebo-controlled clinical trials reviewed by the FDA in support of a drug's indication. The available symptom intensity scores were the mean total scores on the Hamilton Depression Rating Scale (HAMD) (Hamilton,

1960) at double-blind randomization (baseline) and at last observation carried forward (LOCF). For LOCF analysis, patients prematurely terminating from the trial are assumed to experience no further improvement; thus, the last measured HAMD scores are considered the final scores.

Results

Table 1 describes the incidence of suicides and suicide attempts for the 23 201 patients participating in clinical trials evaluating the two antidepressants. For the entire database (Table 1, section A), 32 patients committed suicide, 28 while receiving the investigational antidepressant, 2 while receiving the active comparator, and 2 while receiving placebo. For the 23 201 patients, the overall crude suicide mortality rate (number of suicides/number of patients) was 0.14%. Among the 20 371 patients receiving the investigational antidepressant, the crude suicide mortality rate was 0.14%; among the 1753 patients receiving the active comparator, the crude suicide mortality rate was 0.11%; among the 1077 patients receiving placebo, the crude suicide mortality rate was 0.19%. In those trials that included PEY values (Table 1, section B), 12 patients completed suicide, 9 while receiving the investigational antidepressant, 2 while receiving the active comparator, and 1 while receiving placebo. Using PEY, overall incidence of suicide was 627/100 000 per year (12/1912.9) among 6987 patients. Among patients receiving the active comparator, incidence of suicide was 948/100 000 per year (2/210.9); among patients receiving investigational antidepressants, 596/100 000 per year (9/1509.3); and among patients receiving placebo, 519/100 000 per year (1/192.7). The differences in suicide did not reach statistical significance among the 3 treatment groups ($\chi^2_2 = 0.41$; $p =$ ns).

A total of 172 patients attempted suicide in the complete database (Table 1, section A), 133 while receiving the investigational antidepressant, 24 while receiving the active comparator, and 15 while receiving placebo. For the 23 201 patients, the overall crude suicide attempt rate (number of suicide attempts/number of patients) was 0.75%. Among the 20 371 patients receiving the investigational antidepressant, the crude suicide attempt rate was 0.66%; among the 1753 patients receiving the active comparator, the crude suicide attempt rate was 1.37%; among the 1077 patients receiving placebo, the crude suicide attempt rate was 1.39%. In those trials that included PEY values (Table 1, section B), 108 patients attempted suicide, 95 while taking the investigational antidepressant, 13 while taking placebo and no data was available for those patients taking the active comparator. The overall risk was 6345/100 000 per year (108/1702.0); among patients receiving investigational antidepressants, 6294/100 000 per year (95/1509.3); and among patients receiving placebo 6746/100 000 per year (13/192.7). The differences in rates of suicide attempts did not reach statistical significance among the 2 treatment groups ($\chi^2_2 = 0.05$; $p =$ ns).

Table 2 describes the 7 pivotal studies of the 2 antidepressants. A total of 1938 patients participated in these studies; 1172 (60.4%) received the investigational antidepressant; 161 (8.3%) received active comparator; and 606 (31.3%) received placebo. Table 3 delineates the mean baseline total HAMD scores and mean change in total HAMD at LOCF. Among the 1172 patients receiving the investigational antidepressant, the mean decrease in total HAMD score was 47.9%; among the 161 patients receiving active comparator, 47.5%; and among the 606 patients receiving placebo, 35.5%.

Table 2. Summary of pivotal studies for the 2 FDA-approved antidepressants between 1997 and 1998[a]

Antidepressant	Pivotal studies	Studies with active comparator	Studies without active comparator	Randomized patients		
				Investigational antidepressant	Active comparator[b]	Placebo
Citalopram hydrobromide	4[c]	0	4	835	0	333
Venlafaxine hydrochloride ER	3	2	1	337	161	273
All	7	2	5	1172	161	606

[a] Data are given as number of studies or number of patients. FDA indicates Food and Drug Administration.
[b] Active comparators were paroxetine hydrochloride ($n = 80$), or venlafaxine hydrochloride IR ($n = 81$).
[c] FDA considered 5 pivotal studies, however 1 study did not use HAMD for efficacy analysis and was not included from this meta-analysis.

