



Research report

Clinical features of patients with treatment-emergent suicidal behavior following initiation of paroxetine therapy

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ABSTRACT

Background: Understanding suicidal behavior is an important component of assessing suicidality in psychiatric patients. GlaxoSmithKline (GSK) conducted a meta-analysis of randomized, placebo-controlled trials to compare suicidality in adult patients treated with paroxetine vs. placebo. The goal was to identify emergent clinical characteristics of patients with definitive suicidal behavior (DSB: preparatory act, suicide attempt, completed suicide).

Methods: The dataset comprised 14,911 patients from 57 placebo-controlled paroxetine trials. Possible cases of suicidality were identified and were blindly reviewed by an expert panel, which categorized cases as suicidal or non-suicidal. DSB incidences were compared between paroxetine and placebo. Clinical narratives and case report forms for major depressive disorder (MDD) and anxiety disorder patients with DSB were reviewed. For MDD, rating scale items relating to suicidality, insomnia, agitation, and anxiety were examined.

Results: Overall (all indications) there were no differences between paroxetine and placebo for DSB (50/8958 [0.56%] vs. 40/5953 [0.67%], respectively; OR = 1.2 [CI 0.8, 1.9]; $p = 0.483$). However, in patients with major depressive disorder (MDD), the incidence of DSB was greater for paroxetine (11/3455 [0.32%] vs. 1/1978 [0.05%], OR = 6.7 [CI 1.1, 149.4]; $p = 0.058$). Review of the 11 paroxetine MDD cases revealed common clinical features: symptomatic improvement; younger age (18–30 years); psychosocial stressors; overdose as method; and absent/mild suicidal ideation at the visit prior to the event. There was no evidence for a consistent adverse event profile or onset of akathisia/agitation or a manic/mixed state. Anxiety disorder patients with DSB had a heterogeneous clinical picture.

Limitations: Limitations to the study include the relatively small number of cases and the retrospective nature of the study.

Conclusions: DSB incidence was similar between paroxetine and placebo overall, but a higher frequency of DSB was found for paroxetine in MDD patients, driven by young adults aged ≤ 30 years. Most MDD patients with DSB improved prior to the attempt and experienced a psychosocial stressor. Patients should receive careful monitoring for suicidality during paroxetine therapy.

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1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been effectively used in the treatment of depressive illness and anxiety disorders since the late 1980s. A possible link between the use of SSRIs and suicidal behavior was first described as a case series in the published literature in 1990

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by Teicher and colleagues, who reported that fluoxetine, the first SSRI introduced to the U.S. market, may induce or exacerbate suicidal tendencies (Teicher et al., 1990). A subsequent meta-analysis conducted shortly thereafter did not provide evidence supporting this observation (Beasley et al., 1991), nor did an expert panel convened by the Food and Drug Administration (FDA) in 1991 find compelling evidence for such an association (Department of Health and Human Services, 1991). However, a recent FDA meta-analysis of data from clinical trials in pediatric patients found that SSRIs, including paroxetine, were associated with an increased risk of suicidality (thoughts and behavior) relative to placebo in pediatric patients (Hammad et al., 2006). Partly as a result of this finding, in 2004, the FDA initiated steps to enable its own further examination of the relationship between antidepressant use and suicidality in adult patients by requesting all antidepressant manufacturers to provide specified patient-level data from all acute, double-blind, randomized, placebo-controlled adult studies in major depressive and other psychiatric disorders. The results of this analysis, released in December 2006, suggested the finding of increased short-term risk for suicidality with antidepressant treatment in pediatric patients appears to extend into younger adults (up to age 24) (Department of Health and Human Services, 2006). Rather than awaiting the results of FDA's on-going efforts, GlaxoSmithKline (GSK) initiated its own analysis of the adult suicidality (suicidal ideation and behavior) paroxetine datasets utilizing the methodology developed by FDA for analyzing the pediatric datasets; the results of this analysis were posted at www.gsk.com in May 2006 (GSK 2006 Analysis).

As an understanding of suicidal behavior is an important component of assessing suicidality in psychiatric patients, we sought to identify emergent clinical features shared among patients with suicidal behavior, through review of clinical narratives and case report forms.

2. Methods

2.1. Identification of cases of definitive suicidal behavior

Potential cases of suicidality (suicidal ideation or behavior) were identified in adult, randomized, parallel-group, placebo-controlled trials in which the total number of patients treated with paroxetine and placebo was at least 30. A total of 57 trials were assessed, which included 8,958 paroxetine-treated and 5,953 placebo-treated patients (for complete list of trials, see GSK 2006 Analysis). Each individual trial protocol required that written, informed consent was obtained from each patient after a complete description of the study and relevant procedures were explained. Potential cases of suicidality were identified via adverse event (AE) text string searches of AE terms, review of all serious adverse event (SAE) narratives (including all deaths), and review of the comment fields from the Case Report Forms (CRFs) for all relevant studies, as described elsewhere (Fong et al., 2004). Cases were only included in the list of potential events if they occurred during the double-blind phase of treatment or within one day following the cessation of randomized treatment (as was done in the FDA's analysis). For all potential events, a detailed narrative blinded to information that might

