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Fluoxetine Increases Suicide Ideation Less than Placebo During Treatment of Adults with Minor Depressive Disorder

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Abstract

Objective—Some reports suggest an increase in suicide ideations and behaviors in patients treated with antidepressants. This is an analysis of the impact of fluoxetine on suicide ideations in outpatients with Minor Depressive Disorder.

Methods—Research subjects were adult outpatients with Minor Depressive Disorder (N=162), who received fluoxetine or placebo in a prospective, 12-week, double blind randomized trial. The research participants were evaluated weekly with standard rating scales that included 4 suicide-related items; item 3 of the Hamilton Rating Scale for Depression (HRSD), item 18 of Inventory of Depressive Symptomatology (IDS-C), and items 15 and 59 of the Hopkins Symptom Checklist (SCL-90). Clinically significant intensification of suicide ideation was defined as an increase of 2 on any of these items.

Results—Overall 60/162 subjects (37%) had an increase of 1 point during treatment and 17/162 (10.5%) of 2 points on at least one suicide item, with 12/81 (14.8%) placebo and 5/81 (6.2%) fluoxetine treated subjects having a 2 point gain. Of the study participants with baseline suicide ideation, 9/22 (40.9%) placebo and 3/24 (12.5%) fluoxetine treated had 2 point increase (p=0.04). Survival analysis revealed that subjects on placebo were significantly more likely

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($p=0.050$) to experience a 2 point increase on one or more item, a difference that emerged early and continued throughout the 12-week trial.

Conclusions—Compared to placebo, fluoxetine was not associated with a clinically significant increase in suicide ideation among adults with Minor Depressive Disorder during 12 weeks of treatment.

Keywords

Minor Depressive Disorder; fluoxetine; antidepressant; treatment emergent suicide ideation

Introduction

Soon after the introduction of the selective serotonin reuptake inhibiting (SSRI) antidepressants, case reports linking these drugs to treatment emergent suicide related behaviors and ideations appeared in the literature (Dasgupta 1990; Hoover 1990; Teicher, Glod et al. 1990; Masand, Gupta et al. 1991). The FDA conducted an extensive reanalysis of the existing clinical trial data in response to the public health implications of the potential relationship of antidepressant medications to worsening suicide ideations and behaviors (Hammad, Laughren et al. 2006). This resulted in a class warning for all antidepressants informing of the potential increased risk of suicidal thinking and behaviors for children, adolescents and young adults taking these medications (US Food and Drug Administration 2007).

The relationship between antidepressants and suicide ideations and behaviors has been investigated with a variety of methods including case reports (Dasgupta 1990; Hoover 1990; Teicher, Glod et al. 1990), analysis of large clinical samples of convenience (Gibbons, Brown et al. 2007; Barbui, Esposito et al. 2009), population based epidemiological analysis (Isacsson, Bergman et al. 1996; Gibbons, Hur et al. 2005; Milane, Suchard et al. 2006; Nakagawa, Grunebaum et al. 2007), and reanalysis of previously completed clinical trials (Khan, Warner et al. 2000; Khan, Khan et al. 2003; Leon, Solomon et al. 2011). Despite these efforts, the controversy persists, with multiple publications supporting increased risk of suicide ideations and behaviors due to antidepressant treatment while others report no harm and even possible protective benefit (Healy 1994; Healy, Langmaak et al. 1999; Healy and Whitaker 2003; Lapierre 2003).

One confound in these analyses is the impact of the underlying mood disorder as a potential source of suicide ideations and behaviors independent of medication exposure. Thoughts of death and suicide are very common in depressed patients and are often the motivating factor that brings people into treatment (Simon and Savarino 2007). One strategy to counter this potential confound is to scrutinize the relationship of antidepressant medications to suicide ideations in disorders other than major depressive disorder or in patients with less severe mood symptoms.

This report is a secondary analysis of adult outpatients with Minor Depression who were enrolled in a placebo controlled efficacy trial of fluoxetine for this condition (Judd, Rapaport et al. 2004). The expectation was that due to the lower overall depression severity of these subjects and the low levels of suicide ideation at treatment initiation that a causal relationship between medication exposure and emergent suicide ideations would be more readily observed. One advantage to the use of this dataset is that severity of suicide ideation was measured with four different items in two clinician-rated and one patient-rated scale. The hypothesis was that administration of fluoxetine to research participants with Minor Depression would lead to a greater incidence of treatment emergent suicide ideation than placebo.

