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Assessment of functional outcomes by Sheehan Disability Scale in patients with major depressive disorder treated with duloxetine versus selective serotonin reuptake inhibitors

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Objective We compared functional impairment outcomes assessed with Sheehan Disability Scale (SDS) after treatment with duloxetine versus selective serotonin reuptake inhibitors (SSRIs) in patients with major depressive disorder.
Methods Data were pooled from four randomized studies comparing treatment with duloxetine and SSRIs (three double blind and one open label). Analysis of covariance, with last-observation-carried-forward approach for missing data, explored treatment differences between duloxetine and SSRIs on SDS changes during 8 to 12 weeks of acute treatment for the intent-to-treat population. Logistic regression analysis examined the predictive capacity of baseline patient characteristics for remission in functional impairment (SDS total score ≤ 6 and SDS item scores ≤ 2) at endpoint.
Results Included were 2193 patients (duloxetine $n = 1029$; SSRIs $n = 835$; placebo $n = 329$). Treatment with duloxetine and SSRIs resulted in significantly ($p < 0.01$) greater improvements in the SDS total score versus treatment with placebo. Higher SDS ($p < 0.0001$) or 17-item Hamilton Depression Rating Scale baseline scores ($p < 0.01$) predicted lower probability of functional improvement after treatment with duloxetine or SSRIs. Female gender ($p \leq 0.05$) predicted higher probability of functional improvement after treatment with duloxetine or SSRIs.
Conclusions Treatment with SSRIs and duloxetine improved functional impairment in patients with major depressive disorder. Higher SDS or 17-item Hamilton Depression Rating Scale baseline scores predicted less probability of SDS improvement; female gender predicted better improvement in functional impairment at endpoint. © 2015 The Authors. *Human Psychopharmacology: Clinical and Experimental* published by John Wiley & Sons, Ltd.

KEY WORDS—remission; SDS; MADRS; HAMD-17; duloxetine; SSRIs

INTRODUCTION

Major depressive disorder (MDD) is often associated with functional impairments in affected patients (Papakostas, 2009; Snyder, 2013). These impairments have strong social and economic effects, frequently causing patients to miss work (Rytsälä *et al*., 2005), experience difficulties in social relationships (Dunn *et al*., 2012) and report reduced family functioning (Weinstock *et al*., 2006).

Outcomes of antidepressant treatment in MDD vary greatly among individual patients. Proposed predictive factors of outcome include illness characteristics, comorbid mental disorders (van der Werff *et al*., 2010), genetic polymorphisms, brain metabolism and functional brain asymmetry (Papakostas and Fava, 2008). However, while many of those associations were linked to outcomes in depressive symptoms, their influence on functional outcomes in patients with MDD was not explored.

Nonetheless, there is increasing recognition of the importance of functional outcomes in patients with MDD. Frequently, functional impairments persist even when depressive symptoms are in remission (Nakano *et al*., 2008; Sheehan and Sheehan, 2008; Sheehan *et al*., 2011a). Nakano and colleagues (2008) demonstrated that executive dysfunction remained even when patients with MDD were in remission of their depressive symptoms. Similarly, Sheehan and colleagues (2011a) analysed three

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MDD studies and four generalized anxiety disorder studies and found that in neither patient group did symptom remission and functional remission move in tandem for every patient.

The neurotransmitter norepinephrine plays a role in the regulation of cognition, motivation and intellect (Moret and Briley, 2011). Duloxetine hydrochloride (hereafter duloxetine) is a serotonin and norepinephrine reuptake inhibitor, approved for the treatment of MDD (Eli Lilly and Company, 2014).

A validated and accepted measure of functional outcome in MDD is the Sheehan Disability Scale (SDS) (Sheehan *et al*., 1996; Sheehan and Sheehan, 2008). This three-item scale assesses functional impairments associated with work/school, social life and leisure activities, and family life and home responsibilities in patients with MDD, with higher scores indicating greater functional impairment (Sheehan *et al*., 1996). The SDS has been successfully used to assess changes in functional impairment in patients with MDD during treatment with duloxetine in several clinical trials (Raskin *et al*., 2003; Detke *et al*., 2004; Dueñas *et al*., 2011; Gaynor *et al*., 2011a, 2011b; Sheehan *et al*., 2011b; Mancini *et al*., 2012; Martinez *et al*., 2012; Oakes *et al*., 2012).

The objective of the current study was to compare functional outcomes as assessed with the SDS between treatment with duloxetine and selective serotonin reuptake inhibitors (SSRIs) in patients with MDD by using pooled data from all randomized clinical studies comparing duloxetine with SSRIs that used the SDS to measure patients' functioning and that were sponsored by Eli Lilly and Company. We also explored the roles of patient demographics, disorder duration and baseline symptom severity as predictors of functional outcomes in patients with MDD.

METHODS

We pooled data from four randomized clinical studies that compared the efficacy of duloxetine with an SSRI in the treatment of MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (Table 1). The dataset included three placebo-controlled, double-blind clinical studies (study acronyms of HMAYa, HMAYb and HMCR) and one open-label clinical study (study acronym of HMFT). All studies included an acute treatment phase of at least 8 weeks, compared treatment with duloxetine versus SSRIs and used the SDS to assess the effect of treatment on patient functioning.

