children's attitudes toward physical activity within the school environment.[26]

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Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression

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Abstract

***Objective*—A comprehensive meta-analysis of clinical trial data was performed to assess the possible association of fluoxetine and suicidality (suicidal acts and ideation).**

***Design*—Retrospective analysis of pooled data from 17 double blind clinical trials in patients with major depressive disorder comparing fluoxetine (n=1765) with a tricyclic antidepressant (n=731) or placebo (n=569), or both.**

***Main outcome measures*—Multiple data sources were searched to identify patients with suicidal acts. Suicidal ideation was assessed with item 3 of the Hamilton depression rating scale, which systematically rates suicidality. Emergence of substantial suicidal ideation was defined as a change in the rating of this item from 0 or 1 at baseline to 3 or 4 during double blind treatment; worsening was defined as any increase from baseline; improvement was defined as a decrease from baseline at the last visit during the treatment.**

***Results*—Suicidal acts did not differ significantly in comparisons of fluoxetine with placebo (0·2% *v* 0·2%, p=0·494, Mantel-Haenszel adjusted incidence difference) and with tricyclic antidepressants (0·7% *v* 0·4%, p=0·419). The pooled incidence of suicidal acts was 0·3% for fluoxetine, 0·2% for placebo, and 0·4% for tricyclic antidepressants, and fluoxetine did not differ significantly from either placebo (p=0·533, Pearson's χ^2) or tricyclic antidepressants (p=0·789). Suicidal ideation emerged marginally significantly less often with fluoxetine than with placebo (0·9% *v* 2·6%, p=0·094) and numerically less often than with tricyclic antidepressants (1·7% *v* 3·6%, p=0·102). The pooled incidence of emergence of substantial suicidal ideation was 1·2% for fluoxetine, 2·6% for placebo, and 3·6% for tricyclic antidepressants. The incidence was significantly lower with fluoxetine than with placebo (p=0·042) and tricyclic antidepressants (p=0·001). Any degree of worsening of suicidal ideation was similar with fluoxetine and placebo (15·4% *v* 17·9%, p=0·196) and with fluoxetine and tricyclic antidepressants (15·6% *v* 16·3%, p=0·793). The pooled incidence of worsening of suicidal ideation was 15·3% for fluoxetine, 17·9% for placebo, and 16·3% for tricyclic antidepressants. The incidence did not differ significantly with fluoxetine and placebo (p=0·141) or tricyclic antidepressants (p=0·542). Suicidal ideation improved significantly more with fluoxetine than with placebo (72·0% *v* 54·8%, p<0·001) and was similar to the improvement with tricyclic antidepressants (72·5% *v* 69·8%, p=0·294). The pooled incidence of improvement of suicidal ideation was 72·2% for fluoxetine, 54·8% for placebo, and 69·8% for tricyclic antidepressants. The incidence with fluoxetine was significantly greater than with placebo (p<0·001) and did not differ from that with tricyclic antidepressants (p=0·296).**

***Conclusion*—Data from these trials do not show that fluoxetine is associated with an increased risk of suicidal acts or emergence of substantial suicidal thoughts among depressed patients.**

Introduction

Because depression is an important risk factor for suicide[1-3] there is a need to study the effects of

antidepressants on suicidality (suicidal acts and suicidal ideation) in patients with major depressive illnesses. Though it is generally expected that any treatment that improves the depression is also likely to reduce suicidality, one study did not support this view.[4] It has not been suggested until fairly recently that, paradoxically, worsening of suicidality might in a small subset of patients be associated with the use of antidepressants.[5-10] Five reports[6-10] (one subsequently retracted[11]) have hypothesised that the use of fluoxetine (a serotonin uptake inhibitor) might lead to the emergence or worsening of suicidal ideation in a very small proportion of patients taking this drug. Patients receiving different classes of antidepressants, including fluoxetine, have shown no differences in rates of suicidality,[12] while greater improvement with respect to suicidality has occurred with serotonin uptake inhibitors than with comparative drugs in depressive illnesses.[13-16] Recently Rouillon *et al* reported that maprotiline (a noradrenaline uptake inhibitor) was associated with a greater incidence of suicidal acts than placebo during long term treatment of depression.[12] To examine any possible relation of fluoxetine to the emergence of suicidality, we carried out a comprehensive meta-analysis of all relevant clinical trial data.

Methods

TYPES AND SOURCES OF DATA

The meta-analysis was carried out on the United States investigational new drug depression clinical trial database for fluoxetine; this consists of all double blind, randomised trials of fluoxetine in depression controlled against placebo or tricyclic antidepressants. Trials that had been completed and analysed up to the end of December 1989 were included. The exclusions were: depression trials that had not used a comparative drug, trials that had used a comparator other than placebo or a tricyclic antidepressant, non-blind extensions of controlled trials, non-blind compassionate trials, trials for other potential indications, and pharmacokinetic trials.

For these analyses the clinical trials were organised into five analysis groups: (1) placebo controlled trials (five trials); (2) trials controlled with tricyclic antidepressants (10 trials); (3) trials controlled with placebos and tricyclic antidepressants (two trials); (4) analysis group 1 and the fluoxetine and placebo arms of analysis group 3; and (5) analysis group 2 and the fluoxetine and tricyclic antidepressant arms of analysis group 3. The specific protocols included in each analysis group and the characteristics of the patients studied are summarised in the Appendix.

Potential cases of suicidal acts were first identified electronically by searching two sources: (a) clinical report form data from the trials (for adverse events, reasons for trial discontinuation, Hamilton depression rating scale item 3 scores,[18] and free text comments) and (b) data from the drug experience network for adverse events and outcomes. The drug experience network database contains reports of all serious adverse events (as defined by United States Food and Drug Administration criteria) that have occurred in clinical trials, as well as all adverse events voluntarily reported as part of the manufacturer's (Eli Lilly and Company) post-marketing surveillance.[19] Those clinical comments that had not been transferred to computer were examined by the research staff, and all cases in which it was clear that there had been no suicidal act were eliminated. All remaining cases were then reviewed independently by two Eli Lilly and Company psychiatrists, who were blind to the drug that had been used, to determine whether or not a suicidal act had occurred.