Methods and Materials

Study Overview

This is a *post hoc* analysis of data gathered in an efficacy trial of fluoxetine for the treatment of Minor Depressive Disorder (full details of the completed study are available at (Rapaport, Judd et al. 2002; Judd, Rapaport et al. 2004)). This was a three-site clinical trial conducted at outpatient, academic mood disorder research clinics (University of California, San Diego; University of Pittsburgh; and University of Texas, Southwestern Medical Center in Dallas) between 1994 and 1996. The study consisted of three phases: 1) screening and diagnosis followed by 4 weeks of single blind placebo treatment; 2) 12 week placebo controlled double-blind trial of fluoxetine with those subjects who continued to meet inclusion criteria after the placebo run in; 3) 24 week randomized cross over continuation phase. The analysis presented in this manuscript is based on those subjects who entered the 12-week treatment phase. After the 4-week placebo lead-in, 162 subjects with stable Minor Depressive Disorder entered double-blind treatment, and 81 were assigned to each condition and 59 (72.8%) of each group completed the full 12 weeks. The Institutional Review Board at each institution reviewed and approved of the conduct of the trial and all study participants did provide written informed consent.

Study Participants

The detailed definition of Minor Depression was presented elsewhere (Rapaport, Judd et al. 2002), but was based on symptomatic criteria from the National Institutes of Mental Health Diagnostic Interview Schedule (DIS), and functional impairment measured by the Global Assessment of Functioning (GAF) and the Medical Outcomes Study 36-Item Short Form Health Survey. To enter the acute, 12-week treatment phase subjects had to maintain this diagnosis throughout the 4-week placebo lead in. Subjects were excluded at screening for clinically serious suicide risk defined as HRSD item 3 score of 3 or 4, or an IDS-C item 18 score of 3, or based on the clinical judgment of study physicians.

Assessments

Study participants were evaluated weekly with standard depression rating instruments including the Hamilton Rating Scale for Depression (HRSD)(Hamilton 1960), the clinician rated Inventory of Depressive Symptoms (IDS-C)(Rush, Giles et al. 1986) and the subject rated 90-item Hopkins Symptom Checklist (SCL-90)(Derogatis, Lipman et al. 1973). These three rating scales contain four suicide related items, each with 4 or 5 response levels ranging from none to serious or extremely frequent thoughts of death or suicide: Item 3 of the HRSD, item 18 of the IDS-C; and Items 15 and 59 of the SCL-90 (Table 1).

Statistical Analysis

Clinically significant treatment emergent suicide ideation was defined as 2 point increase over baseline values on any of the 4 items. The 81 participants randomized to each treatment group had sufficiently low scores on all four items at baseline to allow for a 2 point rise during treatment. Smaller increases (1 point) were also analyzed. The entire 162-subject cohort was analyzed for increases in suicide item scores and these analyses were repeated separately on the participants with and without baseline suicide ideation. Baseline suicide ideation was defined as any response above "none" on any of the 4 items across the three scales.

Categorical variables were compared with contingency tables utilizing chi-square or Fisher's Exact statistics. Kaplan-Meier survival analyses (LIFETEST procedure in SAS version 8.2) were performed to compare treatment groups on the time to an increase (1 or 2 points) in suicide ideation symptoms on *any* (i.e., 1 or more) of the four items and the survival

distributions were compared with Wilcoxon test. An overall hazard ratio was derived through Cox proportional hazards regression analysis (SAS PHREG procedure).

Results

Among the 162 subjects who entered the double-blind treatment phase, there were no differences between placebo and fluoxetine treated -groups in demographic, disease or clinical characteristics (Table 2). Across the entire cohort, 60 (37%) subjects experienced an increase of 1 point on at least one item and 17 (10.5%) had a 2 point increment. Of the placebo treated subjects 34/81 (42%) had a 1 point increase on at least one item compared to 26/81 (32.1%) of the fluoxetine treated participants. A similar pattern is observed for those participants with a 2 point increase, with 12/81 (14.5%) placebo and 5/81 (6.2%) fluoxetine treated subjects having this outcome. While numerically more placebo treated subjects had an increase in suicide item scores of 1 or 2 points, these results were not statistically significant.