Among all randomized clinical studies included in the Eli Lilly and Company integrated database for duloxetine efficacy in MDD (cut-off date 18 June 2014), 19 studies administered the SDS. Among these 19 studies, only eight studies included treatment comparisons between duloxetine and active compounds; of these eight studies, two studies did not use treatment with SSRIs as an active control, one study focused on the timing of intervention strategies

Table 1. Clinical study designs

Study acronym	Design	Treatment arms	Mean dose (mg) (SD)	Length of acute phase (weeks)	Baseline symptom thresholds
HMAYa	Randomized, double blind and fixed dose	DLX (40 or 60 mg BID) PRX (20 mg QD) PLB	NA	9	HAMD-17 total score ≥ 15 CGI-S ≥ 4
HMAYb	Randomized, double blind and fixed dose	DLX (40 or 60 mg BID) PRX (20 mg QD) PLB	NA	9	HAMD-17 total score ≥ 15 CGI-S ≥ 4
HMCR	Randomized, double blind and fixed dose	DLX (60, 90 and 120 mg QD) ESC (10 and 20 mg QD) PLB	NA	8	MADRS ≥ 22 CGI-S ≥ 4
HMFT	Randomized, open label and flexible dose	DLX (60–120 mg QD) Generic SSRIs CIT (20–40 mg QD) FLX (20–80 mg QD) PRX (20–50 mg QD) SER (50–200 mg QD)	DLX = 70.8 (22.0) CIT = 33.1 (9.1) FLX = 42.3 (16.1) PRX = 29.0 (8.4) SER = 109.0 (38.8)	12	PHQ-9 ≥ 16 QIDS-SR ≥ 20

BID, twice daily; CIT, citalopram; DLX, duloxetine; CGI-S, Clinical Global Impression-Severity; ESC, escitalopram; FLX, fluoxetine; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NA, not applicable; PHQ-9, Patient Health Questionnaire Depression Scale; PLB, placebo; PRX, paroxetine; QD, once daily; QIDS-SR, 16-item Quick Inventory of Depressive Symptomatology (self-report); SD, standard deviation; SER, sertraline.

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and one study only included MDD patients with residual apathy but without depressed mood.

Prior to patient enrolment, the appropriate institutional review boards reviewed and approved the study protocols. All patients provided written informed consent before receiving any study therapy or undergoing any study procedure, and the studies were performed according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Baseline and treatment assessment scales

Sheehan Disability Scale (Sheehan et al., 1996). The SDS is a disability or functional impairment scale that uses a discan metric. This discan metric anchors the response options by simultaneously using visual–spatial, numeric and verbal descriptive anchors to assess disability or functional impairment across three domains: work/school, social life/leisure activities and family life/home responsibilities. Each domain is scored from 0 (*not at all*) to 10 (*very severely*). The three domains can be summarized to evaluate global functional impairment by adding the scores of each of the three domains, resulting in global SDS score ranges from 0 (*unimpaired*) to 30 (*highly impaired*) (Sheehan *et al*., 1996; Sheehan and Sheehan, 2008). Functional remission was defined as SDS $\leq$6 at endpoint (Sheehan and Sheehan, 2008; Sheehan *et al*., 2011a).

Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1979). The Montgomery–Åsberg Depression Rating Scale (MADRS) is a 10-item scale, with each item rated from 0 to 6. The MADRS total score is the sum of the 10 items and ranges from 0 (*not at all depressed*) to 60 (*severely depressed*) (Montgomery and Asberg, 1979).

Seventeen-item Hamilton Depression Rating Scale (Hamilton, 1960). The 17-item Hamilton Depression Rating Scale (HAMD-17) assesses the severity of depression and produces a total score ranging from 0 (*not at all depressed*) to 52 (*severely depressed*) (Hamilton, 1960).

Clinical Global Impressions of Severity Scale (Guy, 1976). The physician-administered Clinical Global Impressions of Severity Scale records the severity of illness at the time of assessment. The score ranges from 1 (*normal, not at all ill*) to 7 (*among the most extremely ill patients*).

Statistical analyses

Baseline demographics and illness assessment data were summarized for all patients included in the current study. Analysis of covariance (ANCOVA) with a last-observation-carried-forward approach for missing data was used to explore treatment differences between duloxetine and SSRIs on SDS changes during 8 to 12 weeks of acute treatment for the intent-to-treat population, including all patients for whom baseline assessment and at least one post-baseline assessment were available. The ANCOVA models with treatment as fixed effect and baseline SDS total score as covariate were calculated for each study. Effect sizes in each model were calculated for least squares (LS) mean differences between treatment groups divided by the standard deviation (SD) of the residuals provided by the model of this study. Overall, LS mean estimates and effect sizes were calculated as a weighted mean of the corresponding estimates in all studies, with weights based on within-study variance, assuming a fixed study effect. *p*-values were derived from *t*-test for LS mean differences. No corrections of multiple comparisons were applied.

Logistic regression analyses were performed to determine odds ratios (ORs) for SDS total scores $\leq$6 versus $>$6 and for SDS individual item scores $\leq$2 versus $>$2. A logistic regression model was estimated for each study with treatment as fixed effect, and baseline SDS total score or baseline SDS item score as covariate. All ORs were calculated via a meta-analysis approach as a weighted mean of the corresponding log(OR) in all individual studies with weights based on the variance of log(OR).

Logistic regression analyses were also performed to determine potential predictors of remission in functional impairment (SDS total scores $\leq$6 vs $>$6 and SDS individual item scores $\leq$2 vs $>$2). Study, treatment, SDS baseline score, HAMD-17 baseline score, gender, age, race, number of previous episodes and duration of the current episode were included in the analysis model.

Numbers needed to treat (*NNT*s) to reach an SDS total score of $\leq$6 at last-observation-carried-forward endpoint for the pooled dataset for treatment with duloxetine and for treatment with SSRIs were determined by using the following formula:

$$NNT = {}^{1}\!/_{(\text{active treatment event rate} - \text{placebo event rate})}$$

RESULTS

Patient baseline characteristics

Included in the analyses were 2193 patients (duloxetine n=1029; SSRIs n=835; placebo n=329).

