Meta-Analysis of Efficacy and Treatment-Emergent Suicidality in Adults by Psychiatric Indication and Age Subgroup Following Initiation of Paroxetine Therapy: A Complete Set of Randomized Placebo-Controlled Trials

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ABSTRACT

Objective: This meta-analysis of placebo-controlled paroxetine trials examines suicidality incidence in adults, focusing on disorder and age as potential risk factors. The findings are put in context with an efficacy meta-analysis of the same trial datasets.

Data Sources: GlaxoSmithKline paroxetine clinical trial database(s).

Study Selection: All double-blind, randomized, placebo-controlled, parallel-group studies of paroxetine therapy in adults enrolling at least 30 patients total were included in the analysis. The dataset comprised 14,911 patients from 61 trials.

Data Extraction: Possible cases of suicidality were identified and blindly categorized by an expert panel, using methodology previously used by the US Food and Drug Administration. Incidences of suicidal behavior (preparatory act, suicide attempt, or completed suicide) and any suicidality (suicidal behavior or ideation) were compared between paroxetine and placebo. Efficacy assessments were based on standard depression rating scales (eg, Hamilton Depression Rating Scale or Montgomery-Asberg Depression Rating Scale) and Clinical Global Impressions Improvement scale (CGI-I) scores.

Results: In the primary dataset, ie, all disorders combined, there were no significant differences between paroxetine and placebo for overall suicidality (suicidal behavior or ideation: n/n = 83/8,958 [0.93%] vs n/n = 65/5,953 [1.09%], respectively; OR = 0.9 [95% CI, 0.7–1.3]; *P* = .649) or for suicidal behavior specifically (n/n = 50/8,958 [0.56%] vs n/n = 40/5,953 [0.67%], respectively; OR = 1.2 [95% CI, 0.8–1.9]; *P* = .483). However, in patients with major depressive disorder (MDD), a greater incidence of suicidal behavior occurred in paroxetine-treated patients than in placebo-treated patients (n/n = 11/3,455 [0.32%] vs n/n = 1/1,978 [0.05%], respectively; OR = 6.7 [95% CI, 1.1–149.4]; *P* = .058). Across all indications, a higher incidence of suicidal behavior occurred in paroxetine-treated versus placebo-treated adults aged 18 to 24 years (n/n = 17/776 [2.19%] vs n/n = 5/542 [0.92%], respectively; OR = 2.4 [95% CI, 0.9–7.3]). In older age groups, no increase in suicidality was observed. Efficacy was demonstrated in all disorders evaluated, including MDD.

Conclusions: Across all disorders, overall suicidality incidence was similar between paroxetine and placebo. However, a higher frequency of suicidal behavior occurred with paroxetine in MDD, which was largely explained by the higher incidence in young adults. These data support the efficacy of paroxetine therapy; however, they also highlight the need for careful monitoring of suicidality during antidepressant therapy, particularly in younger adults.

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The selective serotonin reuptake inhibitors (SSRIs) have been widely used for the treatment of depressive and anxiety disorders since the late 1980s. While these agents are efficacious and generally well tolerated, standard precautionary statements regarding "suicidality" have existed in SSRI (and other antidepressant) prescribing information for more than a decade. These precautions, however, did not explicitly alert prescribers to the potential that the medication itself could induce suicidality. Concerns about a possible link between SSRI therapy and an increased risk of suicidality in adult patients were first raised for fluoxetine in the early 1990s.[1] However, subsequent meta-analyses conducted shortly thereafter did not provide evidence supporting this association,[2] and an expert panel, convened in 1991 by the US Food and Drug Administration (FDA),[3] concluded that there was no compelling evidence for such an association. Nevertheless, the issue continued to be monitored by the FDA, other regulatory agencies, antidepressant manufacturers, and investigators.[2,4–7] For example, in 2000, Khan and colleagues[4] reported that rates of suicide and attempted suicide did not differ significantly among the placebo- and antidepressant-treated groups in the FDA database, a finding reproduced by Storosum and colleagues[5] in 2001 using the Dutch Medicines Evaluation Board's database. Khan and colleagues' finding[4] regarding suicide based on the FDA database was subsequently confirmed by the FDA in an initial analysis of 9 antidepressants studied in 251 randomized controlled trials.[6] In 2003, Olfson et al[7] reported an inverse relationship between change in use of antidepressants in adolescents and suicide, ie, a 1% increase in adolescent use of antidepressants was associated with a decrease of 0.23 suicides per 100,000 adolescents per year ($P < .001$). In 2004, Grunebaum et al[8] similarly concluded, using a variety of data sources, that the decline in the national suicide rate from 1985 to 1999 appeared to be associated with increased use of antidepressants during that period.

Regarding paroxetine specifically, an analysis conducted by GlaxoSmithKline in 2002 and submitted to the FDA in February 2003 examined the incidence of self-harm in placebo-controlled trials in adult patients with depression (including major depressive disorder [MDD], intermittent brief depression, dysthymic disorder, and bipolar depression). The incidence of self-harm in the paroxetine-treated patients was 2.1% (66/3,192)

compared to 1.9% for placebo (38/2,047); this difference was not statistically significant ($P = .61$).

In late 2002, GlaxoSmithKline began a comprehensive analysis of suicidality in the 6 available double-blind, placebo-controlled pediatric paroxetine trials (MDD, 3 trials; obsessive-compulsive disorder [OCD], 2 trials; and social anxiety disorder, 1 trial). According to an objective search algorithm to find suicidality-related adverse events (suicidal ideation and behavior), 2.7% of pediatric subjects taking paroxetine compared to 1.1% of pediatric subjects taking placebo had a potential suicidality-related adverse event ($P = .07$). When the researchers expanded the analysis to also include events occurring during the 30-day period following the last dose (the "on-therapy plus 30 days following therapy" time period), the frequency of events was 3.4% versus 1.2% for paroxetine and placebo, respectively, which met a conventional threshold for statistical significance ($P = .01$). No statistically significant difference in the frequency of these events within each individual pediatric trial was found between paroxetine and placebo. These findings were submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom and to the FDA in May 2003. The MHRA promptly ruled that paroxetine should not be used in those individuals under the age of 18 years, given the lack of evidence for antidepressant efficacy in the pediatric population. Shortly thereafter, the FDA issued a public health advisory suggesting that paroxetine not be used for the treatment of pediatric MDD until more data were available. Further investigation of paroxetine (and other SSRIs) and suicidality by regulatory bodies and by GlaxoSmithKline followed, as summarized below.