Table 3. Mean total baseline HAMD scores and mean change in total HAMD scores of 4-, 6-, 8-, and 12-wk clinical trials[a]

Investigational drug Protocol no.	Duration[b]	Placebo	Investigational drug	Active comparator
Citalopram hydrobromide				
85A[e]	4	33.7/−9.6 [87 (59)]	33.5/−12.9; 20–80 mg [82 (59)]	na
86141[f]	6	21.0/−5.0 [50 (76)]	22.2/−6.3; 10–30 mg [97 (66)]	na
89303[f]	6	23.7/−10.6 [64 (72)]	24.3/−11.1; 20 mg [68 (75)] 23.0/−13.3; 40 mg [61 (80)]	na
91206[e]	6	24.6/−9.3 [124 (71)]	25.0/−10.8; 10 mg [123 (77)] 24.4/−9.9; 20 mg [128 (71)] 24.4/−12.2; 40 mg [120 (77)] 24.5/−12.1; 60 mg [110 (72)]	na
Venlafaxine hydrochloride ER				
208[e]	12	24.6/−8.7 [91 (47)]	24.4/−14.9; 75–150 mg [85 (58)]	24.0/−12.5[c]; 75–150 mg [81 (48)]
209[e]	8	23.6/−6.8 [100 (51)]	24.5/−11.7; 75–225 mg [91 (66)]	na
367[f]	8	26.6/−13.1 [82 (65)]	26.5/−15.6; 75 mg [83 (64)] 27.1/−14.6; 150 mg [78 (62)]	26.1/−11.3[d]; 20 mg [80 (60)]

[a] HAMD indicates Hamilton Depression Rating Scale (Hamilton, 1960); na, not applicable. Data for placebo-treated patients are given as baseline HAMD score/mean change in HAMD score at last observation [number of patients (percentage of completers)]. Data for investigational drug- and active comparator-treated patients are given as baseline HAMD score/mean change in HAMD score at last observation; oral dose of drug per day [number of patients (percentage of completers)]. Numbers are based on raw table data at baseline. Drug dosages are titrated (range) or fixed (maximum daily dose). Scores are rounded to the nearest tenth.

[b] Duration of trial in weeks.

[c] Active comparator was venlafaxine hydrochloride IR.

[d] Active comparator was sertraline hydrochloride.

[e] The FDA considered this a positive trial.

[f] The FDA considered this a failed trial.

For patients receiving active treatment, and for placebo-treated patients until week 12, total HAMD scores showed a greater decrease as study duration increased. Among depressed patients receiving the investigational antidepressant, the decreases in total HAMD scores were 38.5% in 4-wk trials, 45.1% in 6-wk trials, 53.6% in 8-wk trials, and 61.1% in 12-wk trials. Similarly, among the depressed patients receiving active comparator, the decreases were 43.3% in 8-wk trials and 52.1% in 12-wk trials. Among the placebo-treated patients, these decreases were 28.5% in 4-wk trials, 35.9% in 6-wk trials, 39.6% in 8-wk trials, and 35.4% in 12-wk trials.

The patient study completion rates (Table 3) favoured investigational antidepressants. In the 7 studies, 4 favoured investigational antidepressants, 2 favoured placebo, 1 was equivocal between the investigational antidepressant and placebo, and no study favoured the active comparator.

Discussion

Our aim was to follow-up our previous findings (Khan et al., 2000) in a new sample of patients. Incidence of suicide and suicide attempt was relatively high for patients participating in antidepressant clinical trials. The overall suicide rate was 627/100 000 per year. Our earlier study (Khan et al., 2000) reported the suicide rate as 757/100 000 per year. Interestingly, the Lundby study (Hirshfeld and Davidson, 1998) noted an almost identical suicide rate (650/100 000 per year) in depressed patients. The annual suicide rate for the general population of the USA is 11/100 000 (Vital Statistics, 1999).