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Most patients were female (duloxetine = 67.0%, SSRI = 68.5% and placebo = 67.2%). The mean ages of duloxetine, SSRI and placebo groups were 43.5 (SD: 12.1), 43.7 (SD: 12.6) and 43.5 (SD: 11.6) years, respectively (Supporting information Table 1). At baseline, patients displayed moderate illness severity with mean Clinical Global Impressions of Severity scores ranging from 4.2 to 4.3 and mean SDS total scores ranging from 20.0 to 20.9 across treatment groups (Supporting information Table 2).

Patient disposition

The study completion rates for duloxetine, SSRIs and placebo were 78.1%, 78.2% and 79.9%, respectively. The most common reasons for early discontinuation were lost to follow-up (duloxetine, 6.3%; SSRI, 7.1%; placebo, 4.9%) and adverse events (duloxetine, 5.2%; SSRI, 3.6%; placebo, 3.6%).

Study medication doses

In study HMAY, patients were randomized to duloxetine 60 mg twice daily (BID), duloxetine 40 mg BID, placebo or paroxetine 20 mg once daily (QD) for the 8-week acute treatment period. In study HMCR, patients were randomized to duloxetine 60 mg QD, escitalopram 10 mg QD or placebo. In study HMFT, patients were randomized to flexible-dosed duloxetine or SSRI (citalopram, fluoxetine,

Table 2. Sheehan Disability Scale total and individual item scores at endpoint—data from studies HMAYa, HMAYb, HMCR and HMFT; all randomized patients

	DLX		SSRI		PLB		DLX vs SSRI	DLX vs PLB	SSRI vs PLB
Population	*n*	LSMean (SE)	*n*	LSMean (SE)	*n*	LSMean (SE)	LSMean (effect size)	LSMean (effect size)	LSMean (effect size)
Total									
All patients[a]	847	12.3 (0.3)***	669	12.9 (0.3)***	284	14.4 (0.4)***	−0.4 (−0.1)	−1.9 (−0.3)###	−1.7 (−0.2)##
HAMD-17 ≤ 22[b,c]	529	12.3 (0.3)***	385	12.8 (0.4)***	233	14.2 (0.5)***	−0.2 (0.0)	−1.8 (−0.2)	−1.6 (−0.2)#
HAMD-17 > 22[b,c]	318	12.2 (0.5)***	284	13.1 (0.5)***	51	15.1 (1.0)***	−0.7 (−0.1)	−2.4 (−0.3)#	−2.1 (−0.3)
MADRS ≤ 30[c,d,e]	434	12.1 (0.4)***	269	12.2 (0.5)***	211	14.2 (0.5)***	0.1 (0.02)	−2.1 (−0.3)	−2.2 (−0.3)
MADRS > 30[b,c,d,e]	138	13.9 (0.6)***	121	15.0 (0.7)***	73	15.1 (0.9)***	−1.0 (−0.1)	−1.3 (−0.2)	−0.5 (−0.1)
Item 1									
All patients	847	3.9 (0.1)***	669	4.1 (0.1)***	284	4.8 (0.2)***	−0.2 (−0.1)	−0.8 (−0.3)###	−0.7 (−0.3)###
HAMD-17 ≤ 22[b]	529	3.9 (0.1)***	385	4.0 (0.1)***	233	4.7 (0.2)***	−0.1 (0.0)	−0.7 (−0.3)###	−0.6 (−0.2)##
HAMD-17 > 22[b]	318	3.8 (0.2)***	284	4.3 (0.2)***	51	5.2 (0.4)***	−0.5 (−0.2)#	−1.1 (−0.4)##	−1.1 (−0.4)#
MADRS ≤ 30[a,b]	434	3.9 (0.1)***	269	3.9 (0.2)***	211	4.7 (0.2)***	0.1 (0.0)	−0.8 (−0.3)###	−0.8 (−0.3)###
MADRS > 30[a,b]	138	4.2 (0.2)***	121	4.6 (0.2)***	73	4.9 (0.3)***	−0.4 (−0.1)	−0.7 (−0.3)#	−0.4 (−0.2)
Item 2									
All patients	1023	4.1 (0.1)***	834	4.3 (0.1)***	328	4.9 (0.2)***	−0.2 (−0.1)	−0.7 (−0.3)###	−0.7 (−0.3)###
HAMD-17 ≤ 22[b]	615	4.1 (0.1)***	456	4.2 (0.1)***	262	4.9 (0.2)***	0.0 (0.0)	−0.7 (−0.2)##	−0.7 (−0.3)##
HAMD-17 > 22[b]	406	4.1 (0.1)***	378	4.5 (0.2)***	66	5.3 (0.3)***	−0.4 (−0.1)	−0.7 (−0.3)	−0.7 (−0.3)
MADRS ≤ 30[a,b]	492	4.0 (0.1)***	310	4.0 (0.2)***	242	4.8 (0.2)***	0.2 (0.1)	−0.7 (−0.2)##	−0.8 (−0.3)###
MADRS > 30[a,b]	164	4.7 (0.2)***	147	5.0 (0.2)***	86	5.4 (0.3)***	−0.2 (−0.1)	−0.8 (−0.3)	−0.6 (−0.2)
Item 3									
All patients[a]	1024	4.0 (0.1)***	834	4.2 (0.1)***	329	4.6 (0.1)***	−0.1 (0.0)	−0.5 (−0.2)##	−0.6 (−0.2)##
HAMD-17 ≤ 22[b,c]	615	4.0 (0.1)***	456	4.1 (0.1)***	263	4.6 (0.2)***	0.1 (0.0)	−0.5 (−0.2)#	−0.6 (−0.2)##
HAMD-17 > 22[b,c]	407	4.0 (0.1)***	378	4.4 (0.1)***	66	4.8 (0.3)***	−0.3 (−0.1)	−0.5 (−0.2)	−0.7 (−0.3)
MADRS ≤ 30[c,d,e]	492	3.9 (0.1)***	310	3.9 (0.2)***	243	4.5 (0.2)***	0.2 (0.1)	−0.6 (−0.2)##	−0.7 (−0.3)##
MADRS > 30[c,d,e]	164	4.7 (0.2)***	147	4.9 (0.2)***	86	5.0 (0.3)***	0.0 (0.0)	−0.3 (−0.1)	−0.3 (−0.1)

Effect sizes in each model were calculated for LSMean differences, divided by the standard deviation of the residuals provided by the model of this group. Overall LSMean estimates and effect sizes were calculated as a weighted mean of the corresponding estimates in all groups, with weights based on within-group variance, assuming a fixed group effect. *p*-values were derived from *t*-test for LSMean differences.