DEFINITIONS

A suicidal act was defined as any behaviour undertaken purposefully from which the outcome was likely to be self harm, and where no explicit data suggested that suicide had not been intended.[3] Actions that might be described as suicidal gestures were not excluded. A suicidal act had to have occurred before or during the day following the last day of double blind treatment, in compliance with the trial protocol. This time limit was adopted for three reasons: post-discontinuation data had not been collected as part of the trials; the end of participation in the trial or withdrawal of the study treatment, or both, might have influenced an event occurring after discontinuation; and other drugs might have been started after the end of the study treatment.

Suicidal ideation was identified by the scores on item 3 of the Hamilton depression rating scale. The scale defines these as: 0=absence of such ideation; 1=doubtful or trivial ideation; 2=mild ideation; 3=active suicidal ideation and suggestive behaviours; and 4=severe ideation, usually involving a suicidal act.

Emergence of substantial suicidal ideation was defined as a change in score on item 3 of the Hamilton depression rating scale from 0 or 1 at baseline to 3 or 4 at any time during the double blind treatment. Emergence of substantial suicidal ideation was evaluated only for those patients whose score was 0 or 1 at baseline.

Worsening of suicidal ideation was defined as any increase in item 3 score from baseline at any time during double blind treatment. Worsening was evaluated only for those patients who could worsen during double blind treatment—that is, those whose score was less than 4 at baseline.

Improvement of suicidal ideation was defined as any decrease in item 3 score from baseline to the last evaluation while the patient was in double blind treatment. Improvement was evaluated only for those patients who could improve during double blind treatment—that is, those whose score was greater than 0 at baseline.

DESIGN

Data were analysed from 17 single centre and multicentre randomised, double blind trials including 3065 patients (1765 receiving fluoxetine, 731 receiving tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline), and 569 receiving placebo). Five trials compared fluoxetine with placebo, 10 compared fluoxetine with a tricyclic antidepressant, and two compared fluoxetine with a tricyclic antidepressant and a placebo.

Fluoxetine doses ranged from 20 mg to 80 mg a day (except in one trial where the range was 5 mg to 40 mg a day); in 15 trials the fluoxetine doses were individually adjusted, and in two the patients were randomly assigned to one of several fixed doses. Doses of tricyclic antidepressants were adjusted individually within current manufacturers' guidelines.

In 16 trials the patients met criteria for non-psychotic major depressive disorder (three trials used Research Diagnostic Criteria,[20] nine trials used the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM-III) criteria for symptoms of one month's duration, and four trials required DSM-III criteria[21]). Most patients had a score $\geq$20 on the 21 item Hamilton depression rating scale (one trial used a score $\geq$18 and one trial included a stratum of patients with scores between 14 and 19), and most did not improve their score by 20% or more during the lead in period (approximately one week of single blind placebo treatment). In one trial the patients were diagnosed by DSM-III criteria as having bipolar disorder and being depressed; they had a baseline score $\geq$20 on the 21 item Hamilton depression rating scale and failed to

show a 20% or greater improvement in this score during placebo lead in.

Written informed consent was given appropriately in all cases.

Exclusion criteria included a history of substance misuse within one year; psychotic or organic mental disorder; serious suicidal risk as clinically assessed by the investigator (suicidal ideation was not a criterion; two inpatient trials did not have an explicit exclusion criterion based on serious suicidal risk); and unstable medical conditions or any medical condition precluding use of one of the drugs used in these studies.

Trials lasted five or six weeks with evaluations about once a week, except in one inpatient trial where there were two evaluations a week for the first two weeks of double blind treatment and one outpatient trial where there were two evaluations during the first week and three during the second week of double blind treatment.

ANALYTICAL AND STATISTICAL METHODS

Descriptive statistics, including the incidence of suicidal acts and the emergence of substantial suicidal ideation (the primary measures) and worsening of suicidal ideation and improvement of suicidal ideation, were computed for all individual trials, for analysis groups 4 and 5, and for all trials combined. Inferential statistical analyses were performed for analysis group 4 (fluoxetine *v* placebo), analysis group 5 (fluoxetine *v* tricyclic antidepressants), and all trials combined. All 3065 randomised patients were included in the analysis of suicidal acts. A total of 1999 patients with a baseline score on item 3 of the Hamilton depression rating scale of 0 or 1 and at least one post-baseline score were included in the analysis of emergence of substantial suicidal ideation. The incidence of worsening of suicidal ideation was based on 2995 patients with a baseline score <4 and at least one post-baseline score. The incidence of improvement of suicidal ideation was based on 2053 patients with a baseline score >0 and at least one post-baseline score.

The incidence difference and corresponding 95% confidence interval was used to compare the incidence of the four outcome variables (suicidal acts, emergence of substantial suicidal ideation, worsening of suicidal ideation, improvement of suicidal ideation) between treatments for individual clinical trials. The incidence difference[22] was defined as the incidence in patients treated with fluoxetine minus the incidence in patients treated with the comparator. An incidence difference greater than 0 implies a numerically higher incidence with fluoxetine than with the comparator; an incidence difference less than 0 implies a numerically higher incidence with the comparator than with fluoxetine; and an incidence difference equal to 0 implies equal incidence.

Owing to potential heterogeneity of trials the adjusted incidence difference, which stratifies by trial, was used to compare the incidence of the four outcome variables between treatments in analysis groups 4 and 5. The individual incidence differences were combined across the clinical trials to form the adjusted incidence difference (also referred to as the adjusted risk difference) by using the binomial, unconditional Mantel-Haenszel estimate (Equation 12).[23] This estimate is an average of the incidence differences of the individual trials weighted by sample size. The variance of the Mantel-Haenszel risk difference (Equation 14)[23] was used to form the 95% confidence intervals (Equation 19)[24] for the adjusted incidence differences and the associated p values (Equation 6·37).[25]

When interpreting the adjusted incidence difference we considered the consistency (homogeneity) of the treatment comparisons across trials. To test for lack of homogeneity of treatment comparisons across trials we used the Breslow-Day test.[26,27] Although the Breslow-Day test is designed to test for homogeneity of odds ratios across trials, it was used here to test for a lack of homogeneity of treatment comparisons across trials in general. Results of the Breslow-Day test were not significant in any analysis; however, it is still useful to consider treatment comparisons by individual trial. Figures 1-4 (given below) show the incidence differences and 95% confidence intervals for individual trials as well as the adjusted incidence differences and the 95% confidence intervals for analysis groups 4 and 5 for the four outcome variables and allow visual inspection of the treatment comparisons.