bias assessment (e.g., treatment, disease indication, names of all medications) was prepared. GSK contracted with Columbia University to have independent experts blindly review each case narrative and classify the events into suicidal or non-suicidal categories using the same approach used in the pediatric suicidality review conducted by the FDA. Each narrative was reviewed by three expert raters and was assigned a code according to the following classification: 1, completed suicide; 2, suicide attempt; 3, preparatory acts toward imminent suicidal behavior; 4, suicidal ideation; 5, self-injurious behavior, intent unknown; 6, not enough information (fatal); 7, self-injurious behavior, no suicidal intent; 8, other: accident, psychiatric, medical; 9, not enough information (non-fatal). Categories 1 through 3 are referred to collectively as definitive suicidal behavior (DSB), and these events are the focus of this report. Other suicidality events (e.g., suicidal ideation) are not presented in this manuscript. Cases of definitive suicidal behavior discussed herein include patients with major depressive disorder (MDD) or anxiety disorders: obsessive compulsive disorder (OCD); panic disorder (PD); social anxiety disorder (SAD); and posttraumatic stress disorder (PTSD). All other cases identified in the complete dataset were from the group of patients with intermittent brief depression and are not included in this manuscript (see below).

2.2. Assessment of clinical characteristics

Once classified by the independent suicidality experts, the cases of DSB were reviewed for patterns of clinical characteristics. The case narratives (available at <http://www.gsk.com/media/paroxetine/app4.pdf> [MDD cases] and <http://www.gsk.com/media/paroxetine/app7.pdf> [non-MDD cases]) as well as the original CRFs were reviewed. For all patients, age, gender, days after initiation of study medication that suicidal behavior occurred, and days after the last study visit that suicidal behavior occurred were obtained. Additionally, method of suicide attempt, relationship of attempt to dose change, social stressors, and other adverse events occurring during the study period were identified when available.

For the MDD patients, depression rating scale and suicidality item scores were retrieved, including scores at baseline (except for one patient, where the screening score was used) and scores at the study visit just prior to the event of suicidal behavior (for MDD, all were suicide attempts). Depression rating scales used were the Hamilton Rating Scale for Depression, 17 item (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). The suicidality item for the HAM-D is Item 3, with scoring as follows: 0, absent; 1, feels life is not worth living; 2, wishes he/she were dead or any thoughts of possible death to self; 3, suicidal ideas or gestures; and 4, suicide attempt. The suicidality item for the MADRS is item 10, with anchor scoring as follows: 0, enjoys life or takes it as it comes; 2, weary of life, only fleeting suicidal thoughts; 4, suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intent; and 6, explicit plans for suicide when there is an opportunity, active preparations for suicide. In addition to the suicidality items, scale items related to sleep, anxiety, and agitation were retrieved. For the HAM-D, these were: sleep item scores (sum of items 4, 5, and 6, all insomnia

items); agitation score (item 9); and anxiety item scores (sum of items 10 [psychological anxiety] and 11 [somatic anxiety]). For the MADRS, these were: inner tension (item 3) and reduced sleep (item 4).

For the non-MDD patients, given the heterogeneity of clinical diagnoses and hence of disease state rating scales, and the lack of suicidality rating by standardized assessment scales, a descriptive summary only is presented (i.e., no summary tables).

2.3. Definitive suicidal behavior in patients with intermittent brief depression

Aside from the cases of DSB for MDD and anxiety disorder patients presented in this paper, the only other cases identified in the clinical trials dataset occurred in patients with intermittent brief depression (IBD) (see Table 1). IBD (or recurrent brief depression) is characterized by recurrent episodes of brief depressive periods (typically lasting 2 to 4 days) associated with an increased risk of suicidal behavior (Montgomery et al., 1989; Pezawas et al., 2003). The larger IBD study (Study 057) included patients who exhibited suicidal behavior within 10 days of study entry, and, for both IBD studies, occurrence of suicidal behavior was an outcome measure. Additionally, these studies were different in that they assessed patients with frequent brief episodes of depressive symptoms who had not met criteria for major depressive episode in the past 6 months (study 057) to 1 year (study 106). Many of the patients in these two trials had comorbid Axis II psychopathology. Review of 76 case narratives for subjects in study 057 revealed 68 (89%) with documented or suspected personality disorders; 10 of 12 (83%) reviewed cases from study 106 had personality disorders. As shown in Table 1, 21.48% of paroxetine-treated and 22.73% of placebo-treated IBD patients had episodes of definitive suicidal behavior, indicating no difference in frequency between the two groups (OR = 0.9 [95% CI 0.5, 1.6], $p = 0.89$). Given the lack of difference between the two groups, the methodological differences in the IBD studies, and the unique patient characteristics (no clear Axis I diagnosis, Axis II comorbidity), the IBD cases of definitive suicidal behavior are not presented in this manuscript. Details of the IBD studies can be found at the [GSK Clinical Trials Registry \(http://ctr.gsk.co.uk/welcome.asp\)](http://ctr.gsk.co.uk/welcome.asp) and further information on the IBD data sets can be found at the GSK corporate site (GSK 2006 Analysis).