DLX, duloxetine; HAMD-17, 17-item Hamilton Depression Rating Scale; LSMean, least squares mean; MADRS, Montgomery–Åsberg Depression Rating Scale; *n*, number of affected patients; PLB, placebo; SE, standard error; SSRI, selective serotonin reuptake inhibitor; ANCOVA, analysis of covariance; SDS, Sheehan Disability Scale.

[a]One ANCOVA model was calculated for each study with treatment as fixed effect and baseline SDS total score as covariate.

[b]One ANCOVA model was calculated for each group with treatment, HAMD-17 total score at baseline (≤22/>22), and their interaction as fixed effect and baseline SDS total score as covariate.

[c]Baseline score.

[d]One ANCOVA model was calculated for each group with treatment, MADRS total score at baseline (≤30/>30), and their interaction as fixed effect and baseline SDS total score as covariate.

[e]Not collected in HMFT.

***$p < 0.001$ versus baseline;

###$p < 0.001$ versus comparator;

##$p < 0.01$ versus comparator;

#$p \leq 0.05$ versus comparator.

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paroxetine or sertraline; mean daily doses are displayed in Table 1).

Paroxetine 20 mg QD (GlaxoSmithKline, 2013), escitalopram 10 mg QD (Forest Laboratories, Inc., 2009) and duloxetine 40 mg/day (Eli Lilly and Company, 2014) are the minimum effective doses approved for the treatment of MDD. In some of the studies, the dose of duloxetine used was higher than the minimum effective dose approved for duloxetine (i.e. >40 mg/day), while in those same studies, the dose of the comparator SSRI was the minimum approved dose.

Change from baseline in Sheehan Disability Scale total scores

Patients in all treatment groups displayed significantly ($p < 0.001$) reduced SDS total scores at endpoint (Table 2) compared with baseline, and both treatment with duloxetine and treatment with SSRIs resulted in statistically significantly ($p < 0.01$) greater reductions in SDS total scores compared with placebo. No significant differences in change from baseline in SDS total scores were observed between treatment with duloxetine and treatment with SSRIs (Table 2).

Change from baseline in Sheehan Disability Scale total scores—subgroup analyses

When patients were grouped by baseline illness severity (HAMD-17 ≤22 vs >22), SDS total endpoint scores remained statistically significantly ($p < 0.001$) different from baseline for all treatment groups. Statistically significantly ($p \leq 0.05$) greater reductions in SDS total scores compared with placebo were observed only for patients treated with duloxetine in the HAMD-17 > 22 group and for patients treated with duloxetine or SSRIs in the HAMD-17 ≤ 22 group (Table 2).

When patients were grouped by baseline illness severity measured by MADRS (MADRS ≤30 vs >30), SDS total endpoint scores were statistically significantly ($p < 0.001$) different from baseline for all treatment groups; however, no significant differences between treatment groups were found, potentially because of the small sample size (Table 2).

Change from baseline in Sheehan Disability Scale individual item scores

For all three SDS items, each treatment resulted in statistically significantly ($p < 0.001$) different endpoint scores compared with baseline, and both treatments with duloxetine and treatment with SSRIs were associated with statistically significantly ($p < 0.01$) greater score improvements for all SDS items compared with placebo. No statistically significant differences were observed between treatment with duloxetine and treatment with SSRIs (Table 2).

When patients were grouped by baseline illness severity (MADRS ≤30 vs >30; HAMD-17 ≤22 vs >22), changes from baseline scores remained statistically significant ($p < 0.001$) for all treatment groups. Additionally, in patients with more severe depressive symptoms at baseline (HAMD-17 score > 22), statistically significantly ($p \leq 0.05$) greater improvement after treatment with duloxetine was observed for SDS item 1 compared with treatment with SSRIs. No differences between treatment with duloxetine and treatment with SSRIs were observed for SDS items 2 and 3 (Table 2). For patients with less severe depressive symptoms (MADRS ≤ 30 and HAMD-17 ≤ 22), treatment with both duloxetine and SSRIs resulted in

Table 3. Logistical regression analysis of SDS total scores (≤6 vs >6) and SDS items 1, 2 and 3 scores (≤2 vs >2)—data from studies HMAYa, HMAYb, HMCR and HMFT; all randomized patients

		SDS total (≤6 vs >6)		Item 1 (≤2 vs >2)		Item 2 (≤2 vs >2)		Item 3 (≤2 vs >2)	
Population	Comparison	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
All patients	DLX vs SSRI	1.2 (0.95, 1.53)	0.119	1.2 (0.92, 1.44)	0.220	1.2 (0.95, 1.42)	0.132	1.1 (0.92, 1.37)	0.270
	PLB vs SSRI	0.9 (0.62, 1.32)	0.613	0.6 (0.39, 0.82)	0.003	0.7 (0.48, 0.94)	0.019	0.6 (0.46, 0.88)	0.007
HAMD-17 ≤ 22[a]	DLX vs SSRI	1.3 (0.94, 1.73)	0.122	1.1 (0.83, 1.48)	0.494	1.2 (0.89, 1.50)	0.285	1.1 (0.83, 1.41)	0.580
	PLB vs SSRI	0.9 (0.60, 1.39)	0.684	0.6 (0.38, 0.87)	0.009	0.6 (0.44, 0.92)	0.016	0.7 (0.45, 0.94)	0.022
HAMD-17 > 22[a]	DLX vs SSRI	1.1 (0.76, 1.60)	0.611	1.2 (0.86, 1.75)	0.266	1.2 (0.86, 1.60)	0.317	1.2 (0.86, 1.59)	0.310
	PLB vs SSRI	0.9 (0.37, 2.27)	0.858	0.5 (0.22, 1.25)	0.143	0.9 (0.40, 1.83)	0.693	0.6 (0.26, 1.22)	0.146