In 2003, an Expert Working Group (EWG) of the Committee on Safety of Medicines was convened in the United Kingdom to investigate the ongoing safety concerns with SSRIs, particularly regarding suicidal behavior in youth, for whom the therapeutic effects of these medications were less well established. As part of its review, the EWG conducted a meta-analysis of the adult clinical trials of paroxetine and concluded that, while there was no strong evidence of an increased risk of suicidal behavior/events for adult patients with depression exposed to paroxetine compared to placebo, a modest increase in the risk of suicidal thoughts and self-harm could not be ruled out. The EWG also included available epidemiologic data from the UK General Practice Research Database (GPRD) in their analysis, which indicated that, in adults, there was no increased risk of suicidal behavior with SSRIs compared with tricyclic antidepressants.[9]

During the same time period, the MHRA referred paroxetine to European Union (EU) regulatory authorities for an EU-level review (known as an "Article 31 referral"),[10] with particular attention to potential risk factors for suicidality, including age and gender. This Article 31 referral stemmed from GlaxoSmithKline's findings in the pediatric population. The Article 31 review suggested that, across all indications studied in placebo-controlled trials in adults, the incidence of possible suicidal thoughts and behaviors was similar in the paroxetine and placebo groups (0.8% vs 0.9%, respectively). The findings were also similar in the studies conducted specifically in patients with depressive illness (1.7% vs 1.9%; includes MDD, intermittent brief depression, dysthymia, and bipolar depression). In young adults (18 to 29 years of age), however, for all indications combined, the incidence of possibly suicide-related events was greater in the paroxetine group (1.8%) than in the placebo group (1.4%), although this difference was not statistically significant (OR 1.28 [95% CI, 0.70–2.32]; $P = .46$).[10]

While European regulatory agencies were examining suicidality from adult antidepressant studies, the FDA was conducting a new meta-analysis of individual patient data from the pediatric clinical trials of antidepressants. On the basis of an analysis of 24 pediatric trials of 9 compounds in approximately 4,500 patients, they found that antidepressants were associated with an increased risk of suicidality relative to placebo.[11] The average risk of such events was 4% in pediatric patients taking antidepressants, which was significantly greater than the 2% risk observed among those taking placebo (risk ratio, 1.95 [95% CI, 1.28–2.98]). There were no completed suicides in this dataset. These findings in pediatric patients ultimately resulted in the inclusion of a boxed warning in all antidepressant product labeling. GlaxoSmithKline concurrently reexamined its pediatric paroxetine data, using similar methodology as that being employed by the FDA, and similarly found a higher incidence of suicidality in paroxetine-treated patients (3.4%) compared to those taking placebo (0.9%) (OR = 3.86 [95% CI, 1.45–10.26]).[12]

In December 2004, the FDA initiated steps to reexamine the relationship between antidepressant use and suicidality in adult patients by using similar methodology utilized for their analysis of the pediatric suicidality data. The results of this analysis, released in December 2006, and in contrast to their earlier findings in adults, suggested the increased short-term risk for suicidality with antidepressant treatment in pediatric patients appeared to extend into younger adults (up to age 25 years).[13,14] A suicide-protective effect was suggested in that analysis for elderly subjects using antidepressants. GlaxoSmithKline concurrently initiated its own analysis of the adult suicidality paroxetine datasets utilizing the methodology developed by the FDA for analyzing the pediatric datasets; the results of this analysis were posted at the GlaxoSmithKline Web site in May 2006.[15] This article presents the results of these most recent comprehensive analyses of the onset of suicidality within the complete adult paroxetine dataset, with attention given to the specific disorders treated and age as potential risk factors for suicidality. The analyses presented in this article utilized methodological approaches defined prior to those used by FDA in their analyses of the adult data. Therefore, this article supplements rather than duplicates those analyses.

Recent claims of selective reporting and publication bias have challenged widely accepted views regarding antidepressant efficacy and have placed antidepressant use under renewed scrutiny.[16,17] Therefore, because the potential association between antidepressants and the emergence of suicidality should be considered in the context of the

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Table 1. List of Trials Included in the Meta-Analysis[a]

Trial No.	Definitive Suicidal Behavior or Ideation	Definitive Suicidal Behavior	Rating Scale–Emergent Behavior or Ideation	Indication
276	X	X		MDD
279				MDD
274	X	X	X	MDD
001	X	X	X	MDD
002				MDD
009				MDD
003		X		MDD
115				MDD
128				MDD
251				MDD
448				MDD
449				MDD
487		X		MDD
625				MDD
785				MDD
810		X		MDD
NKD20006[b]	X	X	X	MDD
874	X	X		MDD
442	X	X		MDD
057 (LT)				IBD
106 (LT)				IBD
327		X		Dysthymia
352	X	X		Bipolar disorder
433	X	X	X	Fibromyalgia
201	X	X	X	Detoxification of alcoholic patients
637		X	X	GAD
641	X	X		GAD
642		X		GAD
791		X		GAD
116		X		OCD
118			X	OCD
136				OCD
241 (LTX of 136)				OCD
414	X	X	X	OCD
660			X	OCD
108	X	X	X	Panic disorder
120				Panic disorder
187				Panic disorder
222 (LTX of 120)				Panic disorder
223		X	X	Panic disorder
228 (LTX of 187)				Panic disorder
494	X	X	X	Panic disorder
495		X	X	Panic disorder
497	X	X	X	Panic disorder
384	X	X	X	Panic disorder
410	X	X	X	Panic disorder
400	X	X	X	PMDD
427 (LT)	X	X	X	PMDD
658		X	X	PMDD
677	X	X	X	PMDD
688	X	X	X	PMDD
689	X	X	X	PMDD
711 (LTX of 677, 688, 689)	X	X	X	PMDD
627				PTSD
648		X		PTSD
651		X		PTSD
382		X	X	Social anxiety disorder
454		X	X	Social anxiety disorder
502			X	Social anxiety disorder
790	X	X	X	Social anxiety disorder
661		X	X	Social anxiety disorder

[a]X indicates trials with zero of the events in question (ie, events of definitive suicidal behavior or ideation, definitive suicidal behavior, or rating scale–emergent behavior or ideation).
[b]Paroxetine was the active comparator.
Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, LT = long term, LTX = long-term extension, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

potential benefit offered, we present the suicidality analyses results in tandem with the results of a meta-analysis of efficacy (versus placebo) utilizing the same complete paroxetine clinical trial datasets.

METHOD

Description of Clinical Trials Dataset

Fifty-seven acute double-blind, randomized, placebo-controlled, parallel-group studies of paroxetine therapy in adults, enrolling at least 30 patients total, plus 4 long-term extension studies of 1 or more of those studies (total 61 studies), were included in the analysis (Table 1). This analysis included 23 trials of depressive disorders (19 in MDD, 2 in intermittent brief depression, 1 in bipolar disorder, and 1 dysthymia trial) and 38 trials of other disorders (11 in panic disorder, 6 in OCD, 5 in social anxiety disorder, 4 in generalized anxiety disorder [GAD], 3 in posttraumatic stress disorder [PTSD], 7 in premenstrual dysphoric disorder, 1 in fibromyalgia, and 1 trial in detoxification of alcoholic patients). Intermittent 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.[18,19] The larger intermittent brief depression study (study 057) specifically included patients who exhibited suicidal behavior within 10 days of study entry; for both intermittent brief depression studies, occurrence of suicidal behavior was an outcome measure. These 2 trials, therefore, contributed a relatively large number

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of events to the dataset. One additional trial (29060/298) could not be included because individual patient data were not available. This study has been published previously[20] and is summarized in GlaxoSmithKline's Clinical Trial Registry (http://www.gsk-clinicalstudyregister.com/). Its exclusion had no material effect on our meta-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. All analyses (efficacy and safety) were based on the *intent-to-treat population*, defined as all patients who were randomly assigned and received at least 1 dose of trial medication. Additionally, analyses of change from baseline required that at least 1 postbaseline measurement was taken for the parameter of interest.

