Duloxetine

Meta-analyses of Suicidal Behaviors and Ideation in Clinical Trials for Major Depressive Disorder

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Background: Uncertainty regarding relationships of antidepressant treatment and suicidality encouraged systematic review of data on suicidal behaviors and ideation from Phase II and III clinical trials of duloxetine for major depressive disorder (MDD).

Methods: We evaluated all completed duloxetine trials in MDD with data lock by February 2, 2004. We compared incidence of suicide-related events with duloxetine versus placebo in controlled trials, using Mantel-Haenszel incidence difference (MHID) and exposure time-adjusted rate difference (MHRD) methods, and analyzed changes in Hamilton Depression Scale (HAMD) Item-3 (suicidality) scores.

Results: There were no significant differences in the incidence of suicide-related events with duloxetine versus placebo in 12 placebo-controlled trials (duloxetine, 1812; placebo, 1814 patients). The MHID for suicide-related behaviors was −0.03% (95% confidence interval [CI], −0.48 to 0.42) and MHRD −0.002 (95% CI, −0.02 to 0.02). Changes in HAMD Item-3 suicidality scores showed more improvement with duloxetine (MHID, 9.56%; 95% CI, 4.50 to 14.6; $P < 0.001$) and less worsening of suicidal ideation with duloxetine (MHID, −4.25%; 95% CI, −6.55 to −1.95; $P < 0.001$). Other Item-3 findings showed no consistent pattern; a slightly higher proportion of duloxetine-treated patients with a change from 0 (absent) to 3 was balanced against a higher proportion of placebo-treated patients changing from 0 to 2.

Conclusions: We found no evidence of an increased risk of suicidal behaviors or ideation during treatment with duloxetine compared with placebo in MDD patients. HAMD Item-3 suicidality scores had more improvement and less worsening of suicidal ideation with duloxetine than placebo.

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Suicide was the 11th most common cause of death in the United States in 2002.[1] Severe major depressive disorder (MDD) and bipolar I and II disorders increase risk of suicide more than 20-fold, and most persons who commit suicide have clinical depression.[2–5] Antidepressants are the mainstay of treatment of depression, but despite their well-established efficacy in depression, this efficacy has not translated into consistent reductions of suicidal risk.[5,6] In the early 1990s, case reports suggested increased or new suicidality during treatment with antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs).[7,8] A Food and Drug Administration (FDA) advisory panel concluded in 1991 that there was insufficient evidence to link SSRIs to suicidal behaviors,[9] and most later reports found no clear evidence of either increased or decreased risk of suicidality during antidepressant treatment.[10–16] Nevertheless, some researchers have continued to propose that suicidal risk might be increased in some adults, specifically with SSRIs.[17,18]

In 2004, the British MHRA advised that SSRIs were not recommended for initial treatment of mild depression in children and adolescents because the risk-benefit ratio appeared to be poor.[19] Additional US FDA meta-analyses found evidence of increased risk of suicidal thoughts and behaviors (there were no suicides) in 25 controlled trials of SSRIs involving approximately 4400 children and adolescents diagnosed with MDD, obsessive-compulsive disorder, or other psychiatric disorders.[20] These findings led to a labeling change with a warning of potentially increased risk of suicidality in pediatric patients treated with most antidepressants.[21] In early 2005, the FDA issued a broad labeling and treatment guide for use of antidepressants for all ages and diagnoses.[22] It emphasized the need for close clinical monitoring for potential emerging suicidality and changes in behavior, especially during the initial days and weeks of a course of drug therapy, or at times of dose changes, either increases or decreases.

Recent reviews have further investigated whether SSRIs or other antidepressants are associated with changes in suicidality in adults. In a meta-analysis of approximately