CI, confidence interval; DLX, duloxetine; HAMD-17, 17-item Hamilton Depression Rating Scale; OR, odds ratio; *p*, *p*-value; PLB, placebo; SDS, Sheehan Disability Scale; SSRI, selective serotonin reuptake inhibitor.
[a]Baseline score.

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Table 4. SDS predictor analysis—data from studies HMAYa, HMAYb, HMCR and HMFT; all randomized patients

		Total score ≤ 6 at endpoint		Item 1 ≤ 2 at endpoint		Item 2 ≤ 2 at endpoint		Item 3 ≤ 2 at endpoint	
Parameter	Comparison	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)
Study	HMAYa vs HMFT	<0.0001	0.48 (0.33, 0.71)	<0.0001	0.61 (0.42, 0.88)	<0.0001	0.71 (0.51, 0.99)	<0.0001	0.81 (0.59, 1.13)
	HMAYb vs HMFT		0.74 (0.52, 1.06)		0.84 (0.59, 1.20)		1.04 (0.76, 1.43)		1.11 (0.81, 1.52)
	HMCR vs HMFT		0.33 (0.23, 0.47)		0.47 (0.34, 0.66)		0.46 (0.34, 0.61)		0.38 (0.28, 0.51)
Treatment	DLX vs SSRI	0.069	1.22 (0.96, 1.55)	0.0002	1.16 (0.93, 1.46)	0.0005	1.18 (0.96, 1.44)	0.001	1.13 (0.92, 1.38)
	PLB vs SSRI		0.87 (0.61, 1.24)		0.58 (0.41, 0.82)		0.66 (0.48, 0.90)		0.65 (0.48, 0.89)
SDS total baseline score		<0.0001	0.92 (0.90, 0.94)	<0.0001	0.76 (0.72, 0.79)	<0.0001	0.84 (0.81, 0.88)	<0.0001	0.83 (0.79, 0.86)
HAMD-17 baseline score		0.006	0.96 (0.94, 0.99)	0.003	0.96 (0.94, 0.99)	0.001	0.96 (0.94, 0.99)	0.0008	0.96 (0.94, 0.99)
Gender	Female vs male	0.022	1.31 (1.04, 1.65)	0.001	1.45 (1.16, 1.82)	0.0009	1.41 (1.15, 1.72)	0.006	1.33 (1.09, 1.62)
Age		0.385	1.00 (0.99, 1.01)	0.994	1.00 (0.99, 1.01)	0.308	1.00 (1.00, 1.01)	0.306	1.00 (1.00, 1.01)
Race	African American vs White	0.310	1.10 (0.74, 1.63)	0.051	0.94 (0.64, 1.37)	0.661	1.15 (0.83, 1.58)	0.666	1.12 (0.81, 1.55)
	Other vs White		0.74 (0.48, 1.14)		0.59 (0.39, 0.90)		0.96 (0.69, 1.35)		0.93 (0.66, 1.30)
Number of previous episodes	≤2 episodes vs missing	0.887	1.07 (0.59, 1.94)	0.456	1.10 (0.64, 1.89)	0.734	0.94 (0.58, 1.53)	0.474	0.81 (0.50, 1.32)
	>2 episodes vs missing		1.00 (0.56, 1.81)		0.94 (0.55, 1.61)		0.88 (0.54, 1.42)		0.75 (0.47, 1.22)

Comparison between treatments for SDS total score ≤ 6 at endpoint	Estimate (SE)	OR	*p*-value
DLX vs PLB	0.34 (0.17)	1.40	0.046
DLX vs SSRI	0.20 (0.12)	1.22	0.099
SSRI vs PLB	0.14 (0.18)	1.15	0.438

Comparison	SDS item 1 score ≤ 2 at endpoint			SDS item 2 score ≤ 2 At endpoint			SDS item 3 score ≤ 2 at endpoint		
	Estimate (SE)	OR	*p*-value	Estimate (SE)	OR	*p*-value	Estimate (SE)	OR	*p*-value
DLX vs PLB	0.69 (0.17)	2.00	<0.0001	0.58 (0.15)	1.79	0.0001	0.55 (0.15)	1.74	0.0001
DLX vs SSRI	0.15 (0.12)	1.16	0.204	0.16 (0.10)	1.18	0.115	0.12 (0.10)	1.13	0.115
SSRI vs PLB	0.54 (0.18)	1.72	0.002	0.42 (0.16)	1.52	0.008	0.43 (0.16)	1.54	0.008

CI, confidence interval; DLX, duloxetine; HAMD-17, 17-item Hamilton Depression Rating Scale; OR, odds ratio; PLB, placebo; SDS, Sheehan Disability Scale; SE, standard error; SSRI, selective serotonin reuptake inhibitor.

statistically significant ($p < 0.001$) improvements from baseline for all SDS item scores.

Number needed to treat

At endpoint, 295 (28.7%) patients treated with duloxetine and 212 (25.4%) patients treated with an SSRI had an SDS total score of ≤6, while 71 patients (21.6%) treated by placebo had an SDS total score of ≤6. The *NNT* to reach an SDS total score of ≤6 at last-observation-carried-forward endpoint for the pooled dataset was 14 for duloxetine and 26 for SSRIs.