Identification and Classification of Potential Suicidality Cases

Potential cases of suicidality were identified via text string searches of adverse event terms, review of all serious adverse event narratives (including all deaths), review of all adverse events coded as accidental injuries, and review of the comment fields from the case report forms for all relevant studies, as described elsewhere.[21] Cases were included in the list of potential events only if they occurred during the double-blind phase of treatment or within 1 day following the cessation of randomized treatment (as was done in the FDA's pediatric analysis). For all potential events, a detailed narrative blinded to information that might bias assessment (eg, treatment, disease indication, names of all medications) was prepared. GlaxoSmithKline contracted with Columbia University to have independent experts blindly review each case narrative and classify the events into suicidal or nonsuicidal categories using the same approach used in the pediatric suicidality review conducted by the FDA. Each narrative was reviewed by 3 expert raters and assigned a code according to the classifications specified by the FDA (Table 2). In the event of disagreement between expert raters, the majority rating was taken as the final rating for each case. Suicidal behavior or ideation included codes 1 through 4; suicidal behavior alone included codes 1 through 3. All statistical analyses of suicidality incidence rates in this report were based upon the classifications obtained from this blinded review.

Analysis Objectives

The primary objective of the safety analysis was to compare the incidence of suicidal behavior or ideation for paroxetine versus placebo. Secondary objectives included comparison between paroxetine and placebo of the incidence of other measures of suicidality. These measures included suicidal behavior alone, rating scale–emergent suicidal behavior or ideation, rating scale–emergent suicidal behavior alone, and declining suicidal behavior or ideation (also based on depression rating scale data). Rating scale–emergent suicidal behavior and ideation could be examined for all of the depression clinical trials. Only a subset of the nondepression trials included sequential administration of rating scales containing suicidality items; however, the available data are presented. *Rating scale–emergent suicidal behavior and ideation* on the Hamilton Depression Rating Scale (HDRS) (item 3) or the Montgomery-Asberg Depression Rating Scale (MADRS) (item 10) was defined as any case in which a patient's pretreatment baseline score was 0 or 1 (corresponding to absent or minimal suicidal thoughts) and increased to ≥ 3 (suicidal ideas/gestures or greater) while on double-blind treatment, up to and including 1 day after the cessation of treatment. *Rating scale–emergent suicidal behavior* was defined as any case in which a patient's pretreatment baseline suicide item score was 0 or 1 and increased to 4 (attempt at suicide) for the HDRS or to 6 (explicit plans for suicide) for the MADRS while on double-blind treatment, up to and including 1 day after the cessation of treatment. In any trial in which both the HDRS and MADRS were used, data were assessed independently on each scale, and a patient was considered to have satisfied the definition of emergent ideation or behavior if the criteria were met for 1 or both of the scales. *Declining suicidal ideation* was defined as any case with a baseline HDRS item 3 or MADRS item 10 ≥ 3 reduced to a score of 0 or 1 at endpoint.

Table 2. Classification of Potential Events[a]

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 (nonfatal)

[a]Categories 1–4 were referred to collectively as definitive suicidal behavior or ideation; categories 1–3 were referred to collectively as definitive suicidal behavior.

The efficacy assessment of paroxetine (vs placebo) was based on standard disease-specific rating scale scores (eg, HDRS and/or MADRS for depressive symptoms, the Hamilton Anxiety Rating Scale [HARS] for anxious symptoms, the Yale-Brown Obsessive Compulsive Scale [Y-BOCS] for OCD symptoms, the Liebowitz Social Anxiety Scale [LSAS] for symptoms of social anxiety disorder) or Clinical Global Impressions-Improvement scale (CGI-I) scores, each using a last-observation-carried-forward approach.

Statistical Methods

The statistical methods for this meta-analysis were defined prospectively in an analysis plan.[22] The analysis of suicidality data was conducted by using 2 methods for estimating the common odds ratio and its confidence interval, as well as by testing the null hypothesis that the common odds ratio is equal to 1. The primary analysis weighted the results of each trial by using an exact approach[23] implemented in the statistical software StatXact (Cytel Inc, Cambridge, Massachusetts). This method excludes studies with zero events in both arms but permits the inclusion of

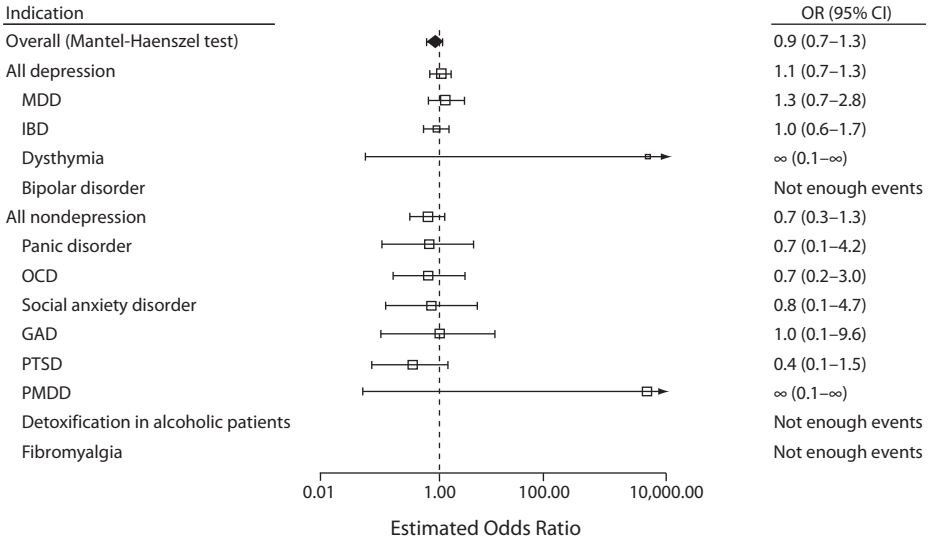
Table 3. Definitive Suicidal Behavior or Ideation by Indication and Treatment