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52,000 adults in 477 randomized controlled trials of SSRIs compared with placebo, Gunnell and colleagues[23] found only suggestive evidence of increased risk of nonfatal self-harm in adults treated with SSRIs that was not adjusted for duration-of-exposure (risk ratio [RR] = 1.57; 95% confidence interval [CI], 0.99–2.55) but little difference in risk of either suicidal thoughts (RR = 0.77; 95% CI, 0.37–1.55) or of completed suicides (RR = 0.85; 95% CI, 0.20–3.40). Martinez and colleagues[24] compared risk of suicides and attempts with SSRIs versus tricyclic antidepressants (TCAs) in a nested case-control analysis involving more than 146,000 patients aged 10 to 89 years, after a first antidepressant prescription for depression. Risks differed little between SSRIs and TCAs: the overall adjusted odds ratio (OR) for nonfatal self-harm was 0.99 (95% CI, 0.86–1.14) and for suicide was 0.57 (95% CI, 0.26–1.25). However, uniquely among persons aged 18 years or younger, there were no completed suicides, but the proportion with self-harm was higher with SSRIs than with TCAs (OR = 1.59; 95% CI, 1.01–2.50). Fergusson and colleagues[25] reviewed published reports of randomized controlled trials (all ages) comparing the incidence of suicide attempts (not adjusted for exposure time) for an SSRI versus placebo (approximately 18,400 patients) and versus alternative antidepressants. They found a higher incidence of suicide attempts with SSRIs versus placebo (OR = 2.28; 95% CI, 1.14–4.55) and SSRIs versus undefined treatments other than TCAs (OR = 1.94; 95% CI, 1.06–3.57) but no difference between SSRIs and TCAs (OR = 0.88; 95% CI, 0.54–1.42).

Duloxetine is a potent and relatively balanced inhibitor of the neuronal transport (''reuptake'') of both serotonin and norepinephrine believed to act by potentiating both serotonergic and noradrenergic neurotransmission in the central nervous system.[26] Duloxetine was FDA-approved for treatment of MDD in 2004, based in part on several double-blind, placebo-controlled clinical trials.[27–29] Given the unresolved status of suicidal risk during antidepressant treatment and the availability now of a large amount of information from duloxetine clinical trials, we present the results of a comprehensive, meta-analytic review of suicidal behaviors and ideation in all Phase II and III clinical trials of duloxetine in the treatment of MDD completed by early 2004.

METHODS

Data Sources

We included all completed duloxetine trials in MDD with data lock by February 2, 2004 that were sponsored by the manufacturer, Eli Lilly and Company (16 trials) and by Shionogi Company, Ltd, (11 trials) who hold the license for the development of duloxetine in Japan. Of the 27 duloxetine trials, 12 were Eli Lilly and Company-sponsored, double-blind, randomized, placebo-controlled, US or international trials (7 also included an active-comparator antidepressant), another 11 were Shionogi-sponsored trials in Japan (3 double-blind active-control; 8 uncontrolled; 0 placebo-controlled), and 4 were Eli Lilly and Company-sponsored open-label trials (uncontrolled).

All patients provided written informed consent after the study was explained and before the performance of any protocol procedures and administration of study drug.

Identification of Potential Suicide-related Adverse Events

Potential suicide-related behaviors or ideation were identified using a comprehensive computerized text search of Eli Lilly and Company and Shionogi databases of clinical trials of duloxetine in MDD. Text fields searched within the Eli Lilly and Company database included all investigator-recorded adverse events coded by MedDRA (Medical Dictionary for Regulatory Activities) terminology[30] (see meddramsso.com), as well as any additional free-text recorded at any time. This procedure ensured that any event that might have been miscoded would be identified for further review. A similar approach using Japanese characters was taken in the Shionogi database. Text strings used to search the Eli Lilly and Company database included the following:

- attempt, cut, gas, hang, hung, jump, mutilat, overdos, damag, harm, inflict, injur, shoot, slash, suic, aggression, asphyxia, burning, death, die, drown, dying, emotion, exhaust, firearm, gun, hostil, ideation, immolat, intent, kill, lac, mani, monoxide, o.d., o/d, plastic, poison, railway, rifle, s.h., s.i., shot, suffocat; od, si, dsh.

Events identified by these search criteria were reviewed manually to determine their potential to be suicide-related. We included only treatment-emergent events defined as those occurring after the first dose and within 24 hours of the final dose and either not present during the pretreatment period or more severe during treatment.

Categorization of Suicidal Events

Categories were determined based on requests from various regulatory authorities (MHRA, FDA, Health Protection Branch of Health Canada) for other Eli Lilly and Company neuroscience compounds and further refined as a result of extensive review of the relevant research literature. Two Eli Lilly and Company clinical research staff trained in the assessment of suicidal events and held blind to treatment independently categorized each event. Their determinations were compared to obtain consensus, with adjudication by a third Eli Lilly and Company reviewer when necessary. Suicide-related thoughts and behaviors (''events'') were categorized as shown in Table 1.

