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Duloxetine for the Treatment of Major Depressive Disorder

By Charles B. Nemeroff, MD, PhD, Alan F. Schatzberg, MD, David J. Goldstein, MD, PhD, Michael J. Detke, MD, PhD, Craig Mallinckrodt, PhD, Yili Lu, PhD, and Pierre V. Tran, MD

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Duloxetine for the Treatment of Major Depressive Disorder

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ABSTRACT ~ Background. *Existing therapies for depression frequently fail to provide full remission. This report evaluates the efficacy and safety of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, in the treatment of major depressive disorder (MDD).*

Method. *Efficacy of duloxetine was evaluated in six double-blind, placebo- and/or active comparator-controlled clinical trials. A study of duloxetine in patients with stress urinary incontinence was also included in the safety assessments. The primary efficacy measure was total score on the 17-item Hamilton Rating Scale for Depression (HAMD-17). Secondary measures included estimated probabilities of response and remission, and changes in the Clinical Global Impressions scale, Patients Global Impression scale, and the Hamilton Rating Scale for Anxiety. Physical symptoms were assessed using Visual Analog Scales for Pain. Safety evaluations included reporting of adverse events, changes in vital signs, electrocardiogram, blood pressure, and laboratory analyses.*

Results. *Duloxetine was significantly superior to placebo in reducing mean HAMD-17 total score in four of the six studies. Significant improvements for duloxetine over placebo were also observed on many secondary efficacy measures across five of the studies. Probabilities of remission >55% were observed in two of the studies, while in a third study the probability of remission with duloxetine treatment was nearly three times that observed with placebo (44% versus 16%). Duloxetine also produced significant improvement in painful physical symptoms compared with placebo, in many cases after only 2 weeks of treatment. The discontinuation rate due to adverse events (14.6%) was similar to those observed with selective serotonin reuptake inhibitors. The most frequently reported adverse events were nausea, dry mouth, fatigue, and insomnia.*

Conclusion. *Duloxetine was demonstrated to be safe and effective in the treatment of MDD. The starting dose with the best balance of efficacy and tolerability is 60 mg per day.* Psychopharmacology Bulletin. *2002;36(4):106-132*

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INTRODUCTION

The World Health Organization recently categorized depression as one of the world's most disabling diseases, affecting nearly 340 million people worldwide and 18 million people in the United States at any given time.[1] Few laypeople realize that major depression and related mood disorders are potentially deadly afflictions; unrecognized major depressive disorder (MDD) is associated with a suicide risk of approximately 15%.[2,3] Beyond the risk of suicide, depressed patients also show a higher risk of mortality from all causes.[4]

However, studies of mortality alone cannot fully characterize the hidden costs and true global impact of mental illness. The Global Burden of Disease Study[1] was initiated in order to objectively evaluate the burden of over 100 common medical conditions by utilizing the metric of disability-adjusted life years (DALYs). The report stated that psychiatric conditions, though responsible for little over 1% of deaths, accounted for almost 11% of the disease burden worldwide.[1] Furthermore, MDD was found to be the fourth largest source of DALYs in 1990, and was projected to rise to second place by 2020. In addition, independent studies have ranked MDD as the third most costly and disabling illness in the United States.[5,6] Given the scope of the public health need, significant improvement in the therapies available to treat major depression has potentially far-reaching beneficial consequences.

The research efforts involved in developing the current generation of antidepressant agents have helped to increase awareness of the diagnosis and treatment of major depression. However, the antidepressant medications currently employed to treat MDD possess a number of limitations, including tolerability (approximately 50% of patients stop treatment within 3 months due to side effects or lack of efficacy[7]) and rather low probabilities of remission typically in the range of 35% to 45%.[8-10] Some tricyclic antidepressants (TCAs) are believed to produce their therapeutic effects by inhibiting the reuptake of both serotonin (5-HT) and norepinephrine (NE), but the undesirable affinity of TCAs for a range of receptors (including muscarinic, cholinergic, α-adrenergic, and histaminergic receptors) can produce side effects ranging from mild (drowsiness) to serious (cardiovascular), particularly in overdose. The newer class of selective serotonin reuptake inhibitors (SSRIs) couple relatively selective 5-HT neurotransmitter activity with far lower affinities for other receptors, and consequently exhibit safety profiles superior to those of TCAs.