Indication	Paroxetine, n/n (%)	Placebo, n/n (%)	Odds Ratio (95% CI)	*P* Value	Heterogeneity Test[a]	Heterogeneity *P* Value
Overall (Mantel-Haenszel)	83/8,958 (0.93)	65/5,953 (1.09)	0.9 (0.7–1.3)	.649	20.825, $df = 34$[a]	.963[a]
All depression	66/3,720 (1.77)	47/2,260 (2.08)	1.1 (0.7–1.7)	.671	< 0.001	.765
MDD	31/3,455 (0.90)	11/1,978 (0.56)	1.3 (0.7–2.8)	.493	< 0.001	.566
IBD	34/149 (22.82)	36/154 (23.38)	1.0 (0.6–1.7)	> .99	0.278	.712
Dysthymia	1/81 (1.23)	0/85 (0.00)	∞ (0.1–∞)	.488	NA	NA
Bipolar disorder	0/35 (0.00)	0/43 (0.00)	NA	NA	NA	NA
All nondepression	17/5,238 (0.32)	18/3,693 (0.49)	0.7 (0.3–1.3)	.293	< 0.001	.513
Panic disorder	3/1,092 (0.27)	3/903 (0.33)	0.7 (0.1–4.2)	.689	0.114	.324
OCD	5/698 (0.72)	4/416 (0.96)	0.7 (0.2–3.0)	.723	0.102	.792
Social anxiety disorder	3/943 (0.32)	3/643 (0.47)	0.8 (0.1–4.7)	> .99	0.148	.524
GAD	2/904 (0.22)	2/697 (0.29)	1.0 (0.1–9.6)	> .99	0.335	> .99
PTSD	3/698 (0.43)	6/510 (1.18)	0.4 (0.1–1.5)	.176	0.134	.406
PMDD	1/820 (0.12)	0/438 (0.00)	∞ (0.1–∞)	> .99	NA	NA
Detoxification of alcoholic patients	0/57 (0.00)	0/60 (0.00)	NA	NA	NA	NA
Fibromyalgia	0/26 (0.00)	0/26 (0.00)	NA	NA	NA	NA

[a]Breslow-Day test used on asymptotic analyses (as opposed to Zelen test for exact analyses).
Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, MDD = major depressive disorder, NA = not applicable, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

studies with zero cells in only one arm, without the need for cell adjustments. Heterogeneity between trials was assessed using the Zelen test or the Breslow-Day test for analyses in which the Zelen statistic could not be calculated. The second approach was to use the Mantel-Haenszel test, with 0.5 continuity correction[24] applied at the level of the trial. This method had previously been used by the FDA in its analysis of the pediatric datasets and was included here for completeness. Unless otherwise indicated, the results using the exact approach are presented. Exact *P* values were calculated by summing all probabilities less than or equal to the observed, and confidence intervals using the mid-p method. Instances in which the 95% confidence interval did not include 1 were considered significant, even when the *P* value exceeded the conventional standard of .05. No adjustment of *P* values was made for multiple comparisons.

Figure 1. Definitive Suicidal Behavior or Ideation (all indications)



Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

RESULTS

Demographic and Background Characteristics

A total of 14,911 subjects were randomly assigned to double-blind therapy with either paroxetine (n = 8,958) or placebo (n = 5,953) during these trials. Subjects with MDD comprised the single largest subset based on specific disorder (5,433/14,911; 36.4% of the total). The mean age in both treatment groups was 41 years (approximately 45 years for the depressive disorder studies and 38 years for the nondepressive disorder studies). Approximately 60% of the overall subjects were female.

Suicidality

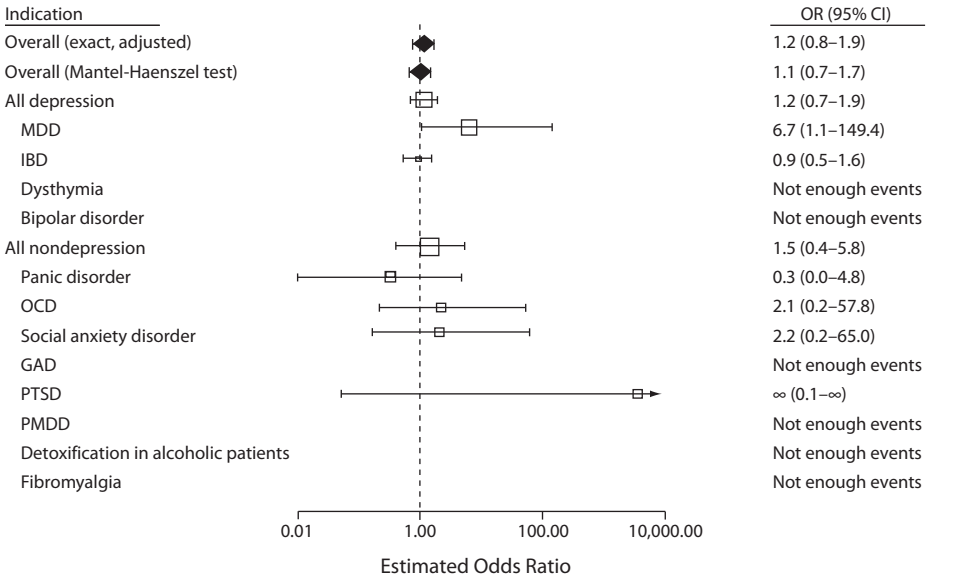
There were no statistically significant differences between adults treated with paroxetine compared to placebo on overall suicidality (ie, behavior or ideation combined). This finding held true for all indications pooled, for depressive disorder studies pooled, for nondepressive disorder studies pooled, and for each indication assessed individually (Table 3, Figure 1). Across all indications, 83/8,958 patients (0.93%) taking paroxetine and 65/5,953 patients (1.09%) taking placebo had such events (OR = 0.9; 95% CI, 0.7–1.3). Results were similar when we assessed suicidal behavior alone across all indications, with 50/8,958 patients (0.56%) taking paroxetine

Table 4. Definitive Suicidal Behavior by Indication and Treatment

Indication	Paroxetine, n/n (%)	Placebo, n/n (%)	Odds Ratio (95% CI)	*P* Value	Heterogeneity Test[a]	Heterogeneity *P* Value
Overall (exact, adjusted)	50/8,958 (0.56)	40/5,953 (0.67)	1.2 (0.8–1.9)	.483	< 0.001	.958
Overall (Mantel-Haenszel)	50/8,958 (0.56)	40/5,953 (0.67)	1.1 (0.7–1.7)	.721	5.813, *df* = 18[a]	.997
All depression	43/3,720 (1.16)	36/2,260 (1.59)	1.2 (0.7–1.9)	.613	0.003	.965
MDD	11/3,455 (0.32)	1/1,978 (0.05)	6.7 (1.1–149.4)	.058	0.269	> .99
IBD	32/149 (21.48)	35/154 (22.73)	0.9 (0.5–1.6)	.890	0.270	.705
Dysthymia	0/81 (0.00)	0/85 (0.00)	Not enough events	NA	NA	NA
Bipolar disorder	0/35 (0.00)	0/43 (0.00)	Not enough events	NA	NA	NA
All nondepression	7/5,238 (0.13)	4/3,693 (0.11)	1.5 (0.4–5.8)	.759	0.018	.426
Panic disorder	1/1,092 (0.09)	2/903 (0.22)	0.3 (0.0–4.8)	.561	0.600	> .99
OCD	3/698 (0.43)	1/416 (0.24)	2.1 (0.2–57.8)	.642	0.338	.659
Social anxiety disorder	2/943 (0.21)	1/643 (0.16)	2.2 (0.2–65.0)	.609	NA	NA
GAD	0/904 (0.00)	0/697 (0.00)	Not enough events	NA	NA	NA
PTSD	1/698 (0.14)	0/510 (0.00)	∞ (0.1–∞)	.497	NA	NA
PMDD	0/820 (0.00)	0/438 (0.00)	Not enough events	NA	NA	NA
Detoxification of alcoholic patients	0/57 (0.00)	0/60 (0.00)	Not enough events	NA	NA	NA
Fibromyalgia	0/26 (0.00)	0/26 (0.00)	Not enough events	NA	NA	NA