In addition to heterogeneity of trials, it was important to consider potential differences in baseline distributions of scores on item 3 of the Hamilton depression rating scale across treatments within trials when comparing worsening and improvement of suicidal ideation. Therefore we performed a test of potential differences in these distributions for treatments in analysis groups 4 and 5. Estimators and test statistics used for these comparisons would have been appropriately adjusted for such differences, but none were found.

The Mantel-Haenszel adjusted incidence difference and its associated p value for analysis groups 4 and 5 constitute the primary inferential analytical method for the four outcome variables. This method adjusts for potential heterogeneity across trials and constitutes the basis for all conclusions discussed. In addition, Pearson's χ^2 tests were used for pairwise comparisons of treatment, combining the data across all 17 trials. This analysis is provided because clinical criteria and trial methods were relatively similar across the 17 trials; it constitutes a secondary inferential analysis for the four outcome variables.

Baseline suicidality was measured by the percentage of patients with passive or active suicidal thinking (score on item 3 of the Hamilton depression rating scale ≥ 2) in all patients. Baseline suicidality was measured for all randomised patients with baseline data (2999 of 3065) who had at least one post-baseline measurement.

For all analyses except for the Breslow-Day test statistical significance was defined as $p<0.05$. For the Breslow-Day test $p<0.1$ was considered significant.

The FREQ procedure in SAS 5.18[27] was used for the Breslow-Day test and Pearson's χ^2 test. The incidence difference for individual trials and the adjusted incidence differences for groups of trials were calculated in an SAS data step.

TABLE I—*Characteristics of patients at baseline*

	No of patients	Men (women) (%)	Median (range) (years)	Mean (SD) score on Hamilton depression rating scale	
				21 Items	Item 3
Analysis group 4:					
Fluoxetine	1322	39 (61)	38 (13-70)	23·5 (5·3)	0·9 (0·9)
Placebo	569	41 (59)	37 (12-70)	25·5 (5·5)	1·1 (0·9)
Analysis group 5:					
Fluoxetine	720	34 (66)	43 (19-90)	27·2 (5·4)	1·3 (1·0)
Tricyclics	731	36 (64)	45 (18-88)	27·2 (5·5)	1·4 (1·0)
All trials:					
Fluoxetine	1765	38 (62)	40 (13-90)	24·4 (5·6)	1·0 (1·0)
Tricyclics	731	36 (64)	45 (18-88)	27·2 (5·5)	1·4 (1·0)
Placebo	569	41 (59)	37 (12-70)	25·5 (5·5)	1·1 (0·9)

Results

PATIENTS' CHARACTERISTICS AT BASELINE

Table I lists the baseline characteristics of the patients included in these analyses for analysis groups 4 and 5 as well as the total combined population organised by type of treatment.

SUICIDAL ACTS AND IDEATION

Table II provides a summary of the incidence of the four outcome variables for each individual trial, for the pooled analysis groups 4 and 5, and for the total combined pool of patients organised by treatment. It can be consulted when examining the results of the inferential analyses described below.

SUICIDAL ACTS

During the single blind placebo lead in period of these trials, three suicidal acts (one fatal) were identified. One of these patients was continued in the trial, randomised to fluoxetine, and completed double blind treatment without any further suicidal act.

Figure I presents the incidence differences for the individual trials and the adjusted incidence differences with 95% confidence intervals and p values for pooled analysis groups 4 and 5. The adjusted incidence difference for fluoxetine compared with placebo was 0·2 (−0·3 to 0·7, p=0·494); for fluoxetine compared with tricyclic antidepressants it was 0·3 (−0·4 to 1·1, p=0·419); neither difference approached significance.

The pooled incidence of suicidal acts was 0·3% for fluoxetine, 0·2% for placebo, and 0·4% for tricyclic antidepressants. Pearson's χ^2 test showed no significant difference for either fluoxetine versus placebo (p=0·533) or fluoxetine versus tricyclic antidepressants (p=0·789).

SUICIDAL IDEATION AT BASELINE

Serious suicidal risk, as clinically assessed by the investigator, was an exclusion criterion (except in two trials), but suicidal ideation was not. Analysis of scores for item 3 on the Hamilton depression rating scale, available for 2999 patients, indicated that 1000 (33%) had suicidal ideation at baseline to the extent that the score was ≥2.

EMERGENCE OF SUBSTANTIAL SUICIDAL IDEATION

Figure 2 presents the data for emergence of substantial suicidal ideation. Emergence of substantial suicidal ideation occurred marginally significantly less often with fluoxetine than with placebo (−1·5 (−3·3 to 0·3), p=0·094) and numerically less often with fluoxetine than with tricyclic antidepressants (−1·8 (−4·0 to 0·4), p=0·102).

TABLE II—*Incidence of suicidal acts, emergence of substantial suicidal ideation, worsening of suicidal ideation, and improvement of suicidal ideation in patients with major depressive disorder in 17 double blind clinical trials**