2.4. Statistical analysis

The common odds ratio (OR) and 95% confidence interval (CI) were adjusted for trial using the exact method of StatXact® (PROC STRATIFY, StatXact for SAS®). Instances where the 95% confidence interval did not include 1 were considered statistically significant, even when the p value exceeded 0.05. No adjustment of p values was made for multiple comparisons. Only the results of DSB are presented in this manuscript; statistical analysis of the complete data can be found at the GSK corporate site (GSK 2006 Analysis).

3. Results

3.1. Major depressive disorder

Our review of 57 placebo-controlled, double-blind clinical trials involving 8958 paroxetine-treated and 5953 placebo-treated adult patients revealed 50 cases (0.56%) of definitive suicidal behavior (DSB) in the paroxetine-treated group, and 40 cases (0.67%) in the placebo-treated group, a non-significant difference (OR = 1.2 [95% CI 0.8, 1.9], $p = 0.48$) (Table 1). In the MDD population, 11 of 3455 (0.32%) paroxetine-treated patients and 1 of 1978 (0.05%) placebo-treated patients had an episode of DSB (Table 1), a statistically significant difference (OR = 6.7 [95% CI 1.1, 149.4], $p = 0.058$). All were suicide attempts, with no completed suicides. Patient demographic characteristics for these MDD patients are shown in Table 2. The single placebo-treated patient was a 67 year old female who attempted suicide 6 days after starting placebo, and was seen the same day for a study visit. Of the paroxetine-treated patients, 7 of 11 were female, and the median age was 29.5 years with a range of 18 to 67 years. Eight of 11 (72.7%) were aged 18 to 30 years (compared to 612 of 3455 [17.7%] of the overall MDD study population). Three of 11 patients attempted suicide within 30 days of starting medication; 7 of 11 patients within 30 to 60 days; and 1 patient at 66 days.

In terms of antidepressant efficacy, all 11 paroxetine-treated patients with DSB had some improvement in their depressive symptoms as measured by standardized depression rating scales; the single placebo-treated patient had worsening of her depressive symptoms (Table 2). For the paroxetine-treated patients, in assessing change in symptoms from study entry to the last study visit prior to the suicide attempt, 6 of 11 patients had a $\geq 50\%$ decrease in their total

Table 1

Cases of definitive suicidal behavior (DSB) identified in the dataset.

Study population	Paroxetine			Placebo		
	Number of cases	Total number of subjects	Percentage	Number of cases	Total number of subjects	Percentage
Major depressive disorder*	11	3455	0.32	1	1978	0.05
Obsessive compulsive disorder	3	698	0.43	1	416	0.24
Panic disorder	1	1092	0.09	2	903	0.22
Social anxiety disorder	2	943	0.21	1	643	0.16
Posttraumatic stress disorder	1	698	0.14	0	510	0.00
Intermittent brief depression†	32	149	21.48	35	154	22.73

The following study populations had no events of definitive suicidal behavior: dysthymia, bipolar depression, generalized anxiety disorder, premenstrual dysphoric disorder, detoxification in alcoholics, and fibromyalgia.

*For events of suicidal behavior, all adult patients with MDD, there was a statistically significant difference between paroxetine and placebo (OR = 6.7 [95% CI 1.1, 149.4]).

†These cases are not discussed in this manuscript; see Methods for details.

Table 2

Demographic characteristics, depression scores, and suicidality item scores, at baseline (B) and at the last study visit prior to the event (VPE), for MDD patients with suicide attempts.

Subject #	Treatment	Age (years)	Sex	Days after first dose (days after dose change)	Days since last visit	Depression rating score (scale)* (B)	Depression rating score (scale)* (VPE)	Percent change [†]	Suicidality item score (scale)* (B)	Suicidality item score (scale)* (VPE)
002.001.000009	Placebo	67	Female	6 (n/a)	0	27 (H)	36 (H)	+33.3	2 (H)	3 (H)
002.004.000089	Paroxetine	19	Female	40 (23)	9	23 (H)	10 (H)	-56.5	1 (H)	0 (H)
009.01E.000260	Paroxetine	51	Female	44 (n/a)	3	21 (H)	5 (H)	-76.2	2 (H)	0 (H)
279.1.12.037	Paroxetine	20	Male	49 (n/a)	13	20 (H) [‡]	12 (H)	-40	3 (H) [‡]	0 (H)
115.003.0000062	Paroxetine	29	Female	55 (34)	13	24 (H)	10 (H)	-58.3	2 (H)	0 (H)
128.001.000759	Paroxetine	30	Male	36 (5)	8	26 (H)	20 (H)	-23.1	2 (H)	1 (H)
251.002.000285	Paroxetine	30	Male	25 (7)	7	27 (H)	17 (H)	-37.0	2 (H)	0 (H)
448.010.000044	Paroxetine	25	Female	49 (31)	4	27 (H)	14 (H)	-48.1	2 (H)	1 (H)
448.019.000391	Paroxetine	27	Female	24 (8)	2	22 (H)	17 (H)	-5	2 (H)	1 (H)
449.021.000788	Paroxetine	18	Female	66 (n/a)	12	21 (H)	0 (H)	-100	1 (H)	0 (H)
625.500.02062	Paroxetine	50	Male	56 (12)	13	32 (M)	9 (M)	-71.8	3 (M)	0 (M)
785.720.00695	Paroxetine	34	Female	26 (19)	5	30 (M)	15 (M)	-50	1 (M)	1 (M)

*Depending upon the study, the Hamilton Rating Scale for Depression-17 (HAM-D, or H) or Montgomery-Asberg Depression Rating Scale (MADRS, or M) score is displayed. The suicidality items for each scale are: HAM-D, item 3; MADRS, item 10 (see Methods for details). If both scales were available, the Hamilton score is displayed.