[a]Breslow-Day test used on asymptotic analyses (as opposed to Zelen test for exact analyses).
Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, MDD = major depressive disorder, NA = not applicable, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

Figure 2. Definitive Suicidal Behavior (all indications)



Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

and 40/5,953 patients (0.67%) taking placebo categorized as having suicidal behavior events (OR = 1.2; 95% CI, 0.8–1.9) (Table 4, Figure 2). No significant differences in the relative frequencies of suicidal behavior events were observed for depressive disorder studies pooled, for nondepressive disorder studies pooled, and for each indication assessed separately, with the exception of MDD. In the MDD subgroup, however, episodes of suicidal behavior occurred in 11 of 3,455 paroxetine patients (0.32%) (all of which were suicide attempts, with no completed suicides) and 1 of 1,978 placebo patients (0.05%) (OR = 6.7; 95% CI, 1.1–149.4; *P* = .058; see Figure 2). There was 1 completed suicide, a 23 year-old man with social anxiety disorder who had received paroxetine.

The percentage of patients with treatment-emergent suicidal behavior or ideation based on the HDRS or MADRS rating scale suicide items was significantly lower in patients taking paroxetine compared to placebo across all indications (0.81% vs 1.20%, respectively [OR 0.7; 95% CI, 0.5–0.9; *P* = .012]) (Table 5). This trend was also seen in patients with MDD specifically (1.08% in paroxetine patients, 1.66% in placebo patients [OR 0.6; 95% CI, 0.4–1.0; *P* = .050]) as well as in patients across all nondepression indications (0.32% paroxetine, 0.68% paroxetine [OR 0.4; 95% CI, 0.2–0.8; *P* = .014]). No differences were noted between groups for rating scale–based emergent suicidal behavior only, but very few events were noted overall (3 events for paroxetine-treated patients, 2 events for placebo-treated patients, or 0.03% in each group).

Influence of Age as a Risk Factor

Although not statistically significant, a higher frequency of both overall suicidality (20/776 [2.58%] vs 7/542 [1.29%], OR = 2.0 [95% CI, 0.8–4.8]) and suicidal behavior alone (17/776 [2.19%] vs 5/542 [0.92%], OR = 2.4 [95% CI, 0.9–7.3]) was found across all indications in young adults (prospectively defined as age 18–24 years) treated with paroxetine compared with placebo (Table 6). In young adults

Table 5. Rating Scale–Emergent Suicidal Behavior or Ideation by Indication and Treatment

Indication	Paroxetine, n/n (%)	Placebo, n/n (%)	Odds Ratio (95% CI)	*P* Value	Heterogeneity Test[a]	Heterogenity *P* Value
Overall (Mantel-Haenszel)	72/8,917 (0.81)	71/5,905 (1.20)	0.7 (0.5–0.9)	.012	27.554, $df = 28$[a]	.488
All depression	55/3,679 (1.49)	46/2,212 (2.08)	0.8 (0.5–1.2)	.222	17.635, $df = 18$[a]	.480
MDD	37/3,414 (1.08)	32/1,930 (1.66)	0.6 (0.4–1.0)	.050	< 0.001	.461
IBD	14/149 (9.40)	14/154 (9.09)	1.0 (0.5–2.3)	> .99	0.408	> .99
Dysthymia	2/81 (2.47)	0/85 (0.00)	∞ (0.3–∞)	.237	NA	NA
Bipolar disorder	2/35 (5.71)	0/43 (0.00)	∞ (0.4–∞)	.198	NA	NA
All nondepression	17/5,238 (0.32)	25/3,693 (0.68)	0.4 (0.2–0.8)	.014	< 0.001	.350
Panic disorder	2/1,092 (0.18)	1/903 (0.11)	1.0 (0.1–32.5)	> .99	0.601	> .99
OCD	4/698 (0.57)	7/416 (1.68)	0.3 (0.1–0.9)	.041	0.159	.159
Social anxiety disorder	0/943 (0.00)	0/643 (0.00)	Not enough events	NA	NA	NA
GAD	3/904 (0.33)	2/697 (0.29)	1.3 (0.2–11.3)	> .99	0.379	.614
PTSD	8/698 (1.15)	15/510 (2.94)	0.4 (0.2–1.0)	.052	0.103	.618
PMDD	0/820 (0.00)	0/438 (0.00)	Not enough events	NA	NA	NA
Detoxification of alcoholic patients	0/57 (0.00)	0/60 (0.00)	Not enough events	NA	NA	NA
Fibromyalgia	0/26 (0.00)	0/26 (0.00)	Not enough events	NA	NA	NA

[a]Breslow-Day test used on asymptotic analyses (as opposed to Zelen test for exact analyses).
Abbreviations: GAD = generalized anxiety disorder, IBD = intermittent brief depression, MDD = major depressive disorder, NA = not applicable, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

Table 6. Definitive Suicidal Behavior or Ideation by Indication, Treatment, and Age as a Risk Factor

	Definitive Suicidal Behavior or Ideation			Definitive Suicidal Behavior Alone		
Disorder	Paroxetine, n/n (%)	Placebo, n/n (%)	Odds Ratio (95% CI)	Paroxetine, n/n (%)	Placebo, n/n (%)	Odds Ratio (95% CI)
Age, 18–24 y						
All indications	20/776 (2.58)	7/542 (1.29)	2.0 (0.8–4.8)	17/776 (2.19)	5/542 (0.92)	2.4 (0.9–7.3)
All depression	15/272 (5.51)	6/149 (4.03)	1.4 (0.5–3.7)	13/272 (4.78)	5/149 (3.36)	1.4 (0.5–4.6)
MDD	5/230 (2.17)	0/104 (0.00)	∞ (0.6–∞)	3/230 (1.30)	0/104 (0.00)	∞ (0.3–∞)
IBD	10/35 (28.57)	6/38 (15.79)	2.1 (0.7–7.1)	10/35 (28.57)	5/38 (13.16)	2.6 (0.8–9.4)
All nondepression	5/504 (0.99)	1/393 (0.25)	3.9 (0.5–93.7)	4/504 (0.79)	0/393 (0.00)	∞ (0.7–∞)
Age, 25–64 y						
All indications	59/7,543 (0.78)	57/5,000 (1.14)	0.7 (0.5–1.0)	32/7,543 (0.42)	34/5,000 (0.68)	0.6 (0.4–1.0)
All depression	48/2,931 (1.64)	40/1,797 (2.23)	0.7 (0.5–1.1)	30/2,931 (1.02)	30/1,797 (1.67)	0.6 (0.4–1.0)
MDD	23/2,713 (0.85)	10/1,567 (0.64)	1.3 (0.6–2.9)	8/2,713 (0.29)	0/1,567 (0.00)	∞ (1.3–∞)
IBD	24/112 (21.43)	30/113 (26.55)	0.8 (0.4–1.4)	22/112 (19.64)	30/113 (26.55)	0.7 (0.4–1.3)
All nondepression	11/4,612 (0.24)	17/3,203 (0.53)	0.4 (0.2–1.0)	2/4,612 (0.04)	4/3,203 (0.12)	0.3 (0.0–2.0)

