Research Article

TIME COURSE OF DEPRESSION-SYMPTOM IMPROVEMENT DURING TREATMENT WITH DULOXETINE

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The aim of this study was to examine the longitudinal response for overall and individual symptoms during the treatment of major depressive disorder. Data were pooled from two 9-week trials, which compared duloxetine 60-mg QD ($n = 251$) with placebo ($n = 261$) in the treatment of MDD. Changes from baseline in the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) and in the Visual Analog Scales for pain were analyzed. Compared to placebo-treated patients, duloxetine-treated patients experienced greater improvement ($P < .05$) in the $HAMD_{17}$ total score at Week 2. The individual symptoms showing the most rapid improvements (Week 1) were depressed mood, guilt, suicidal ideation, work/activities, and psychic anxiety as well as VAS back pain and shoulder pain. At subsequent visits, significant improvements were observed in retardation (Week 2); hypochondriasis (Week 3); general somatic symptoms (Week 5); middle and late insomnia (Week 7); and gastrointestinal (GI) symptoms, genital symptoms (level of sexual interest or ease of sexual arousal), insight, and early insomnia (Week 9). Significant advantages for duloxetine were not achieved at any visit for agitation, somatic anxiety, or weight loss. At Weeks 1 and 2, placebo-treated patients had significantly lower GI symptoms and reported less weight loss compared with duloxetine-treated patients; however, differences were not significant at subsequent visits. Furthermore, duloxetine was superior to placebo on GI symptoms at endpoint compared to placebo-treated patients; duloxetine-treated patients had a significantly higher response rate at Week 2 and a higher remission rate at Week 5. These results may help clinicians establish more accurate expectations regarding treatment with duloxetine. Depression and Anxiety 21:170–177, 2005.

Key words: *duloxetine; depression; antidepressant; pain; efficacy; onset; serotonin; norepinephrine*

INTRODUCTION

It is commonly believed that antidepressant medications exhibit a 2- to 4-week delay following initiation of treatment before clinically meaningful improvements can be observed [Blier, 2001; Nierenberg et al., 2000; Stahl et al., 2001]. In the treatment of major depressive disorder (MDD), clinically meaningful improvement has often been defined based on changes in overall symptoms. While changes in overall symptom severity are crucial to an understanding of an antidepressant's utility, MDD is a multifaceted disease, and it also is important to assess onset of action within individual components of the illness [Katz et al., 1996].

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The present study examines the onset of improvement for both the overall symptoms and the individual symptom domains of MDD using data from two double-blind, placebo-controlled clinical trials in which patients were treated with duloxetine. An understanding of the order and timing of onset for different symptom domains may provide clinicians and patients with more accurate expectations for treatment. It has been suggested that establishing realistic patient expectations is one way to help maximize patient adherence to antidepressant therapy [Masand, 2003].

Duloxetine hydrochloride [(+)-*N*-methyl-γ-(1-naphthalenyloxy)-3-(2-thiopene)-propanamine] is a potent inhibitor of both serotonin (5-HT) and norepinephrine (NE) reuptake (SNRI), lacking significant affinity for muscarinic, histamine$_1$, α_1-adrenergic, dopamine, 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2C}$, and opioid receptors [Bymaster et al., 2001; Wong et al., 1993]. In animal pain models, the potency of duloxetine was comparable to or greater than venlafaxine, amitriptyline, or desipramine and more effective than both the selective NE inhibitor thionisoxetine and the selective serotonin reuptake inhibitor (SSRI) paroxetine in reducing persistent pain-related behaviors in animals [Iyengar et al., 2002]. In all of these models, duloxetine was efficacious at doses which blocked 5-HT and NE reuptake sites in vivo, suggesting that the preclinical effects of duloxetine likely result from dual reuptake inhibition at these sites.

Duloxetine has been studied for the treatment of MDD at doses of 40 to 120 mg/day [Detke et al., 2002a,b; Goldstein et al., 2002, 2004a,b] and can significantly reduce painful physical symptoms associated with MDD [Goldstein et al., 2004b]. Duloxetine was recently approved in the United States for the treatment of MDD and for the management of diabetic peripheral neuropathic pain.