Assessment of the 17-Item Hamilton Rating Scale for Depression Item-3 Data

In additional secondary analyses, investigator-elicited ratings of Item-3 (suicidality) of the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) were assessed in the 12 double-blind placebo-controlled duloxetine trials. Item-3 was scored as follows:

- 0, ''Absent;'' 1, ''Feels life is not worth living;'' 2, ''Wishes he were dead or any thoughts of possible death to self;'' 3, ''Suicide ideas or gestures;'' and 4, ''Attempts at suicide.''

The following HAMD Item-3 outcomes were considered: (*a*) worsening of suicidal ideation (any increase from the

TABLE 1. Categories of Suicide-related Thoughts and Behaviors (''Events'')

Completed suicide (Category 1)	A self-inflicted action resulting in death by injury, poisoning, or suffocation with explicit or implicit evidence of intent to die or with no information with which to determine intent
Nonfatal suicide attempt (Category 2)	A self-inflicted action potentially resulting in injury, poisoning, or suffocation with explicit or implicit evidence of intent to die or with no information with which to determine intent
Aborted suicidal act (Category 3)	Any action stopping short of a directly self-harmful act that a reasonable person would interpret as indicating that a suicidal act or other suicide-related behavior might occur in the immediate future
Instrumental suicidal act (suicidal gesture) (Category 4)	A self-inflicted action potentially resulting in injury, poisoning, or suffocation, with evidence that the person did not intend to die but instead used the appearance of suicidal behavior to attain some other end, such as to seek help or attention or to punish others
Suicidal ideation (Category 5)	Elicited or non-elicited, oral or written ideation of serving as the agent of one's own death, which might vary in specificity of plans and in the degree of suicidal intent, including wishing to be dead but not merely thinking of death or dreaming of death or suicide

maximum score during the pretreatment phase to any time during treatment, for patients with all scores <4 during the pretreatment phase); (*b*) improvement in suicidal ideation (any decrease from the last pretreatment score to the final score, for patients who could improve from a nonzero pretreatment score); (*c*) emergence of substantial suicidal ideation (change from 0 or 1 at every pretreatment assessment to 3 or 4 at any time during treatment, for patients with 0 or 1 at every pretreatment assessment); (*d*) change from 0 at every pretreatment assessment to 4 at any time during treatment, and from 0 to 3, and from 0 to 2.

Analyses of Data From All Double-blind Placebo-controlled Trials

The prespecified primary analysis was a meta-analysis of the proportion of patients (trial incidence) with a suicide-related behavior in all 12 placebo-controlled duloxetine trials, using the Mantel-Haenszel incidence difference (MHID) method.[31] The MHID is the average of individual trial incidence differences (duloxetine minus placebo), including trials with no events (difference, 0), weighting by the number of patients in each trial. The fixed-effect Mantel-Haenszel method is more likely to detect a significant difference than the random-effects method.

We used the Cochran Q-statistic[32] to test for homogeneity of treatment group differences across trials. If treatment group differences were nonhomogeneous, we planned to use the adjusted DerSimonian and Laird[32] random-effects method to analyze incidence differences. However, there was no evidence of heterogeneity in any comparison (all $P \geq 0.208$).

In addition, in sensitivity analyses, we calculated Mantel-Haenszel incidence ratios (MHIRs) (duloxetine/placebo), weighted by the number of events and sample size and considering only trials with at least 1 suicidal event. For trials with events in only 1 treatment arm, we added the constant value of 0.5 to each cell.[33] For analyses with less than 5 events in a treatment arm, we used a modified Mantel-Haenszel exact test based on a Robins-Breslow-Greenland variance estimate.[34,35]

To adjust for potentially unequal exposure times owing to differential dropout rates after randomization, we used the Mantel-Haenszel time-adjusted rate difference method (MHRD)[31] to adjust for time of exposure to treatment (up to suicide-related event or end of trial), with exact CIs obtained by using exact limits from a χ^2 distribution.[33] We also calculated Mantel-Haenszel time-adjusted rate ratios.[36]

To evaluate the $HAMD_{17}$ Item-3 data, we applied the same methods used to analyze the incidence of suicide-related adverse events.