Abbreviations: IBD = intermittent brief depression, MDD = major depressive disorder.

with MDD, there were proportionally more overall suicidality events (suicidal behavior with or without ideation) in subjects treated with paroxetine (5/230 [2.17%]) compared to placebo (0/104 [0%]) than in older adults (aged 25 to 64 years: paroxetine, 23/2,713 [0.85%] vs placebo, 10/1,567 [0.64%]). The same pattern was seen for suicidal behavior in the MDD young adult patients, ie, there were proportionally more events of suicidal behavior in young adults treated with paroxetine (3/230 [1.30%]) compared to placebo (0/104 [0.0%]) than in older adults (8/2,713 [0.29%] for paroxetine vs 0/1,567 [0.0%] for placebo).

Treatment Efficacy

Paroxetine-treated patients with MDD had a significantly greater reduction in HDRS total score from baseline than those treated with placebo (−10.8 vs −8.3, respectively, $P < .001$; Table 7). Similar results were observed for change from baseline on the MADRS total score (−12.2 vs −8.5 for paroxetine and placebo, respectively, $P < .001$; Table 7). Consistent with these findings, when treatment response in MDD was defined as a 50% or greater reduction in the primary outcome measure (HDRS or MADRS total score), significantly more paroxetine-treated patients (52.3%) than placebo-treated patients (37.1%) were considered responders ($P < .001$; Table 7).

In the nondepressive disorder indications, for which *response* was defined as a CGI-I score of "much improved" or "very much improved," significantly more patients taking paroxetine (58.8%) responded compared to those taking placebo (39.9%; $P < .001$; Table 8). Although the data are not shown in Table 8, there were significantly more responders in the paroxetine group versus the placebo group for panic disorder (68.3% vs 47.4%; $P < .001$), OCD (38.3% vs 23.3%; $P < .001$), social anxiety disorder (53.9% vs 31.1%; $P < .001$), GAD (64.5% vs 49.4%; $P < .001$), PTSD (58.2% vs 39.6%; $P < .001$), and premenstrual dysphoric disorder (68.9% vs 42.3%; $P < .001$). There was also evidence of significant improvement for paroxetine compared to placebo based on change from baseline in the total score on disease-specific rating scales in these nondepressive disorder populations (Table 8).

The analysis of declining suicidal ideation (based on rating scale data) for all indications pooled showed a significantly greater proportion of paroxetine-treated patients with declining suicidal ideation as compared to placebo (43.2% vs 33.9%, OR = 1.5 [95% CI, 1.1–2.0]; $P = .004$). This

Table 7. Efficacy Results: MDD Studies by Treatment and Age Group

Endpoint	Paroxetine, n/n (%)		Placebo, n/n (%)	Odds Ratio (95% CI)	*P* Value
≥ 50% Reduction in HDRS or MADRS					
All ages	1,688/3,227 (52.31)		702/1,890 (37.14)	1.8 (1.6 to 2.0)	< .001
18–24 y	102/214 (47.66)		45/98 (45.92)	1.1 (0.7 to 1.7)	
25–64 y	1,317/2,525 (52.16)		538/1,497 (35.94)	1.9 (1.7 to 2.2)	
	N	LS Mean	LS Mean	Estimated Treatment Effect (95% CI)	
HDRS change from baseline					
All ages	4,609	−10.9	−8.4	−2.5 (−3.0 to −2.1)	< .001
18–24 y	282	−10.8	−9.9	−0.9 (−2.8 to 0.9)	
25–64 y	3,671	−10.9	−8.2	−2.7 (−3.2 to −2.1)	
MADRS change from baseline					
All ages	1,759	−12.2	−8.5	−3.7 (−4.7 to −2.7)	< .001
18–24 y	105	−11.9	−8.9	−3.1 (−7.7 to 1.6)	
25–64 y	1,479	−12.2	−8.3	−3.9 (−5.0 to −2.8)	

Abbreviations: HDRS=Hamilton Depression Rating Scale, LS=least squares, MADRS=Montgomery-Asberg Depression Rating Scale, MDD=major depressive disorder.

Table 8. Efficacy Results: Nondepression Studies by Treatment and Age Group

Endpoint	Age Group	Paroxetine, n/n (%)		Placebo, n/n (%)	Odds Ratio (95% CI)	*P* Value
Responders (CGI-I score of 1 or 2)	All	2,867/4,877 (58.79)		1,424/3,565 (39.94)	2.3 (2.1 to 2.5)	< .001
	18–24	280/473 (59.20)		163/378 (43.12)	1.9 (1.5 to 2.5)	
	25–64	2,533/4,288 (59.07)		1,218/3,090 (39.42)	2.2 (2.0 to 2.4)	
Change from baseline: disorder/scale	Age Group	N	Paroxetine LS Mean	Placebo LS Mean	Estimated Treatment Effect (95% CI)	*P* Value
OCD/Y-BOCS	All	1,080	−6.8	−4.1	−2.7 (−3.7 to −1.8)	< .001
Social anxiety disorder/LSAS	All	1,522	−28.1	−16.6	−11.5 (−14.2 to −8.9)	< .001
GAD/HARS	All	1,558	−12.7	−10.9	−1.8 (−2.6 to −1.1)	< .001
PTSD/CAPS-2	All	1,037	−36.8	−26.7	−10.1 (−13.2 to −6.9)	< .001
PMDD/VAS-mood	All	1,092	−35.6	−24.9	−10.8 (−13.7 to −7.8)	< .001

Abbreviations: CAPS-2 = Clinician-Administered PTSD Scale–Version 2, CGI-I = Clinical Global Impressions-Improvement of Illness scale, GAD = generalized anxiety disorder, HARS = Hamilton Anxiety Rating Scale, LSAS = Liebowitz Social Anxiety Scale, LS = least squares, OCD = obsessive-compulsive disorder, PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder, VAS = Visual Analog Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

finding was seen for all depression studies pooled (52.11% vs 38.75%, OR = 1.5 [95% CI, 1.1–2.0]; *P* = .008) and for patients with MDD specifically (63.7% vs 53.4%, OR = 1.7 [95% CI, 1.2–2.4]; *P* = .002). The percentage of patients with declining suicidal ideation in the nondepressive disorder studies was also greater for paroxetine compared to placebo (18.8% vs 13.5%); however, the difference in that dataset was not statistically significant (OR = 1.7 [95% CI, 0.8–3.6]; *P* = .211).

Paroxetine efficacy in young adults aged 18–24 years was generally comparable to that in older adults in populations included in nondepressive disorder studies (Table 8). There was also evidence of efficacy in young adults with MDD that was generally comparable, based on similar mean improvements from baseline across groups, to findings in older adults (Table 7); however, the magnitude of the advantage versus placebo varied on the basis of the depression scale used (ie, HDRS or MADRS).