There were 46 (28.4%) subjects with suicide ideation at baseline, and 28/46 (60.9%) had a 1 point increase on at least one suicide item and 12/46 (26.1%) had a 2 point gain during the 12-week double blind treatment phase. There was a significant difference between treatment groups in worsening suicide item scores in study participants with baseline suicide ideation. Of these subjects, 17/22 (77.3%) placebo and 11/24 (45.8%) fluoxetine treated participants had a 1 point increase ($p<0.04$) and 9/22 (40.9%) placebo and 3/24 (12.5%) fluoxetine had 2 point increase ($p<0.04$). There was no difference between treatment groups for subjects without suicide ideation at baseline, with 17/59 (28.8%) placebo and 15/57 (26.3%) fluoxetine treated participants having a 1 point increase and 3/59 (5.1%) placebo and 2/57 (3.5%) fluoxetine treated having a 2 point increase.

Survival analysis of the full 162-subject sample reveals that those in the placebo group had a significantly greater likelihood ($\chi^2=3.83$; $df=1$; $p=0.050$) of developing a 2 point increase on one or more item (Table 3). There was no difference between treatment groups for a 1 point increase on any of the suicide related items. Among the 46 participants with suicide ideation at baseline, placebo treated subjects were more likely to have an increase of 1 point ($\chi^2=3.79$; $df=1$; $p<0.052$) or 2 points ($\chi^2=4.69$; $df=1$; $p<0.03$) on the suicide related items. Subjects without baseline suicide ideation did not differ in the emergence of suicide ideation during the 12-week treatment period.

The endorsement rate of the four suicide related items varied considerably among the participants entering the double blind phase. At the start of treatment, 15 subjects (9.3%) had an HRSD item 3 score of 1 or 2; 18 (11.1%) had an SCL-90 item 15 score of 2 or 3; 20 (12.4%) had an IDS-C item 18 score of 1 or 2; and 35 (21.6%) had an SCL-90 item 59 score of 2 or 3. The survival distribution functions for a 2 point increase for the 4 items varied considerably in detecting treatment group differences. HRSD item 3 and SCL-90 item 15 were least sensitive in distinguishing treatment groups (Wilcoxon Chi-Square p value for HRSD item 3= 0.319 ; for SCL-90 item 15, $p=0.393$). IDS-C item 18 was more sensitive in detecting treatment group differences (Wilcoxon $p = 0.082$, with earlier increases in the placebo group). SCL-90 item 59 was the most sensitive in detecting treatment group differences in worsening of suicide related item score (Wilcoxon $p = 0.066$, with earlier increases in the placebo group).

Discussion

When compared to placebo, fluoxetine was not associated with clinically significant treatment emergent suicide ideation among adults with Minor Depressive Disorder

participating in a randomized 12-week efficacy trial. In fact, subjects in the placebo group showed an early and sustained increase in suicide ideation compared to those in the fluoxetine group and more of these participants had a 1 and 2 point increase in one of the suicide related items. The hypothesis that fluoxetine treatment would be associated with an increase in suicide ideation over placebo is not supported by these results. The subjects who were most at risk for worsening of suicide ideations, regardless of treatment were those who endorsed this symptom at baseline, with 26.1% having a 2 point increase on at least one item during the trial. The subjects with baseline suicidal ideations who were most likely to have treatment emergent worsening were those receiving placebo. The number needed to harm (NNH) for a 2 point worsening on one of the scales for subjects with baseline suicide ideation treated with placebo is 3.2. The NNH for placebo treatment suggests that worsening suicide ideation is common among patients with untreated Minor Depressive Disorder.