Analysis of Event Data From All 27 MDD Trials

Overall rates of completed and attempted suicide per 100,000 person-years of treatment were calculated for all duloxetine-treated patients across all 27 MDD trials, including placebo-controlled, open-label, uncontrolled, and active comparator trials. Results were compared with historical data on overall rates seen in clinical trials on other antidepressants. Given the small number of patients and events in the active comparator groups in duloxetine trials, only descriptive statistics are provided comparing duloxetine and active comparators.

RESULTS

Suicide-related Events in Double-blind Placebo-controlled Trials

We analyzed the 12 randomized, placebo-controlled trials involving 2996 patients (1812 duloxetine and 1184 placebo). The ratio of patients randomized to duloxetine versus placebo was 1:1 in 7 trials, 2:1 in 4 trials, and 3:1 in 1 trial. Demographic characteristics and baseline depression severity were similar in the duloxetine and placebo groups (Table 2). The mean ± SD treatment exposure time (up to a suicide-related event or end of trial, in days) for duloxetine was 99.7 ± 95.4 (median, 61; range, 2–436) and for placebo, 83.8 ± 80.6 (median, 61; range, 2–455).

All counts refer to the number of patients with an event. Only 1 patient had more than 1 event (2 reports of suicidal ideation) but is only counted once in the analyses. Completed suicides were rare, one on duloxetine and one on placebo. Nonfatal suicide attempts were also infrequent (Table 3). There was no evidence of heterogeneity of incidence differences among the trials for any of the outcomes (Cochran Q

TABLE 2. Baseline Patient Characteristics in Placebo-controlled Trials of Duloxetine in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-defined*, Major Depression

	Duloxetine (n = 1812)	Placebo (n = 1184)
Caucasian, n (%)	1603 (88.5)	1023 (86.4)
Age, mean (SD)	42.1 (12.1)	41.5 (12.7)
Females, n (%)	1193 (65.8)	779 (65.8)
$HAMD_{17}$ total, mean (SD) (range)*	22.4 (3.9) (15–38)	22.0 (3.8) (15–36)
$HAMD_{17}$ Item-3, mean (SD) (range)*	0.93 (0.90) (0–4)	0.88 (0.89) (0–4)

*The $HAMD_{17}$ scores are shown at study entry. No clinically relevant differences were seen between treatment groups for any baseline characteristics.

scores all yielded $P \geq 0.208$), supporting use of the fixed-effect Mantel-Haenszel method. The MHID for all suicide-related behaviors (Categories 1–4) was −0.031 (95% CI, −0.482 to 0.421). None of the MHIDs were statistically significant (all $P \geq 0.562$). The results for the incidence ratios (MHIR) were similar (all $P \geq 0.587$).

Figure 1 summarizes the incidence difference with 95% CIs for suicide-related behaviors in each of the 12 placebo-controlled randomized trials, as well as the MHID. Risk differences fluctuated apparently randomly around the null (zero), ranging from −1.01 to +1.00. Three trials had more suicidal patients with placebo, 2 had more with duloxetine, and 7 had none. Most suicide-related behaviors (8/13) occurred in 1 trial (HMAI), which involved 3:1 randomization to duloxetine versus placebo, and higher baseline depression ratings than in other trials. At study entry, the mean total $HAMD_{17}$ score in trial HMAI was 24.5, and 45.5% had scores more than or equal to 25; in the other 11 trials, the HAMD score averaged 21.8, and only 22.0% of patients scored more than or equal to 25. Trial HMAI studied duloxetine daily doses of 5, 10, and 20 mg that are now known to be subtherapeutic. The 2 suicide-related behaviors in patients given duloxetine in the other trials occurred at 40 and 120 mg daily (see Fig. 1).