DISCUSSION

This meta-analysis of suicidality-related adverse events from the complete set of randomized, placebo-controlled clinical trials of paroxetine in adults did not reveal a significant difference between paroxetine and placebo across all disorders studied either in the incidence of overall suicidality (ie, suicidal behavior or ideation) or in the incidence of suicidal behavior alone. However, there was a higher frequency of suicidal behavior in patients with MDD who were treated with paroxetine compared to placebo. The absolute number of suicide attempts in the paroxetine group was small (11) and the incidence of such events was relatively low (0.32%); nevertheless, this event rate was significantly higher than that observed among patients taking placebo (0.05%; *P* = .058 [95% CI, 1.1–149.4]). Review of the 11 suicide attempt cases in the paroxetine MDD subgroup (described elsewhere[25]) revealed common clinical features: symptomatic improvement, younger age, 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.

The analysis of all studies and indications pooled also found a higher frequency of overall suicidality (suicidal behavior or ideation) and suicidal behavior alone in young adults (18 to 24 years of age) treated with paroxetine compared with placebo (2.58% vs 1.29% for suicidal behavior or ideation; 2.19% vs 0.92% for suicidal behavior alone), although these differences did not reach statistical significance (OR = 2.0 [95% CI, 0.8–4.8] for suicidal behavior or ideation; OR = 2.4 [95% CI, 0.9–7.3] for suicidal behavior alone). By contrast, there were no such increases in the older adult age groups (25–64 years) across all indications. Together, these data suggest that young adults (especially those with MDD) may be at increased risk for suicidal ideation or behavior following the initiation of paroxetine therapy, although the

incidence of such events was much lower than that observed in pediatric patients treated with paroxetine.[12]

In contrast to the suicidality findings based on analyses of adverse events, the percentage of patients with emergent suicidal behavior or ideation based on change in the HDRS or MADRS rating scale suicide items was significantly higher for patients taking placebo compared to paroxetine across all indications (including MDD). This lack of concordance between the incidence of suicidality based on adverse event reports versus rating scale suicide item endpoints was previously observed in the paroxetine pediatric dataset[12] as well as in the FDA's pooled analysis of pediatric data from 9 different antidepressant programs.[11] The reason for this discordance is unclear, but it may have resulted, in part, because rating scale suicide item scores were often not captured on the day, or within several days, of onset of the suicidality adverse event in question or because these scales were not completed due to the suicidality adverse event leading to study withdrawal. Additionally, adverse events are generally elicited in clinical trials by general, nondirect questioning (eg, "Have you experienced any difficulties?") or are reported spontaneously by the patient. The HDRS and MADRS ratings, however, are based on interviews by clinicians who are specifically assessing the patient's depressive symptomatology. Patients may be more likely to report suicidal ideation or behaviors in this setting, irrespective of treatment assignment. Lastly, although it may be that these scales also lack sensitivity for detecting suicidality, this possibility is less likely, as the HDRS item 3 positively correlates with the Scale for Suicidal Ideation,[26] and evidence of positive predictive validity has been reported.[27]

While some have concluded that the analyses of existing clinical trial data confirm that paroxetine use is causally associated with increased suicide attempts,[28] others have suggested that the finding of increased suicidality in populations treated with paroxetine or other antidepressants in clinical trials may be an artifact of selection bias.[29] Our view is that it is not possible to definitively conclude a causal relationship between paroxetine and treatment-emergent suicidal behavior in the MDD population analyzed herein for the following reasons: the findings were predicated on a small number of events in both paroxetine and placebo groups (largely because those who were actively suicidal were excluded from entry); were accompanied by broad confidence intervals; were neither supported by the primary endpoint (suicidal behavior or ideation) analyses nor replicated by other secondary analyses in the non-MDD datasets; involved an analysis of studies in which the randomization process was not stratified by preexisting suicide risk factors (including potential genetic susceptibility[30]) and, consequently, those risks may have been unevenly distributed at baseline; and are inconsistent with the findings from the rating scale suicide item analysis. Although the observed association from a retrospective analysis can be a first step in assessing causality, it cannot alone provide the information necessary to separate potential confounding factors from a true cause and effect relationship.

The finding of evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo (driven largely by the young adult age group) is new and was not found in the Article 31 analysis or in other prior analyses of suicidality conducted by GlaxoSmithKline. The difference in results between the prior Article 31 analysis and the current analysis may be explained either by differences in the datasets included in the analyses or by the methodologies used, including the methods used to identify the relevant events. With respect to the datasets, clinical trials included in the current analysis, consistent with FDA, were restricted to double-blind, placebo-controlled trials with more than 30 total patients, whereas the Article 31 analysis contained a broader dataset. Analysis methodology differed in that the current analysis assessed depressive disorders by specific indication (eg, MDD, intermittent brief depression, etc) in addition to pooled analyses. Consistent with FDA guidance, the young adult group was defined as 18 to 24 years; in the Article 31 analysis, the analogous age range was 18 to 29 years. Additionally, the Article 31 analysis was an unadjusted pooled analysis, which is in contrast to the current meta-analysis in which the analyses were weighted according to the size of the trial. In terms of the methodology used to identify events, detection of cases was enhanced by review of the case report form comment fields and all serious adverse event narratives, and the cases comprising the current analysis were individually reviewed by independent, external experts who were blinded to treatment.

Given the potential risk for treatment-emergent suicidality in some patients, treatment decisions regarding antidepressant use should also be based on efficacy. Some researchers who have conducted meta-analyses of overlapping datasets have concluded that paroxetine and other antidepressants are largely ineffective in treating depression (Kirsch et al,[31] Barbui et al[32]). In contrast, the current analysis provides clear evidence of the efficacy of paroxetine in MDD in adults in accordance with applicable regulatory standards. A recent meta-analysis by Fournier et al,[33] based to a large extent on paroxetine data from only 3 studies, concluded that a clinically relevant benefit of antidepressant medication compared with placebo (using the National Institute for Health and Clinical Excellence [NICE] criterion of a difference of at least 3 points on the HDRS as the threshold for clinical significance[34]) was evident only in patients with very severe symptoms (ie, those with HDRS scores of at least 25). However, as pointed out by Thase,[35] a mean 2-point advantage over placebo on the HDRS is not trivial from a public health perspective. Similarly, Hegerl and Mergl[36] rather persuasively argued that it could be potentially misleading to evaluate the utility of antidepressants based on the NICE criterion because that approach risks erroneously discarding treatments that have demonstrated a clear benefit for patients. Also, to conclude based on limited clinical trial data that antidepressants do not have clinically meaningful effects in subjects with less than very severe symptoms requires one to overlook a number of methodological and analytic issues that often compromise the sensitivity of controlled clinical trials of antidepressants.[35] Consistent with that thinking, it has been postulated by some that the drug-placebo difference in antidepressant trials may actually

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be much greater than previously believed.[37,38] Interrogating data collected only from acute, short-term antidepressant trials also does not provide the full clinical efficacy picture, given that the most robust effects of antidepressants are associated with the prevention of relapse and recurrence.[39] A meta-analysis conducted by Geddes et al[40] demonstrated a 70% reduction in relapse with continuation of antidepressant treatment compared to those who were switched to placebo, which is clearly clinically meaningful.