		Suicidal acts		Emergence of substantial suicidal ideation		Worsening of suicidal ideation		Improvement of suicidal ideation	
Trial	Treatment	No of patients	No (%)	No of patients	No (%)	No of patients	No (%)	No of patients	No (%)
Analysis group 1:									
Trial 1	Fluoxetine	55		39		55	3 (5·5)	32	25 (78·1)
	Placebo	56		41	1 (2·4)	56	8 (14·3)	37	23 (62·2)
Trial 2	Fluoxetine	45		39		45	8 (17·8)	34	27 (79·4)
	Placebo	45		37		42	5 (11·9)	36	21 (58·3)
Trial 3	Fluoxetine	21		9	1 (11·1)	21	4 (19·0)	17	16 (94·1)
	Placebo	19	1 (5·3)	8		19	4 (21·1)	15	12 (80·0)
Trial 4	Fluoxetine	639	1 (0·2)	493	4 (0·8)	611	100 (16·4)	309	206 (66·7)
	Placebo	107		87	3 (3·4)	104	20 (19·2)	48	26 (54·2)
Trial 5	Fluoxetine	285		210	2 (1·0)	277	37 (13·4)	171	131 (76·6)
	Placebo	78		53		77	12 (15·6)	52	30 (57·7)
Analysis group 2:									
Trial 6	Fluoxetine	26		9		26		26	23 (88·5)
	Tricyclic antidepressant	24		8		24	1 (4·2)	24	21 (87·5)
Trial 7	Fluoxetine	56	2 (3·6)	31	2 (6·5)	55	17 (30·9)	40	28 (70·0)
	Tricyclic antidepressant	62		33	3 (9·1)	62	15 (24·2)	49	36 (73·5)
Trial 8	Fluoxetine	55		26		55	5 (9·1)	47	36 (76·6)
	Tricyclic antidepressant	54		28		54	2 (3·7)	49	37 (75·5)
Trial 9	Fluoxetine	79		60	2 (3·3)	77	13 (16·9)	50	35 (70·0)
	Tricyclic antidepressant	80		57		76	8 (10·5)	48	32 (66·7)
Trial 10	Fluoxetine	65		39		62	9 (14·5)	36	31 (86·1)
	Tricyclic antidepressant	65		38	1 (2·6)	64	11 (17·2)	45	31 (68·9)
Trial 11	Fluoxetine	32		19		30	1 (3·3)	20	8 (40·0)
	Tricyclic antidepressant	32		24		32	4 (12·5)	23	11 (47·8)
Trial 12	Fluoxetine	65	1 (1·5)	37		65	9 (13·8)	57	43 (75·4)
	Tricyclic antidepressant	71	2 (2·8)	35	4 (11·4)	71	16 (22·5)	63	45 (71·4)
Trial 13	Fluoxetine	31		15		30	5 (16·7)	22	12 (54·5)
	Tricyclic antidepressant	30		16		30	4 (13·3)	21	8 (38·1)
Trial 14	Fluoxetine	28		10	1 (10·0)	28	3 (10·7)	21	16 (76·2)
	Tricyclic antidepressant	30	1 (3·3)	23	1 (4·3)	30	9 (30·0)	15	11 (73·3)
Trial 15	Fluoxetine	6		3		5	2 (40·0)	3	2 (66·7)
	Tricyclic antidepressant	7		3		6	1 (16·7)	5	5 (100·0)
Analysis group 3:									
Trial 16	Fluoxetine	247	2 (0·8)	140	2 (1·4)	244	43 (17·6)	189	137 (72·5)
	Placebo	235		137	6 (4·4)	232	45 (19·4)	183	97 (53·0)
	Tricyclic antidepressant	246		130	6 (4·6)	241	38 (15·8)	195	141 (72·3)
Trial 17	Fluoxetine	30		22		30	3 (10·0)	24	17 (70·8)
	Placebo	29		17		29	6 (20·7)	25	8 (32·0)
	Tricyclic antidepressant	30		23		30	8 (26·7)	22	12 (54·5)
Analysis group 4†	Fluoxetine*	1322	3 (0·2)	952	9 (0·9)	1283	198 (15·4)	776	559 (72·0)
	Placebo	569	1 (0·2)	380	10 (2·6)	559	100 (17·9)	396	217 (54·8)
Analysis group 5†	Fluoxetine*	720	5 (0·7)	411	7 (1·7)	707	110 (15·6)	535	388 (72·5)
	Tricyclic antidepressant	731	3 (0·4)	418	15 (3·6)	720	117 (16·3)	559	390 (69·8)
All trials combined	Fluoxetine	1765	6 (0·3)	1201	14 (1·2)	1716	262 (15·3)	1098	793 (72·2)
	Placebo	569	1 (0·2)	380	10 (2·6)	559	100 (17·9)	396	217 (54·8)
	Tricyclic antidepressant	731	3 (0·4)	418	15 (3·6)	720	117 (16·3)	559	390 (69·8)

*Details of trials are given in the Appendix.

†Includes 277 patients treated with fluoxetine from trials 16 and 17.

The pooled incidence of emergence of substantial suicidal ideation was 1·2% for fluoxetine, 2·6% for placebo, and 3·6% for tricyclic antidepressants. Pearson's χ^2 test showed a lower incidence with fluoxetine than with placebo (p=0·042) or tricyclic antidepressants (p=0·001).

WORSENING OF SUICIDAL IDEATION

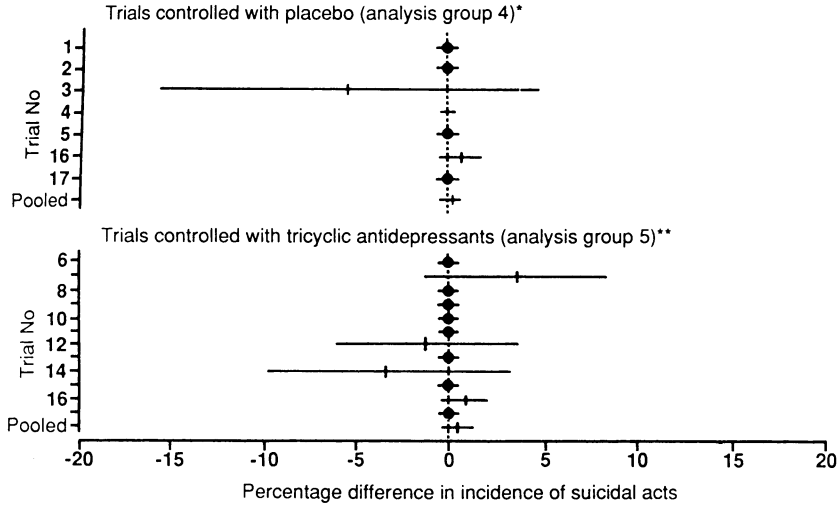
Figure 3 presents the data for worsening of suicidal ideation. For both comparisons worsening of suicidal ideation was similar with fluoxetine and with placebo or tricyclic antidepressants (fluoxetine versus placebo −2·6 (−6·6 to 1·3) p=0·196; fluoxetine versus tricyclic antidepressants −0·5 (−4·2 to 3·2) p=0·793).

The pooled incidence of worsening of suicidal ideation was 15·3% for fluoxetine, 17·9% for placebo, and 16·3% for tricyclic antidepressants. Pearson's χ^2 test showed no significant difference for either fluoxetine versus placebo (p=0·141) or fluoxetine versus tricyclic antidepressants (p=0·542).

IMPROVEMENT OF SUICIDAL IDEATION

Figure 4 presents the data for improvement of suicidal ideation. There was significantly more improvement with fluoxetine than with placebo (18·8 (12·7 to 24·9), p<0·001). Improvement was similar with fluoxetine and tricyclic antidepressants (2·8 (−2·4 to 8·1), p=0·294).