Exposure time-adjusted rates of suicidal events also indicated minor differences between duloxetine and placebo (Table 4). The MHRD for suicide-related behaviors was −0.002 (95% CI, −0.020 to 0.016; $P = 0.838$). None of the MHRDs were statistically significant (all $P \geq 0.497$). Results for the rate ratios (MHRR) were similar (all $P \geq 0.500$). Within 4 weeks of starting treatment, 3 duloxetine-treated (0.17%) and 2 placebo-treated (0.17%) patients experienced suicidal behavior (after 6, 7, and 11 days on duloxetine and after 9 and 16 days on placebo). In the treatment period beyond the first 4 weeks, 6 duloxetine-treated (0.33%) and 2 placebo-treated (0.17%) patients experienced suicidal behavior (after 35, 36, 58, 82, 120, and 179 days on duloxetine and after 222 and 260 days on placebo). Of additional note for duloxetine and placebo combined, although the number of events was small, the rate of suicidal acts within the first 4 weeks (2.5 per 100 person-years) was higher than in later weeks (1.4 per 100 person-years).

$HAMD_{17}$ Item-3 Analyses

Based on Item-3 scores, suicidal ideation improved more often with duloxetine, whereas suicidal ideation worsened more often with placebo (Table 5). Emergence of substantial suicidal ideation (Item-3 score increase from 0 or 1 to 3 or 4) was detected among 7 (0.58%) of 1211 patients on duloxetine and 2 (0.24%) of 818 on placebo (exact $P = 0.115$). No patient experienced a change from 0 to 4 (''attempts at suicide''), during treatment although 2 patients on duloxetine and 2 patients on placebo had an Item-3 score of 0 at baseline and a suicide attempt during the trial (all 4 were discontinued from the trial and therefore had no

TABLE 3. Meta-analysis: Suicide-related Events During Treatment in Placebo-controlled Trials of Duloxetine for Major Depression

	Duloxetine (n = 1812)	Placebo (n = 1184)	MHID (%)		MHIR (%)	
Event Category	n (%)	n (%)	Difference (95% CI)	P*	Ratio (95% CI)	P†
Completed suicide (Category 1)	1 (0.06)	1 (0.08)	−0.049 (−0.257 to 0.159)	0.642	0.495 (0.312–7.821)	0.617
Nonfatal suicide attempt (Category 2)	7 (0.39)	2 (0.17)	0.056 (−0.302 to 0.414)	0.759	1.029 (0.262–4.037)	0.968
All suicide attempts (fatal and nonfatal) (Categories 1 & 2)	8 (0.44)	3 (0.25)	0.007 (−0.407 to 0.421)	0.974	0.900 (0.268–3.031)	0.866
Aborted suicidal act (Category 3)	0	0	—	—	—	—
Instrumental suicidal act (Category 4)	1 (0.06)	1 (0.08)	−0.038 (−0.218 to 0.143)	0.683	0.546 (0.061–4.845)	0.587
All suicide-related behaviors (Categories 1–4)	9 (0.50)	4 (0.34)	−0.031 (−0.482 to 0.421)	0.893	0.848 (0.281–2.553)	0.769
Suicidal ideation (Category 5)	24 (1.32)	12 (1.01)	0.231 (−0.549 to 1.012)	0.562	1.154 (0.600–2.220)	0.667
All Suicide-related events (Categories 1–5)	33 (1.82)	16 (1.35)	0.200 (−0.698 to 1.098)	0.662	1.116 (0.621–2.006)	0.713

*Based on Mantel-Haenszel incidence difference methods.
†Based on Mantel-Haenszel weighted method; in addition, the P value from the exact test of the modified Mantel-Haenszel test for all comparisons was more than or equal to 0.56.