[†]A decrease represents clinical improvement in symptoms.

[‡]For this patient, the screening rating scale scores are shown; baseline scores were not available.

Abbreviations: B = baseline study visit; VPE = study visit prior to the event (suicide attempt); n/a = not applicable (no dose change).

depression scale score (i.e., responders), while the other 5 patients had reductions ranging from 5% to 48.1% (Table 2). Defining depression remission as a score of ≤ 7 on the HAM-D or MADRS, 2 of 11 patients had remitted prior to the suicide attempt. Review of rating scale scores indicated a general pattern of improvement over time before the attempt, without evidence of marked fluctuations of scores. When assessing the suicidality item score at the study visit prior to the suicide attempt, all paroxetine-treated patients had a score of 0 or 1 (Table 2), indicating no active suicidal ideation

as measured by rating scales. Five of 11 patients had been seen by the study physician within 7 days prior to the attempt, and all had been seen within 2 weeks prior to the attempt.

As concern has been raised in the literature that behavioral activation may be a component of antidepressant associated suicidal behavior (Hamilton and Opler, 1992; Teicher et al., 1993), depression rating scale items possibly related to activation (sleep, agitation, and anxiety items) were examined for each patient at study entry and at the last study visit prior to the suicide attempt (Table 3). For paroxetine-treated

Table 3

Assessment of depression rating scale items related to sleep, agitation, and anxiety at baseline (B) and at the last study visit prior to the event (VPE), for MDD patients with suicide attempts.

Subject #	Treatment	HAM-D sleep items score (B)	HAM-D sleep items score (VPE)	HAM-D Item 9 (agitation) score (B)	HAM-D Item 9 (agitation) score (VPE)	HAM-D anxiety items score (B)	HAM-D anxiety items score (VPE)
002.001.000009	Placebo	6	6	2	3	4	5
002.004.000089	Paroxetine	6	1	0	0	3	0
009.01E.000260	Paroxetine	3	0	1	0	3	1
279.1.12.037	Paroxetine	2 [‡]	2	0 [‡]	0	4 [‡]	1
115.003.0000062	Paroxetine	3	2	0	1	5	1
128.001.000759	Paroxetine	4	3	1	1	5	4
251.002.000285	Paroxetine	2	2	1	1	6	4
448.010.000044	Paroxetine	3	3	0	0	6	2
448.019.000391	Paroxetine	2	3	0	0	4	3
449.021.000788	Paroxetine	5	0	0	0	4	0
Subject #	Treatment	MADRS Item 3 (inner tension) Score (B)	MADRS Item 3 (inner tension) Score (VPE)	MADRS Item 4 (insomnia) Score (B)	MADRS Item 4 (insomnia) Score (VPE)		
625.500.02062	Paroxetine	2	2	4	0		
785.720.00695	Paroxetine	4	3	3	0		

Depending upon the study, the Hamilton Rating Scale for Depression-17 (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) score is displayed. If both scales were available, the Hamilton score is displayed. The HAM-D sleep items score is the sum of items 4 (insomnia early), 5 (insomnia middle), and 6 (insomnia late), with a range of scores from 0 (no symptoms) to 6 (severe symptoms). The HAM-D Item 9 score ranges from 0 (no symptoms) to 4 (severe symptoms). The HAM-D anxiety items score is the sum of items 10 (anxiety, psychological) and 11 (anxiety, somatic), with a range of scores from 0 (no symptoms) to 8 (severe symptoms). The score for each MADRS item ranges from 0 (mild or no symptoms) to 6 (severe symptoms). Abbreviations: B = baseline visit; VPE = study visit prior to the event (suicide attempt).

[‡]For this patient, the screening rating scale scores are shown; baseline scores were not available.

Table 4

Identified psychosocial stressors, method of attempt, and other adverse events (AEs), occurring at any time during the trial, for MDD patients with suicide attempts.

Subject #	Treatment	Stressor	Method of attempt	Others AEs
002.001.000009	Placebo	None noted	Suffocation	None noted
002.004.000089	Paroxetine	Angry, fight with spouse	Overdose	Dizziness, lack of energy, headaches
009.01E.000260	Paroxetine	Alcohol use, "precipitating external event"	Overdose	Ear infection
279.1.12.037	Paroxetine	Puppy died, roommate "stole" girlfriend	Stabbed abdomen	Alcohol intolerance, epigastric pain
115.003.0000062	Paroxetine	Pending divorce	Overdose	Insomnia, sinus congestion, indigestion
128.001.000759	Paroxetine	Alcohol, fight with girlfriend, taken into police custody	Hanging	Agitation, hopelessness, anxiety, "being argumentative"
251.002.000285	Paroxetine	"psychosocial stressors"	Overdose	None noted
448.010.000044	Paroxetine	Fight with boyfriend	Overdose	Dizziness, nausea, dilated pupils, back ache, diarrhea, bloody nose, cold symptoms
448.019.000391	Paroxetine	Fight with husband	Overdose	Insomnia, chills, diarrhea, fever, headache
449.021.000788	Paroxetine	Fight with boyfriend	Overdose	Fatigue, dislocated left shoulder, abrasions on knees, left hand pain, excoriations on hands
625.500.02062	Paroxetine	None noted	Overdose	Biting of the tongue, feeling lightheaded
785.720.00695	Paroxetine	None noted	Unclear	None noted