Renewed hopes of improved treatment outcomes were provided by an open-label study in which the combination of the SSRI fluoxetine, and the selective NE reuptake inhibitor desipramine, was shown to demonstrate greater efficacy than either medication alone.[11] In addition, the results of several studies led by the Danish University Antidepressant Group have suggested that the TCA clomipramine, a 5-HT/NE reuptake

inhibitor (SNRI), has greater clinical efficacy than standard doses of SSRIs, including citalopram and paroxetine.[12,13] Some evidence also exists to suggest that certain SSRIs act as dual reuptake inhibitors, especially at higher-than-standard doses.[14] These observations served as impetus for the development of selective dual monoamine reuptake inhibitors, and very recently it has been reported that the probability of remission observed for the SNRI venlafaxine (45%), is higher than that found for standard doses of SSRIs (35%) and placebo (25%).[10] While some studies have suggested equivalent clinical efficacy for SSRIs relative to TCAs,[15] the majority have found that dual SNRIs are more effective.[10,16-19]

Unfortunately, currently available antidepressant medications that are believed to act as dual SNRIs are known to possess significant tolerability issues that limit their applicability and may adversely affect long-term treatment compliance in some patients. Development of sustained hypertension has been reported during treatment with at least one dual-action antidepressant, while others have been associated with somnolence, weight gain, and orthostatic blood pressure changes. Clearly, a more ideal antidepressant would combine the pharmacology and remission rates of a dual-action medication with the safety profile of an SSRI.

In addition to providing successful treatment of the emotional symptoms of MDD, another requirement for antidepressant medications is to improve the associated physical symptoms of depression. A large proportion of depressed patients (as many as 69%) present initially with physical complaints.[20] More specifically, these complaints are often pain-related and may encompass back pain, headache, diffuse musculoskeletal pain, and stomach aches.[21] In fact, a positive correlation has been established between the severity of depression and the number and severity of pain complaints reported by patients.[22] These physical complaints often serve to complicate the diagnosis of depression and can act as potential barriers to achieving remission. Furthermore, a large number of treatment-responsive patients continue to report residual somatic complaints, and these residual symptoms have been shown to be strong predictors of subsequent early relapse.[23] Despite the growing body of evidence suggesting the importance of addressing both emotional and physical symptoms in the treatment of depression, few clinical trials of antidepressants have specifically addressed the treatment of physical symptoms, or attempted to investigate links between reduction in depression and relief of physical symptoms.

Duloxetine hydrochloride [LY248686, (+)-*N*-methyl-3-(1-naphthalenyloxy)-(2-thiophene)-propanamine] is a dual reuptake inhibitor of both 5-HT and NE that lacks significant affinity for muscarinic, histamine H_1, α_1-adrenergic, dopamine D_2, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, and opioid receptors.[24] Based on this neurochemical

profile, it was hypothesized that duloxetine may exhibit efficacy superior to that of single neurotransmitter agents in the treatment of the core emotional symptoms of depression. Furthermore, because both 5-HT and NE act as pain modulators in the descending pain pathways of the spinal cord,[25-27] it was speculated that a medication with SNRI activity might be effective in relieving pain and other physical symptoms often associated with depression. TCAs have frequently been employed to treat chronic pain,[28-31] and there is growing evidence that dual 5-HT/NE reuptake inhibition provides greater analgesic efficacy than an SSRI acting upon 5-HT alone.[29,31]

These data are consistent with the widespread clinical use of the dual 5-HT/NE reuptake inhibitor amitriptyline in the treatment of chronic pain conditions. Notably, preclinical trials involving duloxetine showed that the drug reduced chronic pain in several animal models with greater potency than amitriptyline.[32] These preclinical findings led to the further investigation of the potential for clinical use of duloxetine in the treatment of MDD and its associated physical symptoms.

In addition to assessing the overall safety and efficacy of duloxetine, the studies described here were also intended to provide data concerning the optimal dosing regimen for this new antidepressant medication. The studies utilized duloxetine doses ranging from 40–120 mg/day, and included both once-daily and twice-daily dosing regimens. With regard to patient compliance, it was considered especially important to determine whether a simple, once-daily dosing strategy would be both effective and well tolerated.

This report presents the findings from six double-blind, placebo-controlled clinical trials which evaluated the efficacy of oral duloxetine in patients with MDD. In order to maximize the number of duloxetine-treated patients in the safety analyses, safety was evaluated by pooling the data from these six MDD trials and a study of duloxetine in patients with stress urinary incontinence (SUI).