MATERIALS AND METHODS

STUDY DESIGN

Data from two identical randomized, double-blind, placebo-controlled studies of patients with MDD were pooled for these analyses [Detke et al., 2002a,b]. All patients provided written informed consent prior to any study procedures, in accordance with the Declaration of Helsinki [World Health Organization, 2000]. Patients were randomly assigned (1:1 ratio) to either duloxetine 60-mg q.d. or placebo. The double-blind treatment period lasted 9 weeks. The study drug consisted of three capsules (either 20 mg of duloxetine in each capsule or placebo) taken once daily in the morning. If necessary, the dose could be reduced to two capsules (duloxetine 40-mg q.d. or two capsules of placebo), but had to be escalated back to three capsules after 3 weeks on the study drug and remain so for the majority of the study. Concomitant medications with primarily central nervous system activity were not allowed, with the exception of chloral hydrate (up to 1,000 mg) or zolpidem (up to 10 mg) for insomnia, for no more than 6 nights during the study. Prescription pain medications were not allowed. Antihypertensive medications were not allowed unless the patient had been on a stable dose for at least 3 months. Use of all concomitant medications was recorded at each study visit.

SELECTION OF PATIENTS

Study participants were males and females at least 18 years of age. All patients met criteria for MDD as defined in the DSM-IV [American Psychiatric Association, 1994]. The diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI), a standardized diagnostic interview based on DSM-IV criteria [Sheehan et al., 1998]. All patients were required to have a score ≥ 15 on the 17-item Hamilton Depression Rating Scale (HAMD$_{17}$) [Hamilton, 1960, 1967] and ≥ 4 on the Clinical Global Impression-Severity scale (CGI-S) [Guy, 1976] at both the screening and second study visits, indicating at least moderate severity of illness. Patients were excluded for the following reasons: current Axis I disorder (other than MDD), anxiety disorder as a primary diagnosis within a year of study entry, an Axis II disorder which could interfere with compliance with the study protocol, lack of response of the current depression episode to two or more adequate courses of antidepressant therapy or treatment-resistant depression, serious medical illness, initiating or stopping psychotherapy within 6 weeks prior to enrollment or initiating psychotherapy at any time during the study, a history of substance abuse or dependence within a year of study entry, or a positive urine drug screen.

STATISTICAL METHODS

All randomized patients (placebo: $n = 251$, duloxetine: $n = 244$) with at least one postbaseline assessment were included in the efficacy analyses. Mean changes were assessed using a likelihood-based mixed-effects-model repeated measures (MMRM) approach [Mallinckrodt et al., 2001]. The MMRM model used in the present study was identical to the model specified as the primary analysis in each of the respective protocols [Detke et al., 2002a,b] and included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. Visitwise contrasts of the least squares means from the MMRM analysis were used to assess the magnitude and statistical significance of differences between duloxetine and placebo at each postbaseline visit. Throughout this article, the term "significant" indicates statistical significance ($P < .05$). No adjustments for multiple comparisons were implemented.

The percentages of patients showing improvement at each visit also were tabulated to help assess the clinical

importance of the differences in mean changes. On $HAMD_{17}$ items, meaningful improvement was defined as a $\geq$1-point improvement. On VAS items, improvement was defined as a $\geq$10-point change. Different definitions of improvement were used because HAMD items range from either 0 to 2 or 0 to 4 whereas the VAS items ranged from 0 to 100. Hence, a 1-point shift was meaningful on the $HAMD_{17}$ items, but not meaningful on the VAS.

In addition, the probabilities of response ($\geq$50% reduction in $HAMD_{17}$ total score) and remission ($HAMD_{17}$ total score $\leq$7) also were compared using a categorical MMRM analyses to assess the time course of categorical changes in overall depressive symptoms. The categorical analyses were similar to the MMRM mean change analyses, with the addition of a logit link function and binomial error distribution to account for the nonnormality of the yes/no response and remission outcome variables.