patients, all item scores relating to sleep, agitation, or anxiety were either unchanged or improved during this period, except for one patient (003.0062) for whom the HAMD agitation item (item 9) increased from 0 (none) to 1 (fdg-iteness). The single placebo-treated patient maintained severe insomnia, and had worsening in agitation and anxiety scores during this treatment period (Table 3).

Table 4 summarizes additional clinical features for each patient. Nine of 11 patients treated with paroxetine experienced a psychosocial stressor prior to the event, and 8 of 11 used overdose as a method of suicide attempt (2 included the study drug, paroxetine). Most patients had other adverse events occurring during the study, but there was not a consistent pattern of adverse events shared among the paroxetine-treated patients.

3.2. Non-depression patients

In the non-depression clinical trial database, there were 7 cases of DSB in 5238 subjects (0.13%) in the paroxetine group and 4 cases in 3693 subjects (0.11%) in the placebo group (no significant difference between the groups: OR = 1.5 [95% CI 0.4, 5.8]). All cases of DSB occurred in anxiety disorder subjects (Table 1). For paroxetine, these were: OCD, 3/698 (0.43%); SAD, 2/943 (0.21%); PD, 1/1092 (0.09%); and PTSD, 1/698 (0.14%). For placebo, these were: OCD, 1/416 (0.24%); SAD, 1/643 (0.16%); and PD, 2/903 (0.22%). In contrast to the MDD paroxetine-treated cases, most patients (both paroxetine and placebo) showed only minimal or no improvement in regards to their symptom severity. Also in contrast to the MDD cases, a few episodes of suicidal behavior in the anxiety disorder patients occurred shortly after beginning treatment, with one paroxetine-treated patient making a suicide attempt at 4 days after the first dose, and two different placebo-treated patients making an attempt at days 3 and 5 respectively. However, the remainder of the patients had episodes of suicidal behavior in a time range similar to that of the MDD patients, with a range of 17 to 70 days after the first treatment exposure. Finally, there was 1 completed suicide in the anxiety disorder patient group, a male with social anxiety

disorder treated with paroxetine. Given that these clinical trials involved 14,911 patients with psychiatric disorders, and persons with psychiatric disorders are at greater risk for completed suicide (including those with social anxiety disorder den Boer, 2000), a completed suicide would not be unexpected.

4. Discussion

Our review of 57 placebo-controlled, double-blind clinical trials involving 8958 paroxetine-treated and 5953 placebo-treated adult patients revealed 50 cases (0.56%) of definitive suicidal behavior (DSB) in the paroxetine-treated group, and 40 cases (0.67%) in the placebo-treated group, a non-significant difference (OR = 1.2 [95% CI 0.8, 1.9], $p = 0.48$). However, when assessed alone, MDD adult patients treated with paroxetine had a higher frequency of DSB (11/3,455 [0.32%]) than those treated with placebo (1/1978 [0.05%]), a statistically significant difference when considering that the 95% confidence interval does not include 1 (OR = 6.7 [95% CI 1.1, 149.4]). No difference between paroxetine and placebo in the incidence of DSB was seen for the non-depression group (including anxiety disorders).

Although representing a relatively small number compared to the overall treatment group, the cases of DSB in the MDD group were scrutinized to assess for emergent clinical characteristics. When assessed together, some commonalities emerged from the 11 paroxetine-treated MDD patient cases. First, all paroxetine-treated patients had some improvement in their MDD symptoms (as measured by change in standardized depression rating scales at baseline and at the study visit just prior to the event of definitive suicidal behavior), with 10 of 11 having greater than 20% improvement and 6 of 11 having 50% or greater improvement (often the criterion for "response" to treatment) (Table 2). Second, 8 of 11 (72.7%) patients were aged 30 or younger (compared to 612 of 3455 [17.7%] of the overall MDD study population), suggesting that any increased risk may be more likely in young adults. Third, the majority of patients (9 of 11) experienced a psychosocial stressor prior to the suicide attempt. Fourth, the majority of suicide attempts (8 of 11)

involved overdose. Fifth, all patients either had no or mild/fleeting/passive suicidal ideation as measured by suicidality items on depression rating scales at the study visit just prior to the event, with scores of 0 (7/11) or 1 (4/11) (Table 2). Sixth, there did not appear to be a common adverse event profile among these 11 cases. Seventh, the events of suicidal behavior did not occur in a common discrete time window relative to initiation of medication among these cases; rather, they ranged from 24 to 66 days after the first dose (Table 2). Of interest, none of these attempts occurred early (i.e., within the first 3 weeks) in treatment, a period where the highest risk of suicidality during antidepressant therapy has been identified (Jick et al., 2004; Simon et al., 2006). Further, there was no clear relationship to dose change, with events occurring from 5 to 34 days following a dose change (Table 2).