The pooled incidence of improvement of suicidal ideation was 72·2% for fluoxetine, 54·8% for placebo, and 69·8% for tricyclic antidepressants. Pearson's χ^2 test showed significantly more improvement with fluoxetine than with placebo (p<0·001); fluoxetine and tricyclic antidepressants were not significantly different (p=0·296).

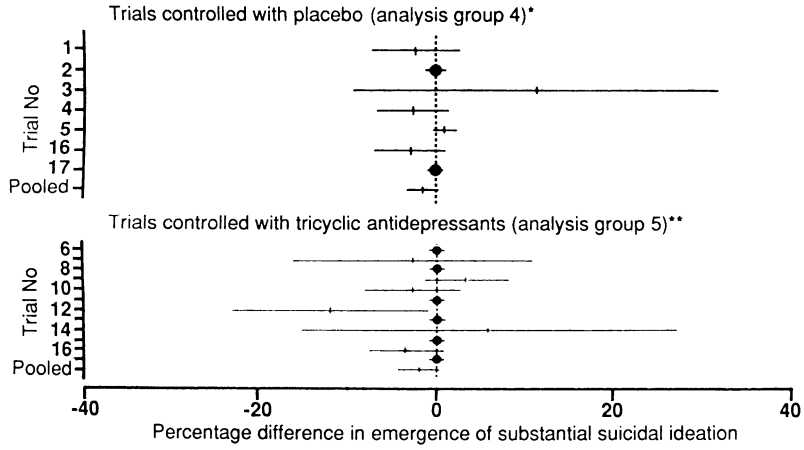


Trial No = as given in Appendix; ◆= observed incidence of 0 in both treatment groups

*Breslow-Day p=0·188; adjusted incidehce difference 0·2(-0·3 to 0·7), p=0·494.

**Breslow-Day p=0·163; adjusted incidence difference 0·3(-0·4 to 1·1), p=0·419.

FIG 1—*Incidence differences and 95% confidence intervals for suicidal acts in trials of fluoxetine controlled with placebo and tricyclic antidepressants*



Trial No = as given in Appendix; ◆= observed incidence of 0 in both treatment groups.

*Breslow-Day p=0·343; adjusted incidence difference -1·5(-3·3 to 0·3), p=0·094.

**Breslow-Day p=0·124; adjusted incidence difference -1·8(-4·0 to 0·4), p=0·102.

FIG 2—*Incidence differences and 95% confidence intervals for emergence of substantial suicidal ideation in trials of fluoxetine controlled with placebo and tricyclic antidepressants*

Discussion

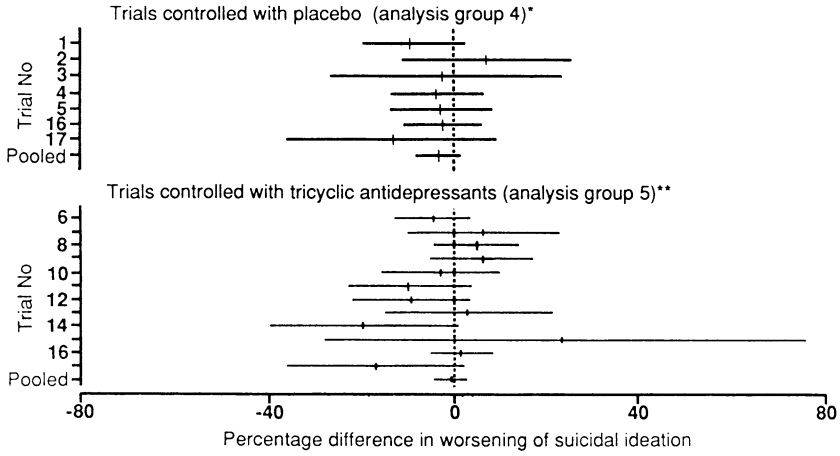
The occurrence of three suicidal acts during the brief placebo lead in period in a population screened to exclude serious suicidal risk emphasises the inherent danger of suicidality in major depressive disorder and its potential for emerging rapidly. The data analysed here, which were systematically collected in a blinded manner from a large total number of patients, do not show either increased risk of suicidal acts or the emergence of substantial suicidal ideation among patients treated with fluoxetine, relative to the risk with a tricyclic antidepressant or placebo. Suicidal acts were infrequent during double blind, controlled trials of fluoxetine lasting up to six weeks (fluoxetine 0·3%, tricyclic antidepressants 0·4%, placebo 0·2%), and the pairwise comparisons by adjusted incidence differences within the pooled analysis groups did not show significant differences between fluoxetine and either placebo or tricyclic antidepressants. It must be kept in mind that if the 95% confidence interval around the adjusted incidence difference for a comparison of interest contains clinically important values (as defined by the reader) then these data may lack sufficient power due to insufficient sample size. However, for fluoxetine versus placebo this interval was −0·3% to 0·7%, and for fluoxetine versus tricyclic antidepressants it was −0·4% to 1·1%.

Substantial suicidal ideation emerged marginally significantly less often with fluoxetine than with placebo (p=0·094, Mantel-Haenszel adjusted incidence difference) and numerically less often with fluoxetine than with tricyclic antidepressants (p=0·102). Worsening to any degree at any time during treatment did not differ with fluoxetine compared with placebo or tricyclic antidepressants. A significantly higher percentage of patients treated with fluoxetine experienced improvement than did patients treated with placebo (p<0·001); there was no significant difference in improvement between patients treated with fluoxetine and those treated with tricyclic antidepressants.

The results of the Pearson's χ^2 analyses for the four outcome variables (suicidal acts, emergence of substantial suicidal ideation, worsening of suicidal ideation, and improvement of suicidal ideation) were consistent with the results obtained with the Mantel-Haenszel adjusted incidence difference analyses. Therefore the χ^2 analyses support the conclusions discussed above drawn from the incidence difference analyses.