TABLE 1. Patient demographics and baseline scores

	Duloxetine ($n=251$)	Placebo ($n=261$)
Gender		
Female	165 (65.7)	182 (69.7)
Male	86 (34.3)	79 (30.3)
Age (mean years)	41.6	41.7
Weight (mean kg)	85.4	82.0
Ethnicity (*n*) (%)		
African descent	16 (6.4)	16 (6.1)
Caucasian	207 (82.5)	212 (81.2)
Hispanic	20 (8.0)	31 (11.9)
Other	8 (3.2)	2 (0.8)
Baseline Scores (mean)		
$HAMD_{17}$ total	20.9	20.8
VAS overall pain	27.2	27.1

$HAMD_{17}$, Hamilton Depression Scale–17-item version; VAS, Visual Analog Scales.

RESULTS

A total of 512 patients were randomly assigned to either duloxetine 60-mg QD ($n=251$) or placebo ($n=261$). No significant differences existed between treatment groups in patient demographics or in baseline illness severity (Table 1). For both treatment groups, mean $HAMD_{17}$ total score was approximately 21, and the mean score for VAS overall pain was approximately 27. The efficacy analyses were based on 495 patients who had a least one postrandomization observation. Patients were not specifically screened to have a minimum severity of pain; therefore, note that approximately 30% of patients scored $>$10 on VAS overall pain at baseline.

$HAMD_{17}$ TOTAL SCORE

Mean changes in the $HAMD_{17}$ total score as well as response and remission rates derived from the total score are summarized in Table 2. Statistically significant differences in mean changes and response rates between duloxetine and placebo first occurred at Week 2 and continued thereafter. Significant differences in remission rates first occurred at Week 5 and continued thereafter. Differences between duloxetine and placebo on all three of these measures of overall symptomatology were comparatively smaller in early weeks and continued to increase throughout the trial. The endpoint treatment $HAMD_{17}$ total Score was 10.3 for duloxetine and 13.66 for placebo. The endpoint $HAMD_{17}$ total Score response and remission rates were roughly double for duloxetine-treated than for placebo-treated patients (Week-9 response: DLX = 62.8, PLA 34.8; Remission: DLX = 42.9, PLA = 21.4).

INDIVIDUAL $HAMD_{17}$ ITEMS

Mean changes in individual items of the $HAMD_{17}$ are summarized in Table 3 while the percentages of patients showing improvement for those items in which

TABLE 2. Visitwise† mean change from baseline on the $HAMD_{17}$ Total Score and visitwise rates of response and remission (MMRM analysis)

		Week											
		1		2		3		5		7		9	
Outcome	Description	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA
$HAMD_{17}$ total score	Mean changes	−2.80	−2.50	−5.55*	−3.86	−6.98*	−5.30	−8.57*	−6.43	−9.94*	−6.72	−10.60*	−7.14
Response rate	Percentage	4.2	2.7	18.1*	10.5	25.6*	17.8	41.6*	30.1	53.0*	32.1	62.8*	34.8
Remission rate	Percentage	1.1	0.5	6.0	3.1	13.5	8.7	25.2*	15.7	33.6*	19.6	42.9*	21.4

†Mean changes assessed with a Categorical MMRM. Visitwise contrasts of least squares means from the MMRM analyses were used to assess treatment group differences at each postbaseline visit. Categorical MMRM analysis of probability to response and remission included a logit function and binomial error distribution to account for *yes/no* outcome variables.

*$P<.05$ vs. placebo.

$HAMD_{17}$, Hamilton Depression Scale–17-item version; DLX, duloxetine; PLA, placebo.

TABLE 3. Visitwise[†] mean change from baseline on the $HAMD_{17}$ items (MMRM analysis)