METHODS

Study Design

All trials were multisite, randomized, double-blind, placebo- and/or active comparator-controlled studies. Depression studies incorporated double-blind, variable-duration placebo lead-in and lead-out periods to blind the patients and investigators to the start and end of active therapy. Study protocols were approved by the ethics committee at each site in accordance with the principles of the Declaration of Helsinki, and all patients had completed signed informed consent documents prior to the administration of any study procedures or study drug. The studies are summarized in Table 1.

Patients

All patients in the depression studies were at least 18 years of age and met criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*),[33] for MDD. The diagnosis of MDD was confirmed by the Mini International Neuropsychiatric Interview,[34] a standardized diagnostic interview based on *DSM-IV* criteria. Depressed patients had both a Clinical Global Impressions Severity (CGI-S) score ≥4 (moderate) and a clinician-rated 17-item Hamilton Rating Scale for Depression (HAMD-17) total score ≥15 at visits 1 and 2.

Patients were excluded for the following reasons: current and primary Axis I disorder (other than MDD); anxiety disorder as a primary diagnosis within 1 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 (treatment-resistant depression); serious medical illness; a history of substance abuse or dependence within 1 year of study entry; or a positive urine drug screen. Concomitant medications with primarily central nervous system activity were not permitted, with the exception of chloral hydrate or zolpidem for insomnia, on no more than 6 nights during the study. Chronic use of prescription analgesic medications was not allowed; episodic use was permitted at the discretion of the physician in charge of the study. Antihypertensive medications were not permitted unless the patient had been on a stable dose for at least 3 months.

All patients in Study 7 were otherwise healthy women 18–65 years of age who had been diagnosed with SUI. Patients with SUI suffer leakage of small amounts of urine during physical movement such as coughing, sneezing, or exercising. Patients were excluded for the following reasons: history of significant cardiac arrhythmia; history of angina or any cardiac ischemic condition; major surgery within 3 months of study entry; pregnancy within 12 months prior to study entry; current use of monoamine oxidase inhibitors, clonidine, α-methyl-DOPA, β-blockers or α-receptor antagonists/agonists; or a history of substance abuse or dependence within 5 years of study entry. Concomitant medication regimens including estrogens, antiestrogens, or diuretics were not permitted unless the dose had been stable for 12 weeks prior to the trial.

Efficacy Measures

The primary and secondary efficacy measures employed in each study are shown in Table 2. Not all measures were used in every study. The primary efficacy measure for all studies of MDD was the HAMD-17 total score,[35,36] where a decrease in total score indicated an improvement in symptoms of depression. Response to treatment was defined as a 50%

TABLE 1

SUMMARY OF CLINICAL TRIALS INVOLVING DULOXETINE

	INDICATION	STUDY DESIGN	TREATMENTS (N)	DURATION OF TREATMENT	NUMBER OF SITES
Study 1	Major depression	Parallel, double-blind, placebo-controlled, randomized	Placebo (122) Duloxetine 60 mg QD (123) Total (245)	9 weeks	18
Study 2	Major depression	Parallel, double-blind, placebo-controlled, randomized	Placebo (139) Duloxetine 60 mg QD (128) Total (267)	9 weeks	23
Study 3	Major depression	Parallel, double-blind, randomized, placebo-controlled, fluoxetine-controlled, forced titration	Placebo (70) Duloxetine 40-120 mg/day* (70) Fluoxetine 20 mg QD (33) Total (173)	8 weeks including titration	8
Study 4	Major depression	Parallel, double-blind, randomized, placebo-controlled, fluoxetine-controlled, forced titration	Placebo (75) Duloxetine 40-120 mg/day* (82) Fluoxetine 20 mg QD (37) Total (194)	8 weeks including titration	11
Study 5	Major depression	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (90) Duloxetine 40 mg/day* (91) Duloxetine 80 mg/day* (84) Paroxetine 20 mg QD (89) Total (354)	8 weeks	22
Study 6	Major depression	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (89) Duloxetine 40 mg QD (86) Duloxetine 80 mg/day* (91) Paroxetine 20 mg QD (87) Total (353)	8 weeks	22
Study 7	Stress urinary incontinence	Parallel, double-blind, placebo-controlled, randomized	Placebo (138) Duloxetine 40 mg/day* (86) Duloxetine 40 mg/day* (137) Duloxetine 80 mg/day* (140)	14 weeks including 2 weeks de-escalation/ placebo lead-out	48

* Duloxetine doses of 40 mg/day, 80 mg/day, and 120 mg/day were administered as 20 mg BID, 40 mg BID, and 60 mg BID, respectively.