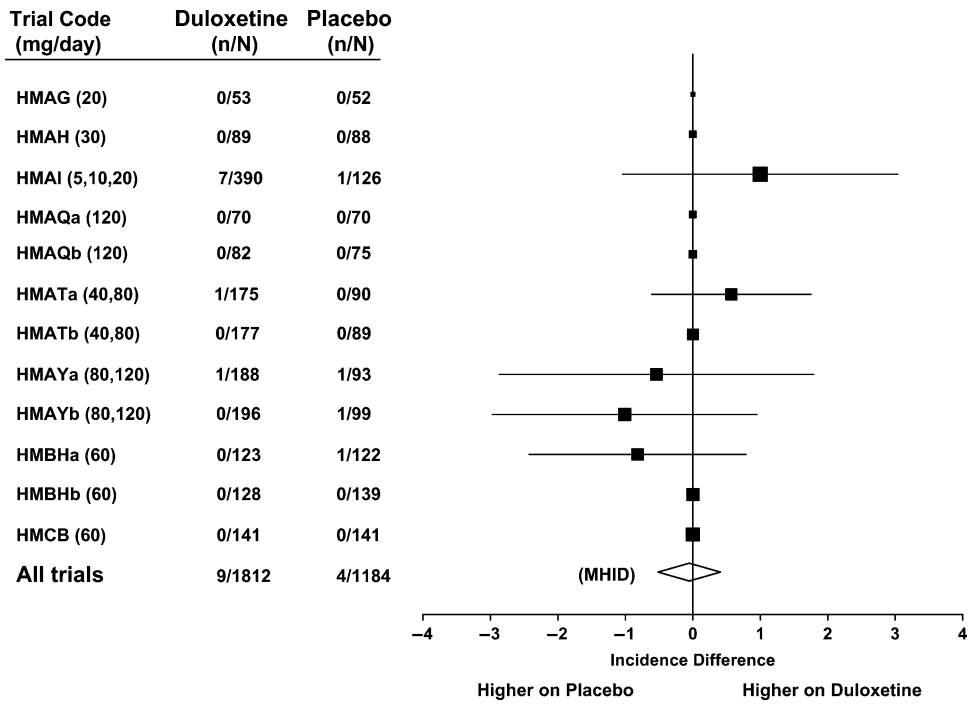

FIGURE 1. Incidence differences and their 95% CI for suicidal behaviors (Categories 1–4) in all 12 randomized, placebo-controlled trials of duloxetine in MDD completed by February 2004 (2996 patients). Studies are in chronological order, with number of patients with suicidal behavior on duloxetine versus placebo and the MHID (−0.031; 95% CI, −0.482 to +0.421; open diamond). Forest plot symbols (filled squares) are proportional to weight based on number of patients/trial. For trials with more than 1 duloxetine treatment arm, the duloxetine doses are provided for each arm (separated by commas).

TABLE 4. Meta-analysis: Exposure Time-adjusted Suicidal Event Rates During Treatment in Placebo-controlled Trials of Duloxetine for Major Depression

	Duloxetine (n = 1812) (493 person-years)*		Placebo (n = 1184) (270 person-years)*		MHRD (%)		MHRR (%)	
Event Category	**n**	**n/person-year**	**n**	**n/person-year**	**Difference (95% CI)**	***P*†**	**Ratio (95% CI)**	***P***
Completed suicide (Category 1)	1	0.002	1	0.004	−0.003 (−0.012 to 0.007)	0.580	0.404 (0.025–6.456)	0.507
Nonfatal suicide attempts (Category 2)	7	0.014	2	0.007	0.002 (−0.012 to 0.017)	0.765	1.256 (0.251–6.298)	0.781
All suicide attempts (fatal and nonfatal) (Categories 1 & 2)	8	0.016	3	0.011	−0.0004 (−0.017 to 0.017)	0.967	0.972 (0.250–3.785)	0.968
Aborted suicidal act (Category 3)	0	0	0	0	—	—	—	—
Instrumental suicidal act (Category 4)	1	0.002	1	0.004	−0.002 (−0.008 to 0.005)	0.643	0.485 (0.012–19.948)	0.696
All suicide-related behaviors (Categories 1–4)	9	0.018	4	0.015	−0.002 (−0.020 to 0.016)	0.838	0.880 (0.247–3.136)	0.844
Suicidal ideation (Category 5)	24	0.049	12	0.044	0.011 (−0.021 to 0.044)	0.497	1.276 (0.627–2.595)	0.500
All suicide-related events (Categories 1–5)	33	0.067	16	0.059	0.010 (−0.028 to 0.047)	0.621	1.166 (0.629–2.163)	0.626

*Exposure time for all event categories is adjusted for time to first suicide-related event.
†Based on normal test of Mantel-Haenszel exposure time-adjusted rate difference.