The data reported here must be viewed in the context of epidemiological findings regarding depression and suicidality: 15% of patients with major depression will die by suicide,[28] 20-40% will show suicidal behaviour,[29] and up to 80% will experience suicidal ideation.[30] Johnson *et al*, have reported that a community sample of persons meeting criteria for DSM-III major depressive disorder had a lifetime incidence of suicidal acts of 15·4% (7·9% if non-comorbid and 19·8% if major depression was accompanied by other diagnoses).[31]

Black *et al* reported that during a two year follow up of 1076 patients hospitalised for depression 25 suicides occurred (0·0116 suicide deaths per patient year not adjusted for deaths by other causes).[4] Fawcett *et al*

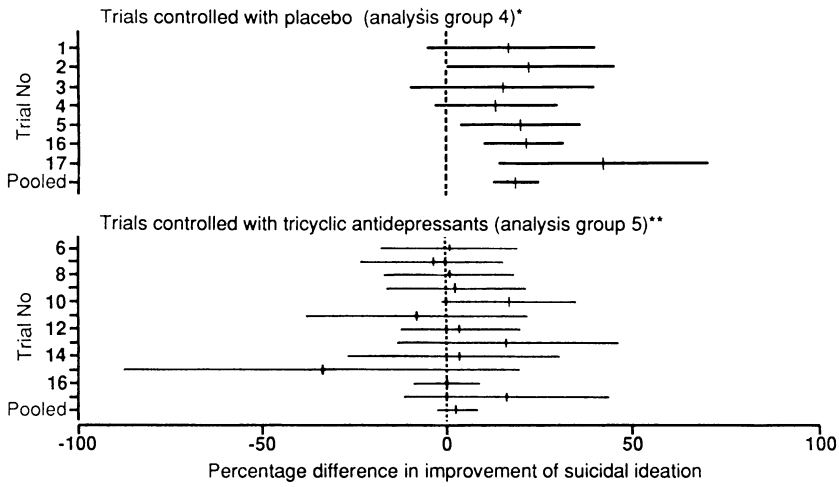


Trial No = as given in Appendix.

*Breslow-Day p=0·724; adjusted incidence difference -2·6(-6·6 to 1·3), p=0·196.

**Breslow-Day p=0·173; adjusted incidence difference -0·5(-4·2 to 3·2), p=0·793.

FIG 3—*Incidence differences and 95% confidence intervals for worsening of suicidal ideation from baseline to highest score in trials of fluoxetine controlled with placebo and tricyclic antidepressants*



Trial No = as given in Appendix.

*Breslow-Day p=0·805; adjusted incidence difference 18·8(12·7 to 24·9), p<0·001.

**Breslow-Day p=0·755; adjusted incidence difference 2·8(-2·4 to 8·1), p=0·294.

FIG 4—*Incidence differences and 95% confidence intervals for improvement of suicidal ideation from baseline to endpoint in trials of fluoxetine controlled with placebo and tricyclic antidepressants*

reported that during a 10 year follow up of 954 depressed patients, 68 suicides occurred (0·0071 suicide deaths per patient year, not adjusted for deaths by other causes).[32] The number of attempts per completed suicide has been variously estimated between eight and 33, with a reasonable estimate being 10 attempts for each fatal suicide.[33,34] Therefore, rates of non-fatal suicidal acts in the cohorts reported by Black *et al* and Fawcett *et al* might be estimated to be 0·116 and 0·071 per patient year, respectively.

Muijen *et al* have reported a significantly greater reduction in suicidal ideation with fluoxetine treatment than with comparators.[14] Sacchetti *et al* have reported that patients with a history of suicidal acts have a higher rate of response (percentage of patients with a 50% or greater reduction in Hamilton depression rating scale score) to fluoxetine and clomipramine than those without a history of such acts and that suicidal patients also show a higher rate of response to these serotonin uptake inhibitors than to nortriptyline and desipramine.[16] Montgomery and Pinder[13] and Wakelin[15] have described studies suggesting that other serotonin uptake inhibitors may also result in significantly better improvement in suicidal ideation. The rate of emergence of suicidal ideation during treatment with fluoxetine presented here is less than half the 3·5% rate suggested in other reports.[6,12] The significant (p<0·001) superiority of fluoxetine compared with placebo with respect to improvement of suicidal ideation and the marginally significant (p=0·094, Mantel-Haenszel adjusted incidence difference; p=0·042, Pearson's χ^2 test) superiority of fluoxetine compared with placebo with respect to emergence of substantial suicidal ideation suggest a potentially beneficial effect for fluoxetine with regard specifically to suicidality. This is consistent with the findings of Muijen *et al* for fluoxetine, as well as with those described by Montgomery and Pinder and Wakelin for other serotonin uptake inhibitors.[13-15]

Though the sample size analysed here was large, the possibility cannot be excluded that some extremely rare phenomenon was not detected. Although item 3 on the Hamilton depression rating scale failed to detect significant differences among the treatment groups with respect to operationally defined emergence of substantial suicidal ideation (baseline score of 0 or 1 increasing to 3 or 4 at any time during treatment), it may not detect important changes in rare, individual patients such as those described by Damluji and Ferguson, Teicher *et al*, and others.[5-7,9,10] It is possible that among the 1·2% of fluoxetine treated, 3·6% of tricyclic treated, and 2·6% of placebo treated patients who experienced the emergence of substantial suicidal ideation there might have been smaller subsets with some very unusual change that differed among the treatments. What these data show is in fact a lack of increased risk with fluoxetine in these clinical trials of up to six weeks' duration. The results obtained here may not be generalisable to a population with different clinical characteristics (patients more seriously suicidal at start of treatment) who have been treated for a longer period.

There is no dispute that both suicidal ideation and suicidal acts are inherent risks associated with depression in general. Therefore, when starting or continuing treatment of any kind with depressed patients clinicians must always remain vigilant for the emergence of suicidal ideation or change in its severity so that appropriate action can be taken.

We thank the following individuals for their review of the data presented here: Dr Jan Fawcett, Rush Medical College and Presbyterian St Luke's Medical Center, Chicago; Dr Jerrold F Rosenbaum, Massachusetts General Hospital, Boston; Gary D Tollefson, St Paul-Ramsey Medical Centre, Minnesota; Dr George Winokur, University of Iowa College of Medicine Psychiatric Hospital, Iowa City; Professor G W Ashcroft, Aberdeen Royal Infirmary, Aberdeen; Professor C L E Katona, University College and Middlesex School of Medicine, London: Professor H Moeller, Neurologic and Psychiatric University Clinic, Bonn; Professor B Mueller-Orlinghausen, Berlin.