		Week											
		1		2		3		5		7		9	
Item No.	Description	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA
1	Depressed mood	−0.60*	−0.41	−0.92*	−0.55	−1.22*	−0.79	−1.35*	−0.89	−1.45*	−0.97	−1.61*	−1.04
2	Feelings of guilt	−0.41*	−0.28	−0.61*	−0.38	−0.74*	−0.48	−0.85*	−0.61	−0.91*	−0.64	−1.03*	−0.63
3	Suicidal ideation	−0.27*	−0.14	−0.38*	−0.20	−0.46*	−0.29	−0.45*	−0.28	−0.49*	−0.30	−0.51*	−0.28
4	Insomnia early	−0.19	−0.24	−0.39	−0.33	−0.40	−0.40	−0.53	−0.51	−0.59	−0.53	−0.64*	−0.45
5	Insomnia middle	−0.04	−0.12	−0.27	−0.18	−0.29	−0.26	−0.41	−0.39	−0.58*	−0.40	−0.57*	−0.43
6	Insomnia late	−0.08	−0.06	−0.18	−0.17	−0.25	−0.24	−0.36	−0.25	−0.51*	−0.25	−0.52*	−0.32
7	Work and activities	−0.40*	−0.27	−0.71*	−0.47	−0.86	−0.71	−1.26*	−0.92	−1.43*	−0.90	−1.62*	−1.06
8	Retardation	−0.15	−0.08	−0.24*	−0.12	−0.31	−0.24	−0.39*	−0.22	−0.50*	−0.25	−0.48*	−0.23
9	Agitation	−0.12	−0.04	−0.15	−0.15	−0.19	−0.25	−0.29	−0.31	−0.32	−0.29	−0.38	−0.34
10	Anxiety (psychic)	−0.46*	−0.18	−0.64*	−0.30	−0.77*	−0.42	−0.84*	−0.44	−0.92*	−0.55	−0.88*	−0.57
11	Anxiety (somatic)	0.01	−0.03	−0.18	−0.16	−0.34	−0.23	−0.46	−0.37	−0.45	−0.41	−0.51	0.47
12	Somatic symptoms–gastrointestinal	0.15*	−0.07	−0.04*	−0.13	−0.08	−0.17	−0.09	−0.16	−0.26	−0.18	−0.27*	−0.14
13	Somatic symptoms–general	−0.12	−0.17	−0.31	−0.26	−0.38	−0.31	−0.59*	−0.40	−0.71*	−0.43	−0.70*	−0.54
14	Genital symptoms	−0.06	−0.14	−0.15	−0.18	−0.18	−0.28	−0.23	−0.31	−0.44	−0.35	−0.53*	−0.36
15	Hypochondriasis	−0.13	−0.18	−0.24	−0.18	−0.34*	−0.18	−0.37	−0.24	−0.41	−0.27	−0.37	−0.35
16	Loss of weight	0.20*	0.02	0.05*	−0.02	0.02	0.01	−0.01	−0.03	−0.05	−0.05	−0.03	−0.00
17	Insight	0.00	−0.01	−0.04	−0.01	−0.05	−0.02	−0.05	−0.03	−0.06*	−0.02	−0.05	−0.04

[†]Mean changes assessed with a Categorical MMRM. Visitwise contrasts of least squares means from the MMRM analyses were used to assess treatment group differences at each postbaseline visit.
*$P < .05$ vs. placebo.
$HAMD_{17}$, Hamilton Depression Scale–17-item version; DLX, duloxetine; PLA, placebo.

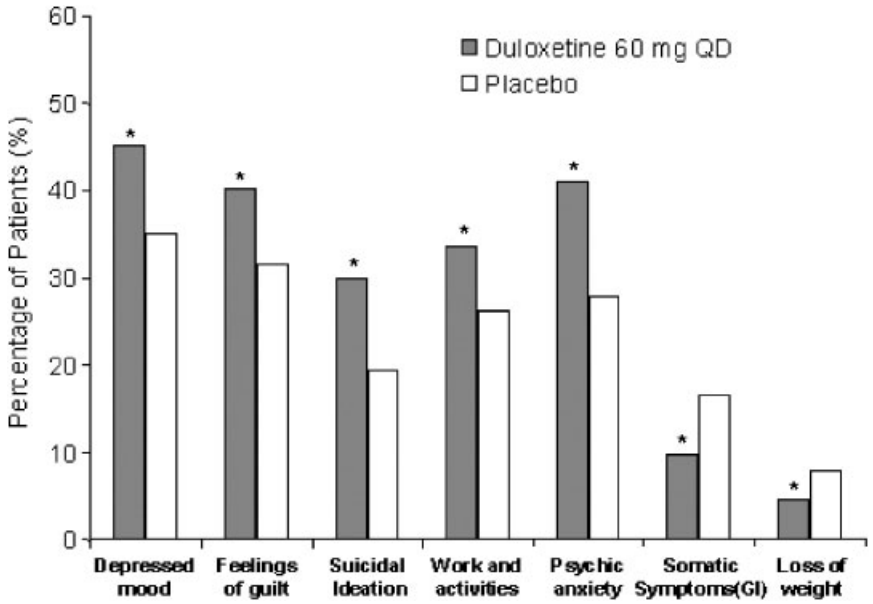

Figure 1. Percentage of patients showing ≥1-point improvement from baseline at Week 1 in selected $HAMD_{17}$ items (Only those items demonstrating a significant between-group difference are shown.) *$P \leq .05$ versus placebo.

significant differences in mean changes existed at Week 1 are shown in Figure 1.