Of interest, most of the commonalities described above overlap with findings from clinical and epidemiological studies of suicide attempters in general. Younger adults have higher rates of suicide attempt than older adults (Simon et al., 2006; Hall et al., 1999; Kessler et al., 2005). Psychosocial stressors are considered a risk factor for suicide attempt in vulnerable (e.g., depressed) individuals (Hall et al., 1999; Oquendo et al., 2004; Horesh et al., 2003; Kelly et al., 2000; Mann et al., 1999; Heikkinen et al., 1997). Many studies have identified overdose as the most common method of suicide attempt (Statham et al., 1998; Donovan et al., 2000), in contrast to violent methods (e.g., hanging) identified more frequently with completed suicide (Donovan et al., 1999). Additionally, studies have found that a majority of patients had only fleeting or no suicidal thoughts prior to the attempt (Hall et al., 1999) or did not disclose such thoughts to a clinician at the last treatment contact before a completed suicide (Earle et al., 1994; Busch et al., 2003).

Although the emerging clinical characteristics of the MDD paroxetine-treated patients who experienced suicidal behavior overlap substantially with features of suicide attempters in general, we did find an association between paroxetine treatment and suicidal behavior when compared to placebo (in adult MDD patients only, driven by those aged 30 and under). However, it is not possible to conclude a causal relationship between paroxetine and treatment-emergent DSB in the MDD population as this finding is predicated on a small number of events in both paroxetine and placebo groups, accompanied by broad confidence intervals; is not supported by other analyses of DSB in the non-MDD datasets; involves an analysis of studies in which the randomization process was not stratified by pre-existing suicide risk factors and, consequently, those risks may have been unevenly distributed at baseline; and is inconsistent with the findings from the rating scale analysis (GSK 2006 Analysis).

The observation that the majority of MDD patients who displayed suicidal behavior improved prior to the suicide attempt is superficially consistent with what has been described as the “rollback phenomenon” described by Detre and Jarecki (1971), where improvement in some symptoms is thought to be implicated in suicidality. Specifically, in this view, improvement in energy may precede improvement in mood, allowing the patient to have the capacity to act upon suicidal thoughts (Bostwick, 2006). Review of the individual case report forms shows that, in general, all symptoms improved over a similar time frame, rather than a dissociation

between mood, suicidal ideation, and energy items. Indeed, none of the 11 MDD paroxetine-treated patients had significant reported suicidal ideation (as measured by rating scales or reported as an adverse event) at the study visit prior to the event, suggesting that improvement in energy allowing the patient to act upon preexisting suicidality did not play a role. Therefore, these cases are not suggestive of the “rollback phenomenon” as typically defined. Whether improvement in depression may itself have played a role in the emergence of DSB is not known. It is possible that patients with improved mood may have been more able to engage in stressful or maladaptive relationships, or that others may put new pressures or expectations on the patient as he/she emerges from the depression, leading to new psychosocial stressors with subsequent development of suicidality. This explanation is speculative, however, and the case report forms do not provide the level of detail to support or refute it.

It has been proposed that selective serotonin reuptake inhibitors (SSRIs) may induce a state of excessive agitation, activation, or an akathisia-like state, which in turn may precipitate suicidal behavior (Hamilton and Opler, 1992; Teicher et al., 1993). Some support for this concept was recently reported in an open trial of fluoxetine, where treatment-emergent suicidal ideation was associated with the development of activation and symptomatic worsening (Perlis et al., 2007). However, review of the MDD paroxetine-treated cases does not support this hypothesis in regards to DSB, either when assessing items derived from standardized rating scales or when reviewing the clinical report forms for adverse events. When assessing rating scale items corresponding to agitation, anxiety, or inner tension (Table 3), only one patient had an increase in score (worsening) for these items. This one exception had an increase in the HAMD agitation score (item 9) from 0 (absent) to 1 (fidgetiness). Additionally, review of the adverse events (AEs) from the case report forms revealed only 1 of 11 MDD cases had an AE of agitation (which had resolved prior to the suicide attempt), and none had recorded AEs of irritability, akathisia, or akathisia-like symptoms. It should be noted that in the paroxetine studies, spontaneous AEs were recorded without systematic queries for specific AEs (e.g., patients were not formally assessed for akathisia). Still, the cases presented here do not support the hypothesis that agitation or akathisia precedes suicide attempts in paroxetine-treated patients.

The finding that the majority of paroxetine-treated suicide attempters were younger adults might reflect a higher prevalence of incipient bipolarity in this population, as earlier age of illness onset has been associated with elevated risk for bipolar II disorder and mixed depressive episodes (Akiskal and Benazzi, 2003). Of note, only one paroxetine-treated patient (279.112.037) had a family history of bipolar disorder, though family history was not formally assessed for the majority (8/11) of patients. Concern has also been raised that antidepressant treatment may result in the emergence of bipolarity (manic or mixed-state), which in turn could precipitate suicidal behavior (Rihmer and Akiskal, 2006; Balázs et al., 2006). We assessed the emergence of insomnia, as measured by items on standardized depression rating scales, since insomnia is often an early symptom of an emerging manic or hypomanic episode (Table 3). Only one patient had an increase in score (worsening) for these items.