TABLE 5. Meta-analyses of $HAMD_{17}$ Item-3 Scores in Placebo-controlled Trials of Duloxetine in Major Depression

	Duloxetine	Placebo	Exact Test	MHID (%)		MHIR (%)	
$HAMD_{17}$ Item-3 Changes	n/N (%)	n/N (%)	*P**	Difference (95%CI)	*P*†	Ratio (95%CI)	*P*‡
Any decrease	673/899 (74.9)	341/529 (64.5)	NA	9.56 (4.50 to 14.6)	<0.001	1.15 (1.07–1.23)	<0.001
Any increase	143/1765 (8.10)	146/1153 (12.7)	NA	−4.25 (−6.55 to −1.95)	<0.001	0.65 (0.51–0.82)	<0.001
Increases from 0 or 1 to 3 or 4	7/1211 (0.58)	2/818 (0.24)	0.115	0.50 (−0.09 to 1.08)	0.095	1.89 (0.63–5.69)	0.256
Increases from 0 to 3	3/581 (0.52)	0/416 (0.00)	0.066	0.68 (−0.01 to 1.38)	0.052	3.35 (0.55–20.5)	0.192
Increases from 0 to 2	12/581 (2.07)	12/416 (2.88)	NA	−0.79 (−2.81 to 1.23)	0.444	0.73 (0.35–1.52)	0.394

*Based on Mantel-Haenszel exact test, controlling for study when cell count is less than 5.
†Based on Mantel-Haenszel difference method.
‡Based on Mantel-Haenszel weighted method; no patient changed from 0 to 4.
n/N indicates proportion of subjects with a change in suicidality Item-3 per subjects at risk. Among 12 individual trials (data not shown), worsening was more likely with placebo (9/12 trials) than with duloxetine (3/12 trials), whereas improvement in suicidality was more likely with duloxetine (10/12 trails) than with placebo (2/12 trials). The N's for the denominators only include patients eligible to change (see methodology section).

further HAMD assessment). Changes from 0 to 3 (''suicide ideas or gestures'') were uncommon (3 patients given duloxetine [0.52%] and none given placebo). Of note, none of these changes occurred within the first month of treatment. In 2 of these 3 patients, the Item-3 score improved while continuing on duloxetine. The third patient discontinued the trial at the time of the suicidal ideation. Finally, changes in Item-3 scores from 0 to 2 (''wishes he were dead or any thoughts of possible death to self'') were detected in 12 patients (2.07%) on duloxetine and 12 (2.88%) on placebo.

Suicide-related Behaviors in Active Comparator Groups

Results from 7 Eli Lilly and Company and 3 Shionogi active-controlled trials showed no clear differences in suicidal risk between duloxetine and active comparators. Suicide-related behaviors occurred in 10 (0.63%) of 1589 duloxetine patients treated for an average of 14 weeks compared with 4 (0.46%) of 861 exposed to other antidepressants for approximately 12 weeks.

Event Analyses From All 27 MDD Trials

Overall, 27 trials (16 Eli Lilly and Company, n = 3833; 11 Shionogi, n = 1123), including placebo-controlled, open label, and active-control studies, involved a total of 4956 patients (mean age, 43.0; 64.3% female) who were exposed to duloxetine for an average of 130 days (range, 1–473 days), with a total of 1770 person-years. The observed rate of completed suicide in duloxetine-treated patients (5 cases) was 283/100,000 person-years and of nonfatal suicide attempts (26 cases), 1461/100,000 person-years.

DISCUSSION

The planned primary meta-analysis of differences in incidence (MHID) of suicidal behaviors during randomized treatment with duloxetine versus placebo did not indicate an association of risk with treatment. Analyses using alternative methods (MHIR, MHRD, and MHRR) and outcomes (completed suicide, nonfatal suicide attempt, and suicidal ideation) also failed to show either increased or decreased risk of suicidal events in association with duloxetine treatment. However, HAMD Item-3 scores, mainly reflecting suicidal ideation, showed that a larger proportion of duloxetine-treated patients had an improvement, and a smaller proportion had worsening compared with placebo-treated patients. There was no consistent evidence of an increased risk on duloxetine because the higher proportion of duloxetine patients with a change from 0 (absent) to 3 was balanced by the higher proportion of placebo patients with a change from 0 to 2.