At Week 1, duloxetine-treated patients had significantly greater improvement compared to placebo-treated patients on 5 of the 17 $HAMD_{17}$ items: Item 1 (Depressed Mood), Item 2 (Feelings of Guilt), Item 3 (Suicidal Ideation), Item 7 (Work and Activities), and Item 10 (Anxiety/Psychic). The percentage of duloxetine-treated patients showing improvement on these outcomes ranged from approximately 30 to 45%, with the corresponding percentages for placebo-treated patients approximately 7 to 13% lower.

The magnitude of improvement with duloxetine compared to placebo tended to increase over time. The statistical significance observed at Week 1 for Items 1, 2, 3, and 10 was maintained for all 9 weeks of the trial. Item 7 was significantly better than placebo at each week, except Week 3. The first week at which significant improvement was observed for other items were as follows: Item 8 (Retardation) at Week 2; Item 15 (Hypochondriasis) at Week 3; Item 13 (General somatic symptoms) at Week 5; Item 5 (middle insomnia), Item 6 (late insomnia), and Item 17 (insight) at Week 7; Item 4 (early insomnia), Item 12 (GI symptoms), and Item 14 (genital symptoms) at Week 9. For outcomes with later onset, the percentage of duloxetine-treated patients showing improvement was generally lower, and the differences from placebo generally smaller, than the items showing faster onset (results not shown).

Significant advantages for duloxetine over placebo were not achieved at any visit for Item 9 (agitation), Item 11 (somatic anxiety), or Item 16 (weight loss). Placebo-treated patients demonstrated significantly greater improvement compared with duloxetine on Items 12 (GI symptoms) and 16 (weight loss) at Weeks 1 and 2; however, these advantages for placebo were transitory. At the end of the trial, duloxetine was superior to placebo on Item 12 (GI symptoms) while there was no significant between-group difference on Item 16 (weight loss). At the end of the 9-week trial, duloxetine-treated patients had significantly greater improvement compared with placebo on 12 of the 17 $HAMD_{17}$ items (Depressed Mood, Feelings of Guilt, Suicidal Ideation, Insomnia Early, Insomnia Middle, Insomnia Late, Work and Activities, Retardation, Anxiety/Psychic, Somatic Symptoms—Gastrointestinal, Somatic Symptoms—General, and Genital Symptoms).

Given the clinical importance of suicide, the percentages of patients who had a worsening on Item 3 (suicidal ideation) are noteworthy. For duloxetine-treated patients, the rate of worsening ranged from 2.8 to 5.5% at the various study visits, and showed no overall temporal trend as the rates at Weeks 1 and 9 were 5.3 and 5.5%, respectively. The percentage of placebo-treated patients with worsening on Item 3 ranged from 7.1 to 9.9% and was higher at each study visit than the corresponding rate for duloxetine.

INDIVIDUAL PAIN ITEMS

Mean changes in individual items of the VAS are summarized in Table 4. Mean changes for duloxetine-treated patients were significantly superior to placebo on two of the six items at Week 1 (back pain and shoulder pain), and on all six of the VAS items at Weeks 2 and 3. From Weeks 5 to 9, duloxetine showed an advantage for three of the six symptoms on the VAS (Week 9: overall pain, back pain, and shoulder pain). At endpoint, the mean VAS overall pain score was 18.08 for duloxetine and 23.11 for placebo.

At Week 1, approximately 25 to 35% of duloxetine-treated patients had at least a 10-point improvement in the various pain scales. In general, percentage rates were similar for placebo- and duloxetine-treated patients, with the exceptions of back and shoulder pain. Compared to duloxetine-treated patients, there were up to 9% fewer placebo-treated patients showing at least a 10-point improvement on measures of back and shoulder pain—a statistically significant difference (Figure 2). At subsequent visits, the percentage of patients showing improvement continued to increase slightly for both treatment groups.