Logistic regression analyses

At endpoint, 295 (28.7%) patients treated with duloxetine and 212 (25.4%) patients treated with an SSRI had an SDS total score of ≤6 (SDS total score at endpoint >6: duloxetine $n = 625$ [60.7%]; SSRIs $n = 546$ [65.4%]; missing data: duloxetine $n = 109$ [10.6%]; SSRIs $n = 77$ [9.2%]). No statistically significant differences between duloxetine and SSRIs were observed when the ORs were examined for reaching an SDS total score of ≤6 (Table 3).

Within the group of patients with an HAMD-17 baseline score of >22, 109 (26.5%) patients receiving treatment with duloxetine and 93 (24.5%) patients treated with an SSRI had an SDS total score of ≤6 at endpoint (SDS total score at endpoint > 6: duloxetine $n = 257$ [62.4%]; SSRIs $n = 247$ [65.2%]; missing data: duloxetine $n = 46$ [11.2%]; SSRIs $n = 39$ [10.3%]). Within the group of patients with an HAMD-17

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baseline score of ≤22, 186 (30.2%) patients receiving treatment with duloxetine and 119 (26.1%) patients treated with an SSRI had an SDS total score of ≤6 at endpoint (SDS total score at endpoint > 6: duloxetine $n = 366$ [59.5%]; SSRIs $n = 299$ [65.6%]; missing data: duloxetine $n = 63$ [10.2%]; SSRIs $n = 38$ [8.3%]). In both the group of patients with an HAMD-17 baseline score of >22 and the group with an HAMD-17 baseline score of ≤22, no statistically significant differences between duloxetine and SSRIs were observed when the ORs were examined for reaching an SDS total score of ≤6 (Table 3).

Similar results were obtained when the ORs were examined for reaching scores of ≤2 for individual SDS items. No statistically significant differences between duloxetine and SSRI treatment groups were observed, neither in the all-patients group nor in subgroups divided by HAMD-17 baseline score (Table 3).

Predictor analyses

When baseline patient characteristics were analysed to predict functional patient outcome at endpoint, patients with higher SDS total baseline scores (more severe functional impairment) and patients with higher HAMD-17 baseline scores (more severe depressive symptoms) at baseline showed lower probability to achieve remission in functional impairment (SDS total score ≤ 6 or SDS individual item scores ≤ 2) at endpoint. However, female gender was associated with a statistically significantly higher probability of remission in functional impairment compared with male gender. No significant differences were observed among race, number of previous episodes and the duration of the current episode (Table 4).

Only patients treated with duloxetine had a statistically significantly ($p = 0.046$) higher probability of achieving an SDS total score of ≤6 compared with placebo treatment; no significant differences were observed between treatment with SSRIs and treatment with placebo or between treatment with duloxetine and treatment with SSRIs (Table 4).

Both patients treated with duloxetine and patients treated with SSRIs had a statistically significantly ($p < 0.01$) higher probability to reach scores of ≤2 for individual SDS items at endpoint compared with those treated with placebo (Table 4).

Change from baseline in 17-item Hamilton Depression Rating Scale scores

All three treatment groups showed statistically significantly ($p < 0.001$) changed HAMD-17 scores at endpoint compared with baseline in the overall patient populations and in patients grouped by HAMD-17 baseline scores. HAMD-17 scores showed statistically significantly ($p \leq 0.05$) greater improvement after treatment with duloxetine and after treatment with SSRIs compared with treatment with placebo without significant differences between duloxetine and SSRI treatments (Table 5).

Table 5. Seventeen-item Hamilton Depression Rating Scale total scores at endpoint—data from studies HMAYa, HMAYb, HMCR and HMFT; all randomized patients

	DLX		SSRI		PLB		DLX vs SSRI	DLX vs PLB	SSRI vs PLB
Population	*n*	LSMean (SE)	*n*	LSMean (SE)	*n*	LSMean (SE)	LSMean (effect size)	LSMean (effect size)	LSMean (effect size)
All patients[a]	1027	10.4 (0.2)***	835	11.2 (0.2)***	329	11.9 (0.3)***	−0.4 (−0.1)	−1.7 (−0.3)###	−1.6 (0.3)###
HAMD-17 ≤ 22[b,c]	615	10.1 (0.3)***	456	10.8 (0.3)***	263	11.6 (0.4)***	−0.4 (−0.1)	−1.6 (−0.3)###	−1.2 (0.2)#
HAMD-17 > 22[b,c]	412	11.1 (0.4)***	379	11.8 (0.4)***	66	13.0 (0.8)***	−0.4 (0.0)	−1.9 (−0.3)#	−2.9 (0.5)##

Effect sizes in each model were calculated for LSMean differences, divided by the standard deviation of the residuals provided by the model of this group. Overall LSMean estimates and effect sizes were calculated as a weighted mean of the corresponding estimates in all studies, with weights based on within-group variance, assuming a fixed study effect. *p*-values were derived from *t*-test for LSMean differences.

DLX, duloxetine; HAMD-17, 17-item Hamilton Depression Rating Scale; LSMean, least squares mean; *n*, number of affected patients; PLB, placebo; SE, standard error; SSRI, selective serotonin reuptake inhibitor; ANCOVA, analysis of covariance.

[a]One ANCOVA model was calculated for each study with treatment as fixed effect and baseline HAMD-17 total score as covariate.

[b]One ANCOVA model was calculated for each study with treatment, HAMD total score at baseline (≤22/>22), and their interaction as fixed effect and baseline HAMD total score as covariate.

[c]Baseline.

***$p < 0.001$ versus baseline;

**$p < 0.01$ versus baseline;

*$p \leq 0.05$ versus baseline;

###$p < 0.001$ versus comparator;

##$p < 0.01$ versus comparator;

#$p \leq 0.05$ versus comparator.