This one exception (subject 448.019.00391) had a single point increase in the total HAMD insomnia score (sum of items 4 through 6), and also had “insomnia” recorded as an adverse event that was present at study withdrawal. Only one other subject (115.003.0000062) of these 11 had insomnia listed as an adverse event, which was present at baseline but had not resolved at study withdrawal. Also, as described above, the cases were not consistently associated with rating scale or reported agitation, irritability, or akathisia, symptoms that might be expected in a manic or mixed state. It should be noted that these studies were not designed to assess this clinical outcome. Still, the available data from the cases presented here do not support the hypothesis that emergent mania precedes suicide attempts in paroxetine-treated patients.

In most of the cases described in this manuscript, investigator attribution regarding the relatedness (or possible association) of treatment with the adverse event of definitive suicidal behavior was recorded in the case report form. For the MDD patients treated with paroxetine, 9/11 cases included investigator attribution assessments. Of these, 7/9 listed medication treatment as “unrelated” to the suicide attempt, 1/9 as “probably unrelated,” and 1/9 as “possibly related.” For the MDD patient treated with placebo, investigator attribution was not available. For the paroxetine-treated anxiety disorder cases of definitive suicidal behavior, medication was considered possibly related in 1 of 7 cases and unrelated in the remaining 6 cases. For events occurring in placebo-treated anxiety disorder patients, medication was considered possibly/probably related in 2 of 4 cases and unrelated in the remaining 2 cases. Thus, for the majority of cases, paroxetine was considered by investigators to be unrelated to the event of suicidal behavior. However, it is important to note that these attributions do not establish causality (or lack thereof) of a specific adverse event with a particular treatment.

There are many limitations to the current review. First, the absolute number of cases to assess was relatively small, and the findings should therefore be interpreted with caution. Second, the current review is a retrospective assessment of case report forms/narratives of patients who experienced suicidal behavior during a placebo-controlled clinical trial with paroxetine. Given that, for most trials, the studies were not prospectively designed to identify suicidal behavior as study endpoints, the case report forms are limited in terms of information that might be collected. For example, history of prior suicide attempt or family history of suicide attempt was generally not available, and documentation of other demographic data was variable depending upon the study and investigator. As a consequence, we focused on those variables that were available for all cases. Further, we did not have data across the full paroxetine and placebo database of suicide non-attempters about the relative frequency of psychosocial stressors for these patients. It is therefore unknown whether the frequency for non-attempters would be different from or similar to that identified for suicide attempters.

In sum, we found an increased frequency, relative to placebo, of definitive suicidal behavior (all suicide attempts) in MDD paroxetine-treated patients. Review of the 11 cases revealed several emergent clinical characteristics: improvement in depression symptoms; younger adult age group; experience of psychosocial stressors; overdose as method;

and absence of or mild/fleeting suicidal ideation at the study visit just prior to the event. The cases did not reveal any consistent adverse event profile; no evidence suggested the onset of akathisia/agitation or a manic/mixed state. It is therefore important that all patients, especially young adults and those who are improving, receive careful monitoring during paroxetine therapy regardless of the condition being treated.

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Conflict of interest

This study was funded by GlaxoSmithKline. The authors are employees of and are shareholders in GlaxoSmithKline.