Because patients were not specifically screened to meet a minimum threshold for pain at baseline, it also is useful to consider the percentage of patients who experienced worsening of pain severity (10-point increase). For example, in overall pain, approximately 30% of patients had baseline scores <10 and therefore could not meet the 10-point threshold for improvement. For overall pain, the percentages of patients

TABLE 4. Visitwise[†] mean change on the visual analog scale items (MMRM analysis)

		Week											
		1		2		3		5		7		9	
Item	Description	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA	DLX	PLA
1	Overall pain	−2.01	1.49	−7.27*	0.51	−4.83*	−1.85	−8.94*	−2.27	−9.53*	−3.96	−9.12*	−3.99
2	Headache	−1.42	−0.75	−5.91*	−1.85	−7.86*	−3.81	−7.29	−4.78	−9.22	−7.49	−8.96	−4.94
3	Back pain	−7.56*	−2.12	−9.07*	−1.64	−10.60*	−2.98	−10.94*	−4.63	−9.58*	−3.99	−10.23*	−4.31
4	Shoulder pain	−4.37*	−0.19	−5.27*	0.88	−5.29*	−0.96	−5.62	−3.83	−6.10*	−2.26	−6.28*	−2.12
5	Interference with daily activities	−1.40	0.63	−3.44*	0.57	−4.80*	0.17	−4.98*	−1.39	−5.73	−2.93	−4.79	−2.97
6	Time experiencing pain while awake	−5.89	−2.73	−9.81*	−1.91	−10.74*	−4.80	−11.80	−7.71	−12.61	−8.11	−11.12	−8.12

[†]Mean changes assessed with a Categorical MMRM. Visitwise contrasts of least squares means from the MMRM analyses were used to assess treatment group differences at each postbaseline visit.

*$P<.05$ vs. placebo.

DLX, duloxetine; PLA, placebo.

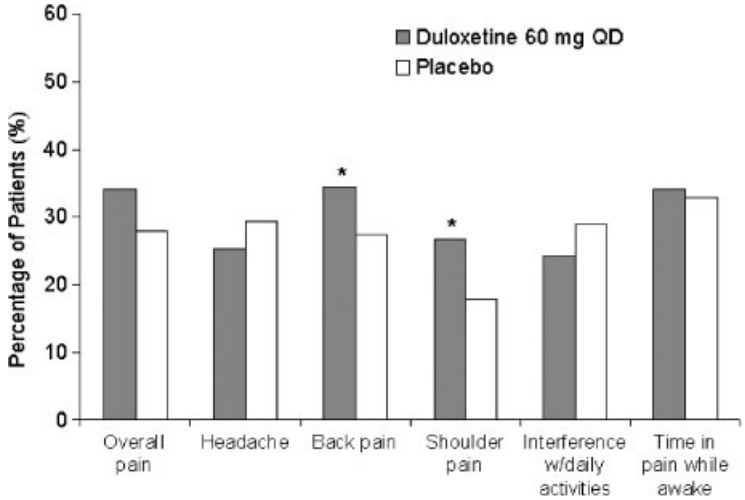

Figure 2. Percentage of patients showing ≥10-point improvement from baseline at Week 1 in VAS pain items. *$P \leq .05$ versus placebo.

experiencing worsening at Week 1 were 22 and 24% for duloxetine and placebo, respectively. At all subsequent visits, the percentage worsening ranged from approximately 10 to 14% for duloxetine compared with 21 to 28% for placebo.

Summaries of the safety and tolerability of duloxetine in the two studies utilized in the present investigation have been reported previously [Detke et al., 2002a,b]. The discontinuation rate due to adverse events was 13.1% for duloxetine-treated patients compared with 3.4% for placebo while discontinuation rates due to perceived lack of efficacy were 4.4 and 11.1% for duloxetine and placebo, respectively.