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DISCUSSION

In the pooled analyses presented here, most analyses measuring functional improvement in patients with MDD produced similar results after treatment with duloxetine and treatment with SSRIs. Both treatments resulted in statistically significantly greater functional improvements compared with placebo in patients with MDD, as assessed by changes in the SDS total and individual item scores. When patients were grouped by baseline severity of their depressive symptoms, patients with less severe depressive symptoms (HAMD-17 $\leq$ 22) showed statistically significantly greater improvements in SDS total scores compared with placebo, after treatment with both duloxetine and SSRIs. Patients with more severe depressive symptoms (HAMD-17 $>$ 22) displayed statistically significantly greater improvements in SDS total scores compared with placebo only after treatment with duloxetine, although this was not supported by a similar analysis using baseline MADRS scores $\leq$30 versus $>$30.

When individual SDS items were analysed, in patients who displayed more severe depressive symptoms at baseline (HAMD-17 $>$ 22), statistically significantly greater improvement after treatment with duloxetine was observed for SDS item 1 (work/school). Moret and Briley (2011) described, previously, that norepinephrine plays an important role in executive functioning with regard to cognition, motivation and intellect; however, additional studies are needed to establish a causal relationship between norepinephrine levels and improvements in certain aspects of executive functioning.

The *NNT*s in this meta-analysis for both the duloxetine and the SSRI groups were higher (less impressive clinically) than reported previously for experimental design studies (Sheehan and Sheehan, 2008). There may be two reasons for this. First, some of the treatment arms in the fixed-dose studies used doses that were too low to achieve good efficacy for some patients. Fixed-dose studies also often have treatment arms that use doses that are too high for other patients, increasing the likelihood of dropouts because of adverse events, before good efficacy is achieved. In fixed-dose studies, we therefore expect less impressive *NNT*s than in flexible-dose designs. Two of the four studies in this meta-analysis were fixed-dose designs. Second, the doses for the comparator SSRI paroxetine in two of the four studies were not comparable in efficacy with the doses of duloxetine used in those studies. Consequently, when the results of all studies are aggregated, the *NNT* for the SSRIs would be expected to be higher (less impressive) than the *NNT* for duloxetine. Therefore, we recommend caution in interpreting any difference in these *NNT*s as suggesting any difference in efficacy between duloxetine and SSRIs.

The results presented here agree with those of prior studies that demonstrated statistically significant functional improvements, as measured by SDS, during treatment with duloxetine (Detke *et al*., 2004; Gaynor *et al*., 2011a, 2011b; Mancini *et al*., 2012) or SSRIs (Detke *et al*., 2004) compared with placebo in patients with MDD. The current analyses are the first analyses known to the authors to compare the effects of duloxetine versus SSRIs on functional improvement in patients with MDD in a large, pooled dataset. This approach allowed the authors to compare the relative efficacy of a serotonin and norepinephrine reuptake inhibitor (duloxetine) with SSRIs in achieving remission of functional impairment in patients with MDD. As mentioned earlier, norepinephrine is reported to play a role in modulating cognition, motivation and intellect (Moret and Briley, 2011), while serotonin may influence psychomotor speed (Constant *et al*., 2005).

Treatment with duloxetine and treatment with SSRIs resulted in similar rates of study completion, and duloxetine was associated with the highest rate of patients discontinuing the studies because of adverse events. Those findings are consistent with results from a meta-analysis that compared treatment response in patients with generalized anxiety disorder among escitalopram, duloxetine, paroxetine, pregabalin, sertraline and venlafaxine XL (National Collaborating Centre for Mental Health commissioned by the National Institute for Health & Clinical Excellence, 2011). In this analysis, duloxetine had the highest probability of response when only patients who did not discontinue pharmacological treatment were analysed because of intolerable side effects; however, it was also associated with the highest risk of discontinuation because of side effects (National Collaborating Centre for Mental Health commissioned by the National Institute for Health &Clinical Excellence, 2011).

Higher SDS total or HAMD-17 baseline scores predicted lower probability of remission in functional impairment defined as SDS total score $\leq$6 or SDS individual item scores $\leq$2 at endpoint after treatment with duloxetine or SSRIs; however, female gender was a predictor for higher probability of functional improvement at endpoint. Gender was described previously as a significant prognostic factor for functional remission in patients with MDD (Mancini *et al*., 2012).

When treatment assignment was analysed as a predictor of functional improvement, patients treated with

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duloxetine had a statistically significantly higher probability of achieving an SDS total score of ≤6 compared with patients treated with placebo. No statistically significant differences were observed between treatment with SSRIs and treatment with placebo or between treatment with duloxetine and treatment with SSRIs. Previously, higher baseline severity of depressive symptoms was associated with a higher probability of patients' depressive symptoms to respond to antidepressant treatment, but not to reach remission of depressive symptoms (Riedel *et al*., 2011).

A limitation of the analyses presented here is the pooling of data from four studies that used different designs and different study durations, one of which was open label, and which had different primary objectives, introducing potential bias for the results reported here. While all four studies applied similar inclusion and exclusion criteria that resulted in comparable study populations, the study designs were different among the included studies. The open-label study did not have a placebo treatment group and did not collect MADRS data, which resulted in reduced sample sizes for the pooled placebo treatment group and for analyses involving MADRS. The relatively small sample size in the placebo group might have affected the statistical power of analyses comparing active treatment versus placebo; however, comparisons between the active treatment and placebo were not the main focus of the analyses presented here. Further, the ratios of race and region among the three treatment groups were different, which might have influenced the observed results. However, the differences between treatment groups with respect to race and region were due to the individual studies being performed in different regions. Therefore, races and regions were comparable between treatment groups within the individual studies, and part of the effect of race and region can be controlled by the study term included into the model. Additional limitations of this meta-analytic study are the retrospective and *post hoc* nature of the study, the many statistical comparisons made, the longer duration of the current depressive episode, the longer duration since the first major depressive episode in the SSRI group, and the possibility that the doses of the duloxetine and the SSRI active comparators may not have been comparable in power. Finally, the studies included in this meta-analysis were neither designed nor powered to examine differences in functional treatment outcome between duloxetine and SSRIs. Meta-analysis is only exploratory, never confirmatory. Any findings in a meta-analysis, which is an observational design, must be later tested using experimental designs.