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reduction in HAMD-17 total score from baseline to endpoint, while remission was defined as a HAMD-17 total score ≤7. Secondary measures included the following: HAMD-17 anxiety (items 10, 11, 12, 13, 15, and 17), core factor (items 1, 2, 3, 7, and 8), Maier (items 1, 2, 7, 8, 9, and 10),[37] retardation (items 1, 7, 8, and 14),[38] and sleep (items 4, 5, and 6) subscales.[39] Improvement in physical symptoms associated with depression was assessed by means of Visual Analog Scales (VAS) of pain severity on six separate measures: overall pain, headaches, back pain, shoulder pain, interference with daily activities, and time in pain while awake. Further details of secondary measures[40-49] are provided in Table 2. In Studies 5 and 6 an assessment was also made of the number of visits to health care providers and number and types of health care providers visited.

The statistical approach employed to establish a dose recommendation was to calculate effect sizes side-by-side for three efficacy measures (HAMD-17 total score, probability of response, and probability of remission) without inferential statistics between doses. However, pooling of

TABLE 2

EFFICACY, HEALTH OUTCOMES, AND PHYSICAL SYMPTOMS MEASURES IN MDD STUDIES

	STUDIES		
MEASURES	1 and 2	3 and 4	5 and 6
Efficacy			
HAMD-17 (Primary measure)	x	x	x
Response and remission	x	x	x
HAMD-17 subscales	x	x	x
MADRS		x	x
HAM-A		x	x
CGI-Severity	x	x	x
CGI-Improvement		x	
PGI-Improvement	x	x	x
Health Outcomes			
SF-36		x	
QLDS	x		x
Physical Symptoms			
SSI	x		x
VAS	x		x

MDD=major depressive disorder; HAMD-17=17-item Hamilton Rating Scale for Depression[34,35]; MADRS=Montgomery-Asberg Depression Rating Scale[40]; HAM-A=Hamilton Rating Scale for Anxiety[41]; CGI=Clinical Global Impressions scale[42]; PGI=Patient's Global Impressions scale[42]; SF-36=Short Form-36 Health Survey[43,44]; QLDS=Quality of Life in Depression Scale[45-47]; SSI=Somatic Symptom Inventory[48]; VAS=Visual Analog Scales.[49]

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efficacy data within each protocol was utilized (ie, data from Studies 5 and 6 were combined, and also from Studies 1 and 2).

Safety Assessments

Evaluated safety measures included treatment-emergent adverse events (including discontinuation and serious adverse events–ie, those involving hospitalization, severe or permanent disability, congenital anomaly, or cancer), laboratory analyses, vital signs, electrocardiograms (ECGs), and the Arizona Sexual Experience Scale (ASEX).[50] ECG findings (including mean changes from baseline to endpoint in QT, corrected QT intervals [QTc], and treatment-emergent prolonged QTc intervals) were evaluated in Studies 5 and 6. Treatment-emergent prolongation in corrected QT intervals was defined as a change from baseline ≥30 msec.

Mean changes in the ASEX were evaluated in Studies 3, 4, 5, and 6. Negative changes in the ASEX indicated improvement in sexual function, while positive changes indicated worsening of sexual function as determined by patient answers to the five-question survey. The ASEX was administered prior to randomization and either once or twice post-baseline, depending upon the study. The rates of occurrence of gender-specific adverse events related to sexual functioning are given for MDD patients only (ie, Studies 1–6).

Hypertension

Patients were considered hypertensive if supine systolic blood pressure was ≥140 mm Hg and an increase from baseline of ≥10 mm Hg occurred, or if supine diastolic blood pressure was ≥90 mm Hg and an increase from baseline of ≥10 mm Hg occurred. These definitions were based on diagnostic criteria from the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure.[51] Sustained hypertension was defined as meeting the above hypertensive criteria for three consecutive visits. The analysis of sustained elevations in blood pressure did not include patients from Study 7, because the patients in this study were seen only three times (at 4-week intervals) during study participation.

Statistical Methods

Efficacy data were analyzed separately for each of the MDD studies; patient sample sizes by treatment protocol are shown in Table 3. For safety assessments, data were pooled from the six double-blind, placebo-controlled depression studies and from the duloxetine (Cymbalta™, 40 mg/day and 80 mg/day) and placebo arms of Study 7 (an SUI study). Because our studies focused on the anticipated therapeutic dose range for duloxetine, the lower dose arm of Study 7 (duloxetine 20 mg/day) was not included in the safety analyses. Table 3 details the number of patients from each study that were included in the safety analysis. All analyses were conducted on an

intent-to-treat basis. All randomized patients were included in the safety analysis and all randomized patients with at least one postbaseline assessment were included in the efficacy analysis.