DISCUSSION

In these analyses, duloxetine demonstrated statistically significant and clinically meaningful separation from placebo in overall measures of symptom improvement as early as Week 2 (Week 2 for mean change in $HAMD_{17}$ total score and response rate, Week 5 for remission rate). When assessing improvement in individual-symptom domains, response was fastest on pain in specific locations (back and shoulder) and on items such as depressed mood, guilt, psychic anxiety, suicidal ideation, and work activities (the item closest to anhedonia) that may be considered the core emotional symptoms of depression. Onset occurred at Week 2 for retardation and Week 3 for hypochondriasis. Subsequent improvements were seen in general somatic symptoms, followed by improvements in sleep, GI, and genital symptoms. Advantages for duloxetine over placebo were not seen at any visit for agitation, somatic anxiety, and weight loss. For most outcomes, once statistical significance was achieved, it was maintained at subsequent visits. The advantage of duloxetine over placebo in terms of mean change and percentage of patients showing improvement generally continued to increase throughout the trial.

Duloxetine was significantly worse than placebo on Items 12 and 16 (GI symptoms and weight) at Weeks 1 and 2, although differences at subsequent visits were not significant. This early, transitory worsening was likely associated with treatment-emergent nausea. For duloxetine, like most SSRIs and SNRIs, nausea is the most frequently reported adverse event. In these two trials, most of the reported nausea occurred early in treatment (approximately 70% of patients who reported nausea had onset on the first 2 days of treatment) and was transitory in nature (median duration 6 days).

These results illustrate that differences in the time courses of response in individual symptoms may be substantial. Our findings suggest that duloxetine-treated patients will have improvement in depressed mood, guilt, psychic anxiety, and suicidal ideation within the first few weeks of treatment, with nearly half showing some improvement at Week 1. Although full-symptom resolution (remission) takes longer, the early improvement in some symptoms may be an important indicator of long-term benefits [Katz et al., 1996].

Results of this investigation also indicate that sleep, nonpainful somatic symptoms, and genital symptoms are typically slower to respond. In situations where these symptoms may pose a significant problem, other interventions early in treatment may be desirable.

Results from this investigation should be interpreted in light of its strengths and limitations. Data were pooled from two trials, each designed to stand alone as an adequate and well-controlled study of the efficacy of duloxetine versus placebo in the treatment of MDD over 9 weeks of therapy. Therefore, these pooled results provide a reliable assessment of the time course

of response to duloxetine treatment; however, these studies were not designed specifically to measure onset of action. Given that the first assessment following initiation of treatment was at Week 1, it was not possible to determine if any of the symptoms responded favorably or unfavorably to treatment before that point. In addition, the scales used in these trials did not include measures of all symptom domains (e.g., cognition).

Furthermore, while pooling of the data was not problematic because the studies were identical, pooling was not specified a priori, and thus all results should be interpreted in the light of post hoc comparisons. Future studies with more frequent measurements during treatment initiation and a comprehensive battery of assessments would be useful in further clarifying response profiles.

It also is important to make a clear distinction between the present results that assessed differential response of individual symptoms to duloxetine treatment and attempts to compare the rapidity of action of different medications. Obviously, the present study can assess only duloxetine, and comparisons with other antidepressants are inappropriate. Therefore, fully characterizing the onset of action of duloxetine will require future studies that include other antidepressants. A head-to-head study designed specifically to assess relative onset of efficacy in overall or individual symptoms in drugs with differing mechanisms of action would be particularly interesting. For example, it is well known that sedating antidepressants (e.g., TCAs, mirtazapine) rapidly improve sleep onset; however, it would be valuable to know the temporal pattern of clinical improvement in all symptom domains for all antidepressants and across different subpopulations (e.g., young, elderly, hospitalized, melancholic, atypical).

CONCLUSIONS

Clinically meaningful response to duloxetine therapy was most rapid for some of the emotional and painful physical symptoms of depression (Week 1), with symptoms of retardation and hypochondriasis responding within 2 to 3 weeks, respectively. Slower responses (5–9 weeks) were achieved for sleep, genital, and nonpainful somatic symptoms. The results presented here may help clinicians establish more accurate expectations for the patient regarding treatment with duloxetine. Further longitudinal studies, designed to assess clinically important changes early in treatment, are warranted.

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DISCLOSURE OF INTERESTS AND AFFILIATIONS

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