CONCLUSION

The results presented here provide further evidence that treatment with both duloxetine and SSRIs is associated with greater functional improvement compared with treatment with placebo in patients with MDD, as measured by SDS, with different outcomes depending on baseline symptom severity. The SDS or HAMD-17 baseline scores, and female gender, predict greater likelihood of remission in functional impairment at endpoint.

CONFLICT OF INTEREST

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Abbott Laboratories[1,2,3]; Actavis[1]; Ad Hoc Committee, Treatment Drug & Assessment Research Review[1]; Alexa[1]; Alza Pharmaceuticals[1]; American Medical Association[2]; American Psychiatric Association Task Force on Benzodiazepine Dependency[1]; American Psychiatric Association Task Force on Treatments of Psychiatric Disorders[1]; American Psychiatric Association Working Group to revise DSM III Anxiety Disorders Section[1]; Anclote Foundation[2]; Anxiety Disorders Resource Center[1]; Anxiety Drug Efficacy Case, U.S. Food & Drug Administration[1]; Applied Health Outcomes/xCenda[1]; Apsen Pharma[3]; AstraZeneca[1,2,3]; Avera Pharmaceuticals[1,2]; BioMarin[1]; Bionomics[1]; Boehringer Ingelheim[3]; Boots Pharmaceuticals[3]; Bristol-Myers Squibb[1,2,3]; Burroughs Wellcome[2,3]; Cephalon[1]; Charter Hospitals[3]; Ciba Geigy[3]; Committee (RRC) of N.I.M.H. on Anxiety and Phobic Disorder Projects[1]; Connecticut & Ohio Academies of Family Physicians[1]; Cortex Pharmaceutical[1]; Council on Anxiety Disorders[1]; CPC Coliseum Medical Center[1]; Cypress Bioscience[1]; Daiichi Sankyo Pharma Development[1]; Daiichi Sumitomo[2]; Dista Products Company[3]; Division of Drugs & Technology, American Medical Association[1]; EISAI[1,2]; Eli Lilly[1,2,3]; Excerpta Medica Asia[3]; Faxmed, Inc[1]; Forest Laboratories[1,2]; Glaxo Pharmaceuticals[3]; GlaxoSmithKline[1,2,3]; Glaxo-Wellcome[2]; Hikma Pharmaceuticals[3]; Hospital Corporation of America[3]; Humana[3]; ICI[3]; INC Research[1,3]; International Clinical Research (ICR)[2]; International Society for CNS Drug Development (ISCDD)[1]; Janssen Pharmaceutica[1,2,3]; Jazz Pharmaceuticals[1,2]; Kali-Duphar[2,3]; Labopharm-Angellini[1,2,3]; Layton Bioscience[1]; Lilly Research Laboratories[1]; Lundbeck[1,2,3]; Marion Merrill Dow[3]; McNeil Pharmaceuticals[3]; Mead Johnson[2,3]; Macmillan[3]; MAPI[1]; Medical Outcome Systems[4]; MediciNova[1,2]; Merck Sharp & Dohme[2,3]; National Anxiety Awareness Program[1]; National

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Anxiety Foundation[1]; National Depressive & Manic Depressive Association[1]; National Institute of Drug Abuse[2]; National Institutes of Health (NIH)[2]; Neuronetics[1]; NovaDel[1]; Novartis Pharmaceuticals Corp[1,2]; Novo Nordisk[3]; Organon[1,3]; Orion Pharma[1]; Parexel International Corporation[1]; Otsuka[1]; Parke-Davis[2,3]; Pfizer[1,2,3]; Pharmacia[1]; Pharmacia & Upjohn[1,3]; PharmaNeuroBoost[1,3]; Philadelphia College of Pharmacy & Science[1]; Pierre Fabre, France[1]; Quintiles[2]; ProPhase[1]; Rhone Laboratories[3]; Rhone-Poulenc Rorer Pharmaceuticals[3]; Roche[1]; Roerig[3]; Sagene Pharma[1]; Sandoz Pharmaceuticals[2,3]; Sanofi-Aventis[1,2,3]; Sanofi-Synthelabo Recherche/Sanofi-Aventis[1,2]; Schering Corporation[3]; Sepracor[1]; Shire Laboratories, Inc[1]; Simon and Schuster[3]; SmithKlineBeecham[1,2,3]; Solvay Pharmaceuticals[1,3]; Sunovion[2,3]; Takeda Pharmaceuticals[1,2,3]; Tampa General Hosp[1]; University of South Florida Psychiatry Center[2]; University of South Florida College of Medicine. TAP Pharmaceuticals[2,3]; Targacept[1]; TGH-University Psychiatry Center[3]; Tikvah Therapeutics[1]; Titan Pharmaceuticals[1]; United Bioscience[1,2,3]; The Upjohn Company[1,2,3]; U.S. Congress-House of Representatives Committee[1]; USF Friends of Research in Psychiatry, Board of Trustees[1]; Warner Chilcott[2,3]; World Health Organization[1]; Worldwide Clinical Trials[2]; Wyeth-Ayerst[1,2,3]; ZARS[1]; Zeneca Pharmaceuticals[2]; Neuronetics[1]

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SUPPORTING INFORMATION

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