In the case of Studies 1, 2, 5, and 6, the protocols specified a likelihood-based, mixed-effects model repeated measures (MMRM) approach as the primary analysis for continuous efficacy measures. For Studies 3 and 4, analysis of covariance (ANCOVA) was specified as the primary analysis. Further details of the statistical methods and the rationale for their use are detailed in the literature.[52,53] All hypotheses were tested using a two-sided α=0.05.

In safety data, mean changes in vital signs and laboratory analytes were evaluated using analysis of variance (ANOVA), while ANCOVA was used to evaluate the ASEX scores. Categorical data (adverse events, abnormal laboratory results or vital signs, and QTc values) were assessed using Fisher's exact test. Abnormal laboratory values were determined based on established reference limits.[54] Rank-transformed laboratory analytes were analyzed using the ANOVA model.

Efficacy results presented throughout this paper are from the MMRM analyses unless otherwise noted. The term "mean" is used throughout to indicate "least squares mean". The term "significant" indicates statistical significance ($P \leq .05$).

RESULTS

Patient Characteristics and Disposition

In the seven trials under study, a total of 1,755 patients were randomly allocated to placebo (n=723), duloxetine 40 mg/day (n=314),

TABLE 3

NUMBERS OF RANDOMIZED PATIENTS INCLUDED IN DULOXETINE SAFETY ANALYSIS

		DULOXETINE DOSE			
Study	Placebo	40 mg/day*	60 mg QD	80 mg/day*	120 mg/day*
1	122	-	123	-	-
2	139	-	128	-	-
3	70	-	-	-	70
4	75	-	-	-	82
5	90	91	-	84	-
6	89	86	-	91	-
7†	138	137	-	140	-
Total					
Efficacy†	585	177	251	175	152
Safety†	723	314	251	315	152

*Doses of 40 mg/day, 80 mg/day and 120 mg/day were administered as 20 mg BID, 40 mg BID, and 60 mg BID, respectively.

†Patients in Study 7 were included in the safety analysis only. All other study patients were included in efficacy and safety analyses.

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duloxetine 60 mg QD (n=251), duloxetine 80 mg/day (n=315), or duloxetine 120 mg/day (n=152) (Table 3). Patient age range was 18.0–82.9 years, with a mean of 43.55 years; 85.6% were Caucasian and 73.7% were female. No significant differences existed between treatment groups on any measure of baseline demographics.

Efficacy

Definitive evidence for the efficacy of duloxetine in the treatment of MDD was demonstrated (duloxetine significantly superior to placebo) in four of six studies (Studies 1, 2, 3, and 6). In each of these studies, duloxetine demonstrated significant superiority over placebo on the primary efficacy measure (HAMD-17 total score). Additional supportive evidence for the efficacy of duloxetine (significant superiority of duloxetine on multiple secondary outcomes) was obtained from Study 5. Table 4 presents a summary of efficacy findings from the six studies of duloxetine in MDD.

Figure 1 depicts graphically the difference in mean change (with confidence intervals) between duloxetine and placebo treatment groups on HAMD-17 total score (the primary efficacy measure) for all six MDD studies. While duloxetine demonstrated superiority over placebo at all studied doses (40–120 mg/day), the most robust efficacy was shown at doses of 60 mg/day and higher; 60 mg QD in Studies 1 and 2, 80 mg/day in Study 6, and titration to 120 mg/day in Study 3. Duloxetine at 80 mg/day (Study 6) also demonstrated significant superiority to paroxetine 20 mg QD on the primary efficacy measure.

Figure 2 summarizes the estimated probability of remission at the endpoints of Studies 1, 2, 3, and 6 (ie, those studies in which duloxetine demonstrated superiority on the primary efficacy measure). In Studies 1, 3, and 6 (80 mg/day) the probabilities of remission were all significantly greater than for the corresponding placebo groups. Most notably, the probability of remission for duloxetine-treated patients in Study 3 (56.1%) was significantly superior to placebo (31.5%, *P*=.022) and the difference from fluoxetine approached significance (*P*=.055), while the probability of remission for duloxetine-treated patients (80 mg/day) in Study 6 (57.2%) was significantly superior to the rates observed for both placebo (25.4%, P=.002) and 20 mg/day paroxetine (33.6%, *P*=.022).