The small differences in rates of suicide and attempted suicide (Table 1) among those assigned to antidepressants (investigational or active comparators) compared to those assigned to placebo did not approach statistical significance. The data so far (previous study (Khan et al., 2000) and current report for a combined total of 42 840 depressed patients) suggest that antidepressants (investigational agents or active comparators) do not alter the high suicide rate among depressed patients participating in antidepressant clinical trials ($>$ 60 times that in the general population). In this context, it is interesting to note that Isacsson et al. (1996), reported that suicide rate was decreased by 1.8 times among those treated with antidepressants compared to those not treated with antidepressants. These finding were based on Swedish epidemiological data between 1990 and 1991.

Regarding efficacy, patients who were assigned to placebo treatment experienced substantial symptom reduction, although not of the magnitude experienced by those assigned to antidepressants. These results are similar to those from our earlier analysis (Khan et al., 2000). Interestingly, the magnitude of symptom reduction with placebo did not appear to be related to the outcome of the study. Specifically, among the studies deemed 'positive' by the FDA staff compared to those deemed 'failed' studies (see Table 3), the magnitude of change in mean total HAMD score with placebo did not demonstrate any pattern. However, firm conclusions cannot be derived as the number of studies for this analysis is limited ($n = 7$).

The less-than-impressive difference between drug and placebo in this and other studies of clinical trials does not speak directly to the effectiveness of antidepressants in clinical practice. Participants in antidepressant clinical trials are a highly selected group, not representative of the general population of depressed patients. They are not actively suicidal; they are almost always moderately (not severely or mildly) depressed outpatients; and they are free of comorbid physical or psychiatric illness. They are likely to have a higher placebo response rate than depressed patients who are more severely ill.

Moreover, patients who are assigned to placebo treatment in clinical trials are not untreated. The capsule they receive is pharmacologically inert, but hardly inert with respect to its symbolic value and its power as a conditioned stimulus. In addition, placebo-treated patients receive all the components of the treatment situation common to any treatment, i.e. a thorough evaluation; an explanation for distress; an expert healer; a plausible treatment; expectation of improvement; a healer's commitment, enthusiasm, and positive regard; and an opportunity to verbalize their distress. Frank and Frank (1991) make a compelling case that these ingredients of the treatment situation are the active ingredients of all the psychotherapies.

Finally, our findings must be interpreted in light of both the limitations and strengths of the FDA database. Because clinical trials are designed strictly to test hypotheses regarding the efficacy and safety of new agents, the data generated in these trials and the analytic techniques applied are not ideally suited to test other hypotheses. With regard to suicide, for example, time of exposure to a treatment regimen was not always available and exposure time differed among the treatment regimens. With respect to efficacy, the FDA provides summary reports of the clinical trials which include certain descriptive statistics, such as mean HAMD scores, but measures of variance are not always included and individual patient data and some commonly used measures of treatment outcome, such as responses rates, are not included. Accordingly, it is not possible to carry out subgroup analyses, to combine trial results in formal meta-analyses, or to apply the most suitable analytic approaches in comparing outcome with placebo

and antidepressants. Further, because clinical trials are not designed to identify the optimal effect of antidepressants but rather to rapidly assess their efficacy, dose, duration and patient characteristics may not be ideally suited to identify the optimal effect. Accordingly, clinical trials may identify the lower bound of the effect size.

On the other hand, because the FDA database is singularly large, the incidence of infrequent events such as suicide and suicide attempts can be assessed with relative accuracy. Equally important the data from all clinical trials are included. So, unlike meta-analyses based on published reports, the FDA database is not biased by the exclusion of the negative studies less likely to be published.

In conclusion, depressed patients assigned to placebo in clinical trials experience about 75% of the symptom reduction, and are at no greater risk for suicide than those patients assigned to antidepressants. These findings are to some extent counterintuitive. They challenge some fiercely held assumptions about the ethical conduct of clinical trials and about the value and potency of our treatments. Nonetheless we hope they will usefully inform the debate about the best way to evaluate new treatments.

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