Simply pooling data from different trials and treating them as 1 large trial do not take into account the randomization within individual trials and may therefore produce a distorted result.[20] The overall proportion of patients with suicidal behaviors was greater with duloxetine than placebo (Table 3). This apparent difference was due to 1 trial (HMAI), which had the most severely depressed patients and most (8/13) of the suicidal behaviors, as well as the highest randomization ratio, with 3 times as many patients randomized to duloxetine as to placebo. Hence, simply adding numerators (patients with events) and denominators (patients at risk) across trials leads to an artificial overrepresentation of suicidal cases among duloxetine-treated patients and illustrates the necessity of using appropriate meta-analytic methods[32] when combining data from different trials.

Exposure time-adjusted analyses are important in addition to the analyses of the proportion of patients with events because longer exposures allow more time during which adverse events may occur. In the trials examined, treatment exposure time was 20% longer with duloxetine than placebo, indicating that analyses adjusting for exposure time are important. No increased risk of suicide-related events was found with duloxetine, whether or not the analyses adjusted for exposure time.

In some antidepressant studies, more suicide-related behaviors were observed in the early phases of treatment.[3,37] Our analyses of both duloxetine and placebo treatment groups were consistent with this, but we did not find any evidence of more suicidal events on duloxetine versus placebo within the first 4 weeks of treatment. In addition,

there was no evidence of a time clustering of suicide-related behaviors in the duloxetine studies, beyond 4 weeks.

In the 27 trials involving 4956 duloxetine-treated MDD patients, there were 5 suicides (283/100,000 person-years of treatment). This figure compares favorably with rates reported with SSRIs (593/100,000 person-years) or other antidepressants (757/100,000 person-years) in depression trials reported to the FDA.[15] In the 4956 duloxetine-treated patients, there were 26 nonfatal suicide attempts (1469/100,000 person-years), which also compares favorably with rates reported with SSRIs and other antidepressants (2087/100,000 person-years), comparator antidepressants (3429/100,000 person-years), or placebo (2698/100,000 person-years) in antidepressant trials reported to the FDA.[12]

Suicide rates are approximately 20 times higher among patients with depression than in the general population,[3,5,38–41] even higher among those ill enough to require antidepressant treatment or hospitalization,[3,42] and similarly high with active-drug or placebo treatment in controlled antidepressant trials.[12,15] Consistent with these findings, the overall rate of completed suicides on duloxetine in the present trials (283/100,000 person-years) was approximately 20 times greater than the international average of 14.5/100,000 person-years in the general population.[43] Also, as expected, the rate of nonfatal suicide attempts in the duloxetine trials (1469/100,000 person-years) was higher than estimated rates in the general population (range, 149–1007/100,000 person-years).[44–46]

Use of scale data (HAMD Item-3) provides an additional means of systematically assessing suicidality (primarily ideation) in clinical trial subjects. Consistent with the antidepressant effect of duloxetine, significantly more duloxetine-treated patients had improvement, and significantly fewer had worsening of suicidal ideation compared with placebo on Item-3. Similar reductions in ratings of suicidal ideation rated by Item-10 of the Montgomery-Åsberg depression rating scale have recently been found in placebo-controlled trials of escitalopram,[47] and in HAMD Item-3 scores in comparisons of SSRIs versus placebo.[10,48]

Overall, therefore, the adverse event data analyzed did not suggest a reduction in suicide-related behaviors with duloxetine compared with placebo, but significantly more duloxetine-treated patients had improvement and fewer had worsening of suicidal ideation compared with placebo, based on HAMD Item-3 scores. Results from other antidepressant trials are consistent with these findings of reduced suicidal ideation without change in risk of suicidal acts.[10,47] These observations suggest that reductions in suicidal ideation may not lead to a reduction in suicidal behavior. Interestingly, the only treatments with strong evidence of beneficial effects on suicidal behaviors are clozapine in schizophrenia[49,50] and lithium salts in bipolar disorder and perhaps other manic-depressive illnesses.[5,51,52]

CONCLUSIONS

Small numbers of observed completed suicides and suicide attempts limit the power of statistical analyses to detect meaningful differences between treatments, even in large databases such as in this report of several thousand patients. Nevertheless, we found no evidence of a treatment-related increase or decrease in risk of suicide-related events (behaviors or ideation), although analyses of HAMD Item-3 (suicidality) scores indicated more improvement and less worsening of suicidality (primarily ideation) with duloxetine than with placebo.

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