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Appendix

TABLE AI—*Double blind clinical trials of fluoxetine versus placebo in depression*

Trial No (reference No)	1 (1,2)	2 (Unpublished)	3 (3)	4 (4-8)	5 (9)
Investigator (city, state or province)	Fabre (Houston, Austin, TX) Finnerty, Goldberg (Boston, MA) Rickels, Case (Philadelphia, PA)	Cohn (Long Beach, CA)	Simeon (Ottawa, ON)	Branconnier (Brookline, MA) Cohn (Long Beach, CA) Crimson (Austin, TX) Dunner (Seattle, WA) Fabre (Houston, TX) Feighner (Encinitas, CA) Fieve (New York, NY) Mendels (Philadelphia, PA) Shrivastava (New York, NY) Smith (Portland, OR)	Chouinard (Montreal, PQ) Cohn (Long Beach, CA) Dessain (Brookline, MA) Fabre (Houston, TX) Feighner (Encinitas, CA) Fieve (New York, NY) Grosser (Salt Lake City, UT) Mendels (Philadelphia, PA) Nysewander (Tucker, GA) Woerner (Springfield, IL)
Total No of patients	111	90	40	746	363
Frequency of visits during double blind phase	Weekly	2/Wk week 1, 3/wk week 2, remainder weekly	Weekly	Weekly	Weekly
Weeks of double blind treatment	5	6	6	6	6
Placebo lead in (length)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)
Placebo response exclusion criteria	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20; or HAMD ≥20% decrease or HAMD <14	HAMD ≥20% decrease or HAMD <20
Diagnostic system	RDC	DSM-III	DSM-III	DSM-III	DSM-III
Diagnostic criteria	MDD	MDD	MDD	MDD	MDD
Inpatient or outpatient	Outpatient	Outpatient	Inpatient or Outpatient	Outpatient	Outpatient
Serious suicidal risk exclusionary	Yes	Yes	Yes	Yes	Yes
Start and finish (month/year)	9/79 to 1/82	11/83 to 5/86	4/84 to 3/88	1/84 to 3/85	9/84 to 3/86
Median (range) age (years)	39 (18-67)	41 (22-62)	16 (12-17)	37 (18-70)	38 (18-65)
% Women	69	50	55	58	61
% White	90	92	100	89	90
Fluoxetine:					
No of patients	55	45	21	639	285
Median (range) days treated	60 (20-80)	60 (20-80)	30 (10-30)	20, 40, or 60 fixed	5, 20, or 40 fixed
Baseline HAMD score:	31 (1-43)	35 (2-47)	41 (5-49)	41 (1-60)	42 (1-56)
Mean (range) 21 items	27·1 (21-40)	25·0 (20-31)	24·6 (19-34)	20·6 (14-35)	25·3 (14-40)
Mean (range) item 3	0·9 (0-3)	0·9 (0-2)	1·8 (0-3)	0·7 (0-4)	0·9 (0-3)
No of suicidal acts				1	
No of patients with score 0 or 1 at baseline and ≥1 double blind score	39	39	9	493	210
No of patients with emergence of substantial suicidal ideation			1	4	2
Placebo:					
No of patients	56	45	19	107	78
Median (range) days treated	34 (4-40)	35 (2-40)	42 (23-49)	42 (5-60)	40 (1-48)
Baseline HAMD score:					
Mean (range) 21 items	27·1 (20-42)	24·1 (20-30)	24·6 (16-35)	20·7 (14-37)	25·8 (20-42)
Mean (range) item 3	1·0 (0-3)	1·0 (0-2)	1·8 (0-3)	0·7 (0-3)	1·0 (0-3)
No of suicidal acts			1		
No of patients with score 0 or 1 at baseline and ≥1 double blind score	41	37	8	87	53
No of patients with emergence of substantial suicidal ideation	1			3	

TX = Texas, MA = Massachusetts, PA = Pennsylvania, CA = California, ON = Ontario, WA = Washington, NY = New York, OR = Oregon, PQ = Québec, UT = Utah, GA = Georgia, IL = Illinois. HAMD = Hamilton psychiatric rating scale for depression; RDC = Research Diagnostic Criteria; MDD = major depressive disorder; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition.

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TABLE A2—*Double blind clinical trials of fluoxetine versus tricyclic antidepressants*