References

- Akiskal, H.S., Benazzi, F., 2003. Family history validation of the bipolar nature of depressive mixed states. *J. Affect. Disord.* 73, 113–122.
- Balázs, J., Benazzi, F., Rihmer, Z., Rihmer, A., Akiskal, K.K., Akiskal, H.S., 2006. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. *J. Affect. Disord.* 91, 133–138.
- Beasley Jr., C.M., Dornseif, B.E., Bosomworth, J.C., Saylor, M.E., Rampey Jr., A.H., Heiligenstein, J.H., Thompson, V.L., Murphy, D.J., Masica, D.N., 1991. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 303, 685–692.
- Bostwick, J.M., 2006. Do SSRIs cause suicide in children? The evidence is underwhelming. *J. Clin. Psychol.* 62, 235–241.
- Busch, K.A., Fawcett, J., Jacobs, D.G., 2003. Clinical correlates of inpatient suicide. *J. Clin. Psychiatry* 64, 14–19.
- den Boer, J.A., 2000. Social anxiety disorder/social phobia: epidemiology, diagnosis, neurobiology, and treatment. *Compr. Psychiatry* 41, 405–415.
- Department of Health and Human Services, Public Health Service, Food and Drug Administration. Psychopharmacological Drugs Advisory Committee. September 20, 1991. Available at: www.fda.gov/ohrms/dockets/ac/prozac/2443T1.PDF (accessed September 10, 2008).
- Department of Health and Human Services, Public Health Service, Food and Drug Administration. Psychopharmacological Drugs Advisory Committee. December 13, 2006. Available at: www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf (accessed September 10, 2008).
- Detre, T.P., Jarecki, H.G., 1971. *Modern Psychiatric Treatment*. Lippincott, Philadelphia, PA.
- Donovan, S., Kelleher, M.J., Lambourn, J., Foster, T., 1999. The occurrence of suicide following prescription antidepressant drugs. *Arch. Suicide Res.* 5, 181–192.
- Donovan, S., Clayton, A., Beeharry, M., Jones, S., Kirk, C., Waters, K., Gardner, D., Faulding, J., Madeley, R., 2000. Deliberate self-harm and antidepressant drugs. Investigation of a possible link. *Br. J. Psychiatry* 177, 551–556.
- Earle, K.A., Forquer, S.L., Volo, A.M., McDonnell, P.M., 1994. Characteristics of outpatient suicides. *Hosp. Community Psychiatr.* 45, 123–126.
- Fong, R., Lipschitz, A., Carpenter, D.J., Wetherhold, E.A., Krulwicz, S., Perera, P., 2004. Suicidality in clinical trials: using multiple search strategies. Washington (DC), Am Acad Child Adolesc Psychiatry (AACAP) 51st Annual Meeting, October 19–24 (abstract number NRP-223).
- GSK 2006 Analysis. Available at: www.gsk.com/media/par_current_analysis.htm (accessed September 10, 2008).
- GSK Clinical Trial Registry available at: <http://ctr.gsk.co.uk/welcome.asp> (accessed September 10, 2008).
- Hall, R.C., Platt, D.E., Hall, R.C., 1999. Suicide risk assessment: a review of risk factors for suicide in 100 patients who made severe suicide attempts. Evaluation of suicide risk in a time of managed care. *Psychosomatics* 40, 18–27.
- Hamilton, M.S., Opler, L.A., 1992. Akathisia, suicidality, and fluoxetine. *J. Clin. Psychiatry* 53, 401–406.
- Hammad, T.A., Laughren, T., Racoosin, J., 2006. Suicidality in pediatric patients treated with antidepressant drugs. *Arch. Gen. Psychiatry* 63, 332–339.
- Heikkinen, M.E., Henriksson, M.M., Isometsa, E.T., Marttunen, M.J., Aro, H.M., Lonnqvist, J.K., 1997. Recent life events and suicide in personality disorders. *J. Nerv. Ment. Dis.* 185, 373–381.
- Horesh, N., Sever, J., Apter, A., 2003. A comparison of life events between suicidal adolescents with major depression and borderline personality disorder. *Compr. Psychiatry* 44, 277–283.
- Jick, H., Kaye, J.A., Jick, S.S., 2004. Antidepressants and the risk of suicidal behaviors. *JAMA* 292, 338–343.

- Kelly, T.M., Soloff, P.H., Lynch, K.G., Haas, G.L., Mann, J.J., 2000. Recent life events, social adjustment, and suicide attempts in patients with major depression and borderline personality disorder. *J. Pers. Disord.* 14, 316–326.
- Kessler, R.C., Berglund, P., Borges, G., Nock, M., Wang, P.S., 2005. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990–1992 to 2001–2003. *JAMA* 293, 2487–2495.
- Mann, J.J., Waternaux, C., Haas, G.L., Malone, K.M., 1999. Toward a clinical model of suicidal behavior in psychiatric patients. *Am. J. Psychiatry* 156, 181–189.
- Montgomery, S.A., Montgomery, D., Baldwin, D., Green, M., 1989. Intermittent 3-day depressions and suicidal behaviour. *Neuropsychobiology* 22, 128–134.
- Oquendo, M.A., Galfalvy, H., Russo, S., Ellis, S.P., Grunebaum, M.F., Burke, A., Mann, J.J., 2004. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am. J. Psychiatry* 161, 1433–1441.
- Perlis, R.H., Beasley Jr., C.M., Wines Jr., J.D., Tamura, R.N., Cusin, C., Shear, D., Amsterdam, J., Quitkin, F., Strong, R.E., Rosenbaum, J.F., Fava, M., 2007. Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes. *Psychother. Psychosom.* 76, 40–46.
- Pezawas, L., Angst, J., Gamma, A., Ajdacic, V., Eich, D., Rossler, W., 2003. Recurrent brief depression—past and future. *Prog. Neuro-psychopharmacol. Biol. Psychiatry* 27, 75–83.
- Rihmer, Z., Akiskal, H., 2006. Do antidepressants t(h)reat(en) depressives? Toward a clinically judicious formulation of the antidepressant-suicidality FDA advisory in light of declining national suicide statistics from many countries. *J. Affect. Disord.* 94, 3–13.
- Simon, G.E., Savarino, J., Operskalski, B., Wang, P.S., 2006. Suicide risk during antidepressant treatment. *Am. J. Psychiatry* 163, 41–47.
- Statham, D.J., Heath, A.C., Madden, P.A., Bucholz, K.K., Bierut, L., Dinwiddie, S.H., Slutske, W.S., Dunne, M.P., Martin, N.G., 1998. Suicidal behaviour: an epidemiological and genetic study. *Psychol. Med.* 28, 839–855.
- Teicher, M.H., Glod, C., Cole, J.O., 1990. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am. J. Psychiatry* 147, 207–210.
- Teicher, M.H., Glod, C.A., Cole, J.O., 1993. Antidepressant drugs and the emergence of suicidal tendencies. *Drug Safety* 8, 186–212.