The results of this analysis are consistent with other reports of the impact of fluoxetine on suicide ideation. In one meta-analysis of the clinical trial database of double-blind, placebo controlled studies of fluoxetine in subjects with major depressive disorder conducted by the manufacturer (17 trials with 1765 fluoxetine, 731 tricyclic antidepressant and 569 placebo exposed participants), that also utilized a 2 point increase of HRSD item 3, placebo treatment resulted in slightly more worsening of suicide ideation than fluoxetine (Beasley, Dornseif et al. 1991). This group repeatedly performed and published meta-analyses of their clinical trial database as it expanded with completed studies, and consistently reported no evidence of fluoxetine-induced treatment emergent suicide ideations or behaviors compared to placebo (Tollefson, Fawcett et al. 1993; Beasley, Ball et al. 2007). A recent pooled analysis of fluoxetine and venlafaxine clinical trials found that fluoxetine and venlafaxine improved suicide ideations and depressive symptoms with no evidence of treatment emergent suicide ideas or behaviors (Gibbons, Brown et al. 2012). Meta-analysis of the bupropion clinical trial database yields the same result of no treatment emergent suicide ideations and of improvement in depression severity (Wightman, Foster et al. 2010). Analysis of the complete set of clinical trials of paroxetine conducted by the manufacturer also revealed no difference between active drug and placebo in treatment emergent suicide ideations or behaviors across all indications investigated (Carpenter, Fong et al. 2011). However, among subjects with Major Depressive Disorder there were more suicide attempts in the paroxetine group than in placebo (0.32% paroxetine versus 0.05% placebo). Thus the results of meta-analyses performed on clinical trial results for three classes of antidepressant medication are in agreement with our findings.

The results of this study help clarify whether depressive symptom severity is a factor that confounds efforts to detect the relationship of antidepressant exposure to treatment emergent suicide ideation. The participants in this study had a depression spectrum illness, Minor Depressive Disorder, with symptom severity approximately half that (baseline HRSD₁₇₌₁₁) observed in most published efficacy trials of antidepressant medications in Major Depressive Disorder. Among the 71.6% of the total sample who had no suicide ideation at baseline, there was negligible emergent ideation and no difference between treatment groups. These results are in agreement with publications investigating the development of SSRI-related treatment emergent suicide ideations and behaviors in other psychiatric and non psychiatric conditions (Beasley, Potvin et al. 1992; Wheadon, Rampey et al. 1992; Goldstein, Rampey et al. 1993; Warshaw and Keller 1996; Tauscher-Wisniewski, Disch et al. 2007; Phillips and Kelly 2009).

The four suicide related items included in the assessment instruments differed considerably in their ability to detect changes in suicide ideation. SCI-90 item 59 (self-reported thoughts of death or dying) was the most sensitive item in both regards; however, this is the only one of the four that does not specifically refer to suicide thoughts or actions. Evidence suggests

that thoughts of dying as a symptom are more persistent and slower responding than frank ideas of suicide (Szanto, Mulsant et al. 2003). Translating these results to clinical practice suggests that clinicians should query a number of different symptoms related to thoughts of death and suicide to adequately assess for this throughout the course of treatment. General questions about thoughts of death and dying as well as more specific focus on suicide ideations and behaviors should be routine in all clinical assessments of patients with mood disorders.

There are certain limitations to this study that need to be considered when evaluating the results. This is a secondary analysis of an efficacy trial that was not specifically designed or powered to address the potential relationship between fluoxetine treatment and suicide ideation. The total number of subjects in the subgroups who experienced a worsening of suicide ideation is small so the study may be under-powered to fully evaluate this effect. Another potential limitation is the focus on rating scale-based assessment of suicide risk, with no other outcome measures such as adverse event reports, as has been employed in other analyses of this question. However none of the subjects attempted suicide or were withdrawn from the trial for critical worsening of suicide ideation or behaviors. Patients with HRSD item 3 score or IDS-C item 18 above 2 were excluded as were those considered at high suicide risk by the investigators during screening. Therefore, the study sample may have been depleted of those most at risk to experience antidepressant-induced treatment emergent suicide ideations and behaviors and so underestimate this outcome. A final consideration is that this trial included adults with minor depressive disorder, with mean age of 43.5 yrs. so the results cannot be extrapolated to adolescents and young adults.

In conclusion, fluoxetine treatment was not associated with worsening of suicide ideations compared to placebo in adult outpatients with Minor Depressive Disorder participating in a 12-week, placebo controlled efficacy trial. Significantly more placebo treated participants had worsening of suicide ideations during the trial. Subjects most at risk for worsening of suicide ideations, regardless of treatment were those who had this symptom at baseline before treatment was initiated. This analysis does not address the potential risks of antidepressants in children, adolescents or young adults with Minor Depressive Disorder.

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Table 1

Suicide related questions from three depression symptom severity rating scales; HRSD (Hamilton Rating Scale for Depression) clinician rated; IDS-C (Inventory of Depressive Symptoms) clinician-rated; SCL-90 (Symptom Checklist 90) patient self-rated.