Duloxetine also demonstrated significant superiority over placebo on a range of secondary measures, most notably in Studies 1, 2, 3, and 6 (80 mg/day). As shown in Table 4, duloxetine was superior to placebo on all five of the HAMD-17 subscales in Study 1, and achieved superiority over placebo in four of the five subscales in Studies 3 and 6 (80 mg/day). In Studies 1 and 3 duloxetine was significantly superior to placebo on the anxiety/somatization subscale of the HAMD-17, while duloxetine

was also superior to placebo on this subscale at 80 mg/day in Studies 5 and 6. Duloxetine (80 mg/day) was also significantly superior to paroxetine (20 mg QD) on the anxiety/somatization subscale in Study 6. Furthermore, duloxetine was superior to placebo on HAMD-17 Item 1 (Depressed Mood) in Studies 1, 2, 3, and 5 (P<.005 in each case), and superior to placebo on the Patients Global Impression-Improvement (PGI-I) scale in Studies 1, 2, and 3 (*P*<.015 in each case). In the case of the CGI-S efficacy measure, duloxetine (60 mg QD) demonstrated superiority over placebo as early as week 1 of treatment, and sustained this improvement throughout the course of the study. Collectively, these results provide substantial evidence to support the claim of duloxetine's efficacy, especially at doses of 60 mg/day and above.

A statistically significant improvement for duloxetine-treated patients over placebo was seen in VAS–overall pain severity in Study 6.

TABLE 4

SUMMARY OF MDD STUDY RESULTS ANALYZED BY PRIMARY AND SECONDARY EFFICACY MEASURES

TESTING MEASURE	STUDY 1	STUDY 2	STUDY 3
	60 mg QD	60 mg QD	120 mg/day*
HAMD-17			
Total Score	S	S	S
Subscale–Core	S	S	S
Subscale–Maier	S	S	S
Subscale–anxiety/somatization	S	NS	S
Subscale–retardation/somatization	S	S	S
Subscale–sleep	S	NS	NS
Item #1 Score	S	S	S
Response to Treatment	S	S	NS
Remission	S	NS	S
MADRS	-	-	S
HAM-A	-	-	NS
CGI			
Severity	S	NS	S
Improvement	-	-	S
PGI-I	S	S	S
QLDS	NA	NA	-
SF-36			
Physical component	-	-	S
Mental component	-	-	S
General health perceptions	-	-	NS
Mental health	-	-	S

HAMD-17=17-Item Hamilton Rating Scale for Depression; MADRS=Montgomery Asberg Depression Rating Scale; HAM-A=Hamilton Rating Scale for Anxiety; CGI=Clinical Global Impressions; PGI-I=Patient's Global Impressions of Improvement; QLDS=Quality of Life in Depression Scale; SF-36=Short Form-36 Health Survey.

Furthermore, significant superiority of duloxetine over placebo from baseline to endpoint was also seen for the VAS-headaches score in Study 5 (duloxetine 80 mg/day), for the VAS-back pain score in Study 1, and for HAMD-17 Item 13—"somatic symptoms (general)"—in Studies 1 (P=.013) and 6 (P=.039).

The differences in VAS scores between duloxetine and placebo treatment groups were of approximately the same magnitude at early and late visits, with somewhat larger, and often statistically significant, differences being noted at intermediate visits. This pattern of differences is in contrast to the depression trajectories, in which differences between drug and placebo tended to increase over time. Given that differences between treatments fluctuated, but did not consistently increase or decrease, a set of mean changes for the six VAS measures in Studies 1 and 2 were derived from the main effect of treatment. This

STUDY 4	STUDY 5		STUDY 6	
120 mg/day*	40 mg/day*	80 mg/day*	40 mg/day*	80 mg/day*
NS	NS	NS	S	S
NS	S	S	NS	S
NS	S	S	NS	S
NS	NS	S	NS	S
NS	S	NS	NS	S
NS	NS	NS	NS	NS
NS	S	S	NS	NS
NS	NS	NS	NS	S
NS	NS	NS	NS	S
NS	NS	NS	NS	S
NS	NS	NS	NS	S
NS	NS	S	NS	NS
NS	-	-	-	-
S	NS	S	NS	NS
-	NS	NS	NS	S
NS	-	-	-	-
NS	-	-	-	-
NS	-	-	-	-
NS	-	-	-	-

* Doses of 40 mg/day, 80 mg/day, and 120 mg/day were administered as 20 mg BID, 40 mg BID, and 80 mg BID, respectively.
S=statistically significant ($P \leq .05$); NS=not significant; -=testing measure not used in study; NA=not applicable (not enough observations for repeated measures analysis).