Trial No (reference No)	6 (10)	7 (Unpublished)	8 (Unpublished)	9 (11)	10 (12, 13)	11 (Unpublished)	12 (14-16)	13 (Unpublished)	14 (Unpublished)	15 (Unpublished)
Investigator (city, state or province)	Bremner (Olympia, WA) Shopsin (New York, NY)	Davis (Chicago, IL) Feighner (Encinitas, CA) Rosenbaum (Ann Arbor, MI) Stokes (New York, NY)	Feighner (Encinitas, CA) Kiev (New York, NY) Masco (New Port Richey, FL)	Cohn (Long Beach, CA) Feighner (Encinitas, CA)	Fawcett (Chicago, IL) Preskorn (Wichita, KS) Zung (Chapel Hill, NC)	Friedhoff (New York, NY)	Chouinard (Montreal, PQ) Feighner (Encinitas, CA) Masco (New Port Richey, FL)	Cole (Belmont, MA)	Bowden (San Antonio, TX) Rosenbaum (Ann Arbor, MI) Schatzberg (Belmont, MA)	Mann (New York, NY)
Total No of patients	50	118	109	159	130	64	136	61	58	13
Frequency of visits during double blind phase	Weekly	2/Wk first and second wks, remainder weekly	Weekly	Weekly	Weekly	Weekly	Weekly	Weekly	Weekly	Weekly
Weeks of double blind treatment	5	6	6	6	6	6	5	6	6	6
Placebo lead in (length)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)	Yes (one week)
Placebo response exclusion criteria	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20
Diagnostic system	RDC	DSM-III	DSM-III	DSM-III	DSM-III	DSM-III	RDC	DSM-III	DSM-III	DSM-III
Diagnostic criteria	MDD	MDD (1 month)	MDD (1 month)	MDD (1 month)	MDD (1 month)	MDD (1 month)	MDD	MDD (1 month)	MDD (1 month)	MDD (1 month)
Inpatient or outpatient	Outpatient	All initially inpatient, moved to outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Outpatient	Inpatient (amended to inpatient or outpatient)	Inpatient (amended to inpatient admission then outpatient)
Serious suicidal risk exclusionary	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Start and finish (month/year)	1/80 to 10/80	10/81 to 8/84	5/81 to 3/88	5/81 to 2/88	12/85 to 5/88	1/86 to2/88	3/80 to 11/83	12/85 to 3/88	5/87 to 6/89	9/88 to 9/89
Median (range) age (years)	43 (23-69)	42 (19-69)	39 (20 to 67)	69 (61-90)	46 (22-71)	70 (65-81)	45 (19-69)	39 (19-62)	38 (19-64)	38 (23-67)
% Women	58	81	55	57	62	66	70	57	59	92
% White	100	86	94	97	96	95	96	98	86	77
Fluoxetine:										
No of patients	26	56	55	79	65	32	65	31	28	6
Median (range) days treated	60 (40-80)	80 (20-80)	80 (20-80)	40 (20-80)	20 (20-40)	20 (20-40)	80 (20-80)	20 (20-40)	20 (20-60)	20 (20-20)
Baseline HAMD score:	35 (5-42)	28 (1-48)	42 (2-48)	40 (3-49)	42 (3-52)	43 (8-66)	35 (1-40)	40 (3-57)	42 (7-51)	39 (10-42)
Mean (range) 21 items	35·7 (20-44)	27·9 (17-39)	30·1 (19-42)	25·0 (20-39)	25·0 (20-37)	24·4 (7-35)	28·5 (20-41)	26·7 (19-38)	25·4 (19-34)	25·5 (22-31)
Mean (range) item 3	1·8 (1-3)	1·3 (0-3)	1·7 (0-3)	0·9 (0-3)	1·0 (0-3)	1·0 (0-2)	1·6 (0-3)	1·5 (0-3)	1·6 (0-3)	1·3 (0-4)
No of suicidal acts		2					1			
No of patients with score 0 or 1 at baseline and ≥1 double blind score	9	31	26	60	39	19	37	15	10	3
No of patients with emergence of substantial suicidal ideation		2		2					1	
Tricyclic antidepressant:	Imipramine	Imipramine	Doxepin	Doxepin	Amitriptyline	Doxepin	Amitriptyline	Doxepin	Desipramine	Nortriptyline
No of patients	24	62	54	80	65	32	71	30	30	7
Median (range) days treated	175 (75-300)	175 (25-300)	200 (50-300)	100 (25-200)	150 (0-200)	150 (50-150)	175 (50-300)	150 (50-200)	150 (50-300)	50 (50-50)
Baseline HAMD score:	35 (5-36)	29 (1-49)	42 (2-50)	29 (1-48)	29 (1-50)	43 (1-50)	35 (2-43)	22 (1-46)	42 (7-48)	42 (15-42)
Mean (range) 21 items	37·7 (30-46)	27·0 (6-43)	28·0 (19-38)	25·9 (18-37)	24·4 (20-34)	24·8 (20-30)	28·0 (19-43)	28·3 (22-46)	25·7 (19-36)	25·9 (20-30)
Mean (range) item 3	1·8 (1-3)	1·5 (0-3)	1·6 (0-3)	0·9 (0-3)	1·2 (0-3)	1·0 (0-2)	1·7 (0-3)	1·4 (0-3)	0·9 (0-3)	2·0 (0-4)
No of suicidal acts							2		1	
No of patients with score 0 or 1 at baseline and ≥1 double blind score	8	33	28	57	38	24	35	16	23	3
No of patients with emergence of substantial suicidal ideation		3			1		4		1	

WA = Washington, NY = New York, IL = Illinois, CA = California, MI = Michigan, FL = Florida, KS = Kansas, NC = North Carolina, PQ = Québec, MA = Massachusetts, TX = Texas.
HAMD = Hamilton psychiatric rating scale for depression; RDC = Research Diagnostic Criteria; MDD = major depressive disorder; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition.

TABLE A3—*Double blind clinical trials of fluoxetine versus tricyclic antidepressants versus placebo in depression*

Trial No (reference No)	16 (17-22)	17 (23)
Investigator (city, state or province)	Abuzzahab (Minneapolis, MN) Bremner (Olympia, WA) Cohn (Long Beach, CA) Dunner (Seattle, WA) Goldstein (Miami, FL) Grosser (Salt Lake City, UT) Feighner (Encinitas, CA)	Cohn (Long Beach, CA)
Total No of patients	728	89
Frequency of visits during double blind phase	Weekly	Weekly
Weeks of double blind treatment	6	6
Placebo lead in (length)	Yes (one week)	Yes (one week)
Placebo response exclusion criteria	HAMD ≥20% decrease or HAMD <20	HAMD ≥20% decrease or HAMD <20
Diagnostic system	DSM-III	DSM-III
Diagnostic criteria	MDD (1 month)	Bipolar depression
Inpatient or outpatient	Outpatient	Outpatient
Serious suicidal risk exclusionary	Yes	Yes
Start and finish (month/year)	11/80 to 4/84	6/82 to 9/84
Median (range) age (years)	39 (18-70)	39 (18-70)
% Women	66	66
% White	94	96
Fluoxetine:		
No of patients	247	30
Median (range) days treated	80 (20-80)	60 (20-80)
Baseline HAMD score:	41 (1-55)	42 (3-48)
Mean (range) 21 items	27·1 (15-44)	27·7 (21-40)
Mean (range) item 3	1·3 (0-4)	1·1 (0-3)
No of suicidal acts	2	
No of patients with score 0 or 1 at baseline and ≥1 double blind score	140	22
No of patients with emergence of substantial suicidal ideation	2	3
Tricyclic antidepressant:	Imipramine	Imipramine
No of patients	246	30
Median (range) days treated	175 (25-300)	138 (50-300)
Baseline HAMD score:	40 (1-55)	42 (2-57)
Mean (range) 21 items	27·6 (20-44)	26·0 (20-37)
Mean (range) item 3	1·4 (0-3)	1·0 (0-2)
No of suicidal acts		
No of patients with score 0 or 1 at baseline and ≥1 double blind score	130	23
No of patients with emergence of substantial suicidal ideation	6	
Placebo:		
No of patients	235	29
Median (range) days treated	29 (1-50)	22 (6-45)
Baseline HAMD score:		
Mean (range) 21 items	27·4 (17-45)	27·2 (20-35)
Mean (range) item 3	1·3 (0-3)	1·3 (0-2)
No of suicidal acts		
No of patients with score 0 or 1 at baseline and ≥1 double blind score	137	23
No of patients with emergence of substantial suicidal ideation	6	

MN = Minnesota, WA = Washington, CA = California, FL = Florida, UT = Utah.
HAMD = Hamilton psychiatric rating scale for depression; MDD = major depressive disorder; DSM-III = Diagnostic and Statistical Manual of Mental Disorder, 3rd edition.

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