Scale	Item	Question / Anchor
HRSD	3	Suicide 0= Absent 1= Feels life is not worth living 2= Wishes he were dead or any thoughts of possible death to self 3= Suicidal ideas or gestures 4= Attempts at suicide (any serious attempt rates 4)
IDS-C	18	Suicidal Ideation 0= Does not think of suicide or death 1= Feels like life is empty or not worth living 2= Thinks of suicide/ death several times a week for several minutes 3= Thinks of suicide/ death several times a day in depth, or has made specific plans or attempted suicide
SCL-90 (in past week how much were you bothered by)	15	Thoughts of ending your life 0= Not at all 1= A little bit 2= Moderately 3= Quite a bit 4= Extremely
SCL-90 (in past week how much were you bothered by)	59	Thoughts of death or dying 0= Not at all 1= A little bit 2= Moderately 3= Quite a bit 4= Extremely

Table 2Demographic and Clinical Characteristics of Patients Treated with Fluoxetine vs. Placebo^a

Characteristic		Treatment Group		Significance
		Fluoxetine (N=80) ^b	Placebo (N=81) ^b	
<u>Demographics:</u>				
Gender - Female	N (%)	52 (65.0)	43 (53.1)	$\chi^2=2.36$; df=1; p=0.124
Race - Caucasian	N (%)	74 (92.5)	71 (87.6)	$\chi^2=1.06$; df=1; p=0.304
Age	Mean(sd) [Range]	43.5 (12.2) [24-72]	43.5 (11.3) [18-72]	t=0.04; df=1, 159; p=0.972
<u>Past Major Depression</u>	N (%)	24 (35.3)	28 (41.8)	$\chi^2=0.60$; df=1; p=0.438
<u>Last Treatment Week Completed:</u>	Mean(sd) [Range]	10.0 (3.7) [0-12]	10.1 (3.6) [0-12]	t=0.17; df=1, 159; p=0.864
<u>Baseline Scores:</u>				
IDS-C (30-item)	Mean(sd) [Range]	20.0 (6.4) [4-37]	19.6 (6.3) [7-33]	t=0.44; df=1, 156; p=0.664
HAM-D (17-item)	Mean(sd) [Range]	11.3 (3.7) ^c [3-22]	10.6 (3.5) [2-20]	t=1.36; df=1, 158; p=0.174
HAM-D (28-item)	Mean(sd) [Range]	13.0 (4.5) ^c [3-28]	12.1 (4.1) [4-27]	t=1.35; df=1, 158; p=0.180
Global Assessment of Functioning	Mean(sd) [Range]	66.2 (4.1) [55-70]	66.5 (4.2) [52-70]	t=0.52; df=1, 159; p=0.602
Suicide ideation at Baseline	N (%)	24 (30)	22 (27.2)	$\chi^2=0.159$; df=1; p=0.690

^aPatients randomly assigned to 12 weeks of double-blind treatment with fluoxetine vs. placebo.^bThe modified intent-to-treat sample consists of 80 of 81 patients randomly assigned to fluoxetine treatment who had a low enough rating on all 4 suicide related items at baseline to allow for a 2 point increase during treatment; all 81 patients assigned to the placebo group met this criterion.^cN=79 of 80 patients had a HAM-D total score at their baseline (randomization) visit.

Survival Analysis Results: Time to Development of a 2 Point Increase in Any of Four Suicide Related Items for Patients Treated with Fluoxetine vs. Placebo^a

Table 3

Treatment Week	Cumulative Probability of 2 Point Increase on Any Item(s), by Treatment Group				Wilcoxon Test for Equality of Survival Distribution Functions
	Fluoxetine (N=81)		Placebo (N=81)		
	P	(95% CI)	P	(95% CI)	
Week 1	.000	<i>b</i>	.051	(.002-.099)	
Week 2	.013	(.000-.039)	.064	(.010-.118)	
Week 3	.021	(.000-.052)	.077	(.018-.136)	
Week 4	.029	(.000-.065)	.104	(.036-.172)	
Week 8	.060	(.003-.118)	.128	(.053-.204)	
Week 12	.077	(.012-.142)	.164	(.079-.250)	

$\chi^2=3.83$; df=1; p=0.050

^a Patients randomly assigned to 12 weeks of double-blind treatment with fluoxetine vs. placebo.

^b Standard error of event probability cannot be computed when event rate=.000.