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measure essentially estimates the treatment effects pooled across all patient visits and has a similar interpretation as an area under the curve analysis. Using this type of analysis, mean changes (ie, improvements) were significantly greater for duloxetine than placebo in five of the six measures in Study 1 (Figure 3) and for two of the six measures in Study 2 (Figure 4). When the VAS data were expressed as a percentage reduction in pain severity over the entire duration of the study, duloxetine-treated patients in Studies 1 and 2 (60 mg QD) demonstrated improvements in the range of 20.9% to 45.8% in the six measures, compared with placebo-treated patients who generally showed improvements in the range 5% to 20% (Figures 3 and 4).

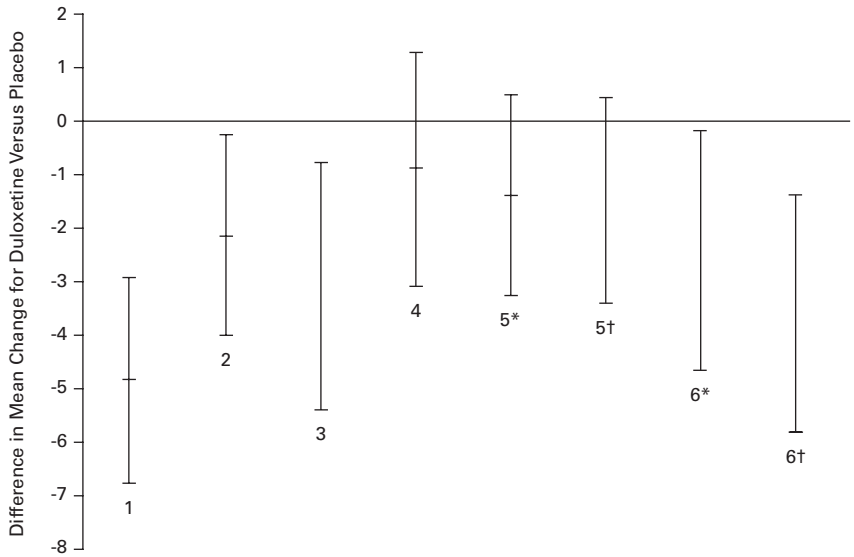
Efficacy: Subgroup Analysis

A subgroup analysis was performed on pooled efficacy data from three of the studies which demonstrated superiority over placebo on the HAMD-17 total score (Studies 1, 2, and 6). The results of this analysis

FIGURE 1

DIFFERENCE IN MEAN CHANGE IN HAMD-17 TOTAL SCORE FROM BASELINE TO LAST VISIT FOR DULOXETINE VERSUS PLACEBO

Labels on individual bars indicate study number. Error bars represent 95% confidence intervals. Data based on the six depression studies.



*=duloxetine 40 mg/day (administered as 20 mg BID);
†=duloxetine 80 mg/day (administered as 40 mg BID).

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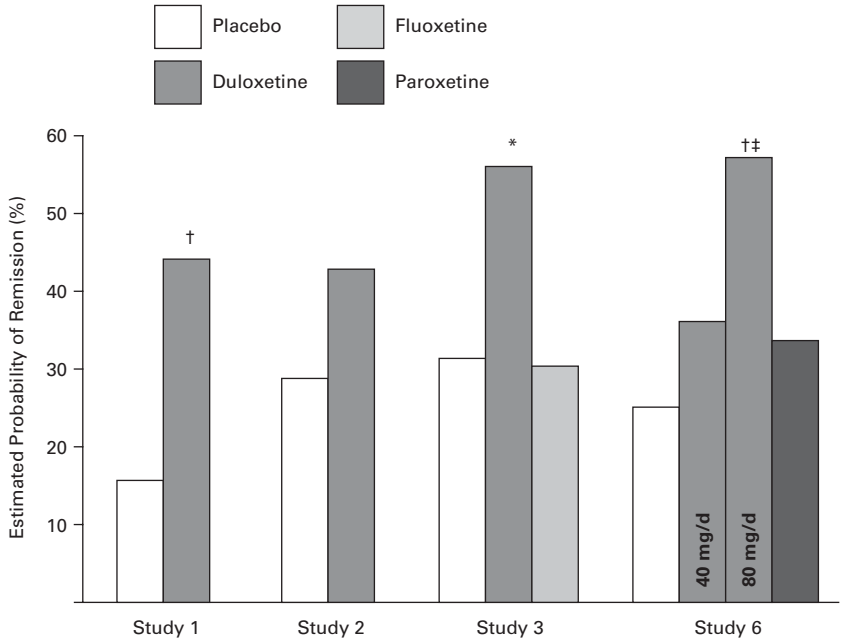
showed that the efficacy of duloxetine was similar regardless of age (<55 or ≥55), gender, or racial origin (Caucasian or other) based on non-significant treatment-by-subgroup interactions.