Regarding the efficacy of paroxetine compared to other antidepressants, Cipriani et al[41] compared the efficacy of 12 different antidepressants, including paroxetine, and concluded that paroxetine is not as effective, nor as well tolerated, as some other antidepressants. However, the majority of trials utilized in that meta-analysis, while utilizing a double-blind randomization scheme, were not placebo-controlled; furthermore, the adequacy of the treatment blinding was also unclear for most of those trials.[41]

In the current analysis, in addition to the benefit observed in MDD, efficacy was also demonstrated for paroxetine in OCD, social anxiety disorder, GAD, PTSD, and premenstrual dysphoric disorder. The benefit of paroxetine in reducing symptoms of depression and anxiety was confirmed on a variety of endpoints, including change from baseline in disorder-specific ratings scales (eg, HDRS, MADRS, HARS, LSAS, Y-BOCS) as well as on both global- (CGI) and depression-specific (50% reduction in HDRS/MADRS) classifications of response, in studies conducted across more than a decade. Furthermore, an efficacy analysis including only patients with suicidal ideation present at baseline provided evidence that paroxetine reduced the preexisting suicidality in these patients compared to placebo.

The antidepressant efficacy of paroxetine in the young adult MDD population was less consistently documented. On the one hand, CGI responder rates and improvement on the MADRS were comparable to the outcomes of older adults. On the other hand, outcomes on the HDRS for young adults were not significant compared to placebo and were numerically smaller than observed for older adults. Likewise, for this 18- to 24-year-old group, the calculated confidence intervals for score reduction (improvement) on either scale were broader than for older adults and included 0, suggesting a greater variability of response in younger adults. As the HDRS and MADRS generally are found to have comparable psychometric performance in studies directly comparing these measures, this discrepancy could be either the result of a chance occurrence or an indication that the HDRS is selectively less sensitive to detecting change in young adults than the MADRS. By contrast, the evidence for the efficacy of paroxetine in young adults with anxiety disorders was generally comparable to that obtained in older adults.

The use of SSRIs, including paroxetine, has been associated with increased suicidality (suicidal ideation or behavior) in children and adolescents in placebo-controlled clinical trials.[11,12] Debate continues to persist as to whether this association extends to the adult population as a whole, and the literature regarding this subject is voluminous and mixed. For example, most ecological studies, in adolescents as well as in adults, have shown that increases in antidepressant use in a population are either associated with decreases in population suicide or suicide attempt rates or have shown no relationship.[7,8,42–56] In 2 such studies, which examined large outpatient health plan claims databases, Simon et al[55,56] compared the rate of suicide attempts before and after initiation of antidepressant treatment and determined that the peak period of suicide attempts occurred in the month *prior* to initiation of treatment, not after. Likewise, recent observational studies (eg, case-control and cohort studies) have generally not identified an increased risk for suicidal behavior in adults treated with SSRIs as compared to other antidepressants[57,58] or to no antidepressant treatment.[59–63] In a systematic review of 8 observational studies, Barbui et al[64] concluded that use of SSRIs may be associated with a reduced risk of suicide in adults with depression. Exceptions to this include a study by Juurlink et al,[65] which found an increased risk of suicide in the elderly during the first month of SSRI therapy compared with other antidepressants, and a case-control study by Valuck et al,[66] which found, upon examination of suicide attempt risk by phase of treatment, that the highest risk for suicide attempt was associated with antidepressant initiation. The Valuck et al[66] study also found an increased risk for suicide attempt during the first 14 days following antidepressant discontinuation. Forensic studies in individuals who committed suicide have generally found that a relatively low percentage of the suicide victims had detectable levels of an antidepressant in their blood at the time of death.[67–69]

Individual randomized, double-blind, placebo-controlled trials have not shown evidence of increased risk of suicidality for antidepressants versus placebo. However, individual studies generally have limited ability to detect such effects because they are too small and typically exclude at-risk subjects. Examination of the SSRI data in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which enrolled over 4,000 subjects, found that treatment of MDD with an SSRI was more likely to be associated with a decrease rather than an increase in suicidal ideation in those with suicidal ideation at entry.[70] Emergent suicidal ideation did also occur, although infrequently, in some subjects who did not have suicidal ideation at the start of treatment. Importantly, there was a strong inverse relationship between response and suicidal ideation, ie, reduction of suicidal ideation was strongly related to response and remission.[70]

Meta-analyses of placebo-controlled clinical trial data have not detected an increase in completed suicide in patients treated with antidepressants as compared to placebo.[6,71] In contrast, 2 other meta-analyses, one of the published literature[72] and the other of MHRA drug registration data,[73] suggested a possible increased frequency of suicide attempts during antidepressant treatment. Finally, in its recently completed meta-analysis of data provided by the manufacturers of 11 antidepressants, the FDA found that the increased short-term risk for suicidality with antidepressant treatment in pediatric patients appears to extend to younger adults (up to age 25).[13,14] This increased risk was not seen between the

ages of 25 and 64 years, while in subjects aged 65 and older, there was a reduced risk of suicidality with antidepressant treatment.[13,14] Thus, the FDA's most recent findings for antidepressants as a class are similar to the findings for paroxetine observed in the current analysis. Regarding the risk of suicidal acts associated with individual antidepressant agents, the most recently published data from Schneeweiss et al[74,75] found no clinically relevant variation in risk by type or class of antidepressant medication either in adults or in children and adolescents.

Limitations

There are a number of limitations to this analysis, including (1) the small incidence and absolute number of events; (2) the lack of studies prospectively designed to identify suicidal behavior specifically (except for the intermittent brief depression studies); (3) exclusion of subjects from studies (again, except for intermittent brief depression) if they were considered at risk of suicidality, which limits the generalizability of these data; and (4) the retrospective nature of this meta-analysis. Additionally, the dataset included only events within the double-blind, placebo-controlled phase of acute treatment trials; events occurring during the taper or the follow-up phases of the studies were not included (consistent with FDA methodology).

In conclusion, we found an increased frequency, relative to placebo, of suicidal behavior (all of which were suicide attempts) in MDD patients treated with paroxetine. Review of these MDD cases revealed that the majority of events occurred in younger adults. A trend for potentially increased suicidal behavior or ideation in paroxetine-treated young adults was also observed in the overall (all indications) group. It is therefore important that all patients, especially young adults, receive careful monitoring during paroxetine therapy regardless of the condition being treated and irrespective of whether they appear to be improving or not. However, the results also provide evidence substantiating the efficacy of paroxetine in adults with MDD and other disorders, although efficacy among young adults with MDD was less consistently documented. Taken together, these safety and efficacy data indicate that paroxetine can be a favorable treatment option in conjunction with appropriate clinical monitoring.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others).

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