Efficacy: Effect-Size Analysis

For each studied dose regimen of duloxetine (40 mg/day, 60 mg QD, 80 mg/day, and titration to 120 mg/day), the effect size for change may be calculated as the difference in mean change between the placebo group and the duloxetine dose group (positive difference shows drug superiority) divided by the pooled sample standard deviation of the two treatment groups. Calculation of effect sizes for change in HAMD-17 total score, using pooled dose data, revealed that the 60 mg QD duloxetine dose had the largest effect size—the effect sizes for both duloxetine 60 mg QD and 80 mg/day exceeded 0.35. In the case of the estimated probability of response, effect sizes calculated from pooled

FIGURE 2

ESTIMATED PROBABILITIES OF REMISSION IN STUDIES SHOWING SUPERIORITY OVER PLACEBO ON THE PRIMARY EFFICACY MEASURE



* *P*<.05 versus placebo.
† *P*<.005 versus placebo.
‡ *P*<.05 versus paroxetine.

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dose data increased from 0.13 for duloxetine 40 mg/day to 0.37 for duloxetine 60 mg QD, with effect sizes for both duloxetine 60 mg QD and 80 mg/day being significantly greater than zero. Pooled remission probability data showed an effect-size increase from the lowest dose (duloxetine 40 mg/day) to the highest dose (duloxetine 120 mg/day). However, a pairwise comparison of increments in effect size between doses showed that the most notable gain in effect size was from duloxetine 40 mg/day to duloxetine 60 mg QD. Thus, the effect-size calculations indicate that a duloxetine dose of 60 mg QD represents the lowest dose with consistent, robust efficacy. In making these across-dose comparisons, however, it is important to note the design differences between trials (see Discussion section).

Safety: Adverse Events

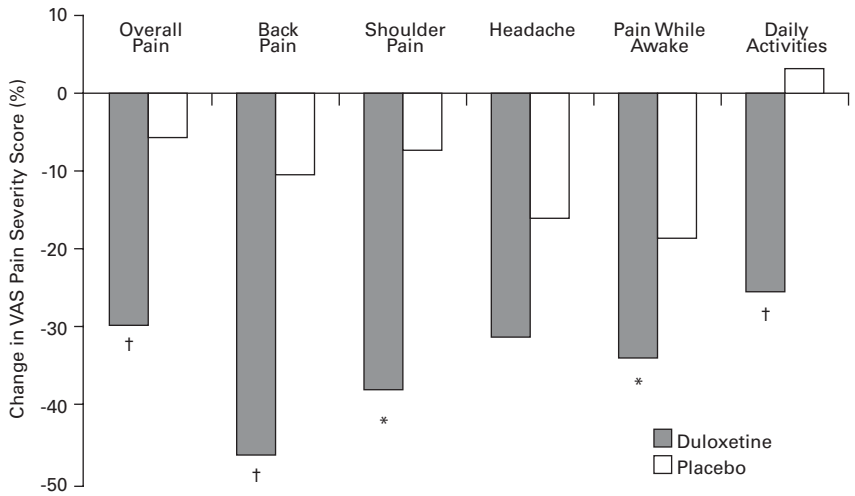
The incidence of discontinuation due to adverse events was significantly greater for duloxetine when compared with placebo (14.6% versus 5.0%, respectively; $P<.001$). However, in the active comparator-controlled MDD studies, the rates of discontinuation due to adverse events did not differ significantly between duloxetine and paroxetine (13.6% versus 10.2%; $P=.329$) or between duloxetine and fluoxetine (9.9% versus 5.7%, $P=.440$). The only adverse events for which the discontinuation rate in duloxetine-treated patients was significantly greater than the rate seen for placebo-treated patients were nausea (2.4% versus 0.3%; $P<.001$) and dizziness (1.1% versus 0.1%; $P=.019$). The only other event causing discontinuation in ≥1.0% of duloxetine-treated patients and with at least two times the placebo rate was somnolence (1.0% versus 0.3%; $P=.138$). Although statistical analyses between once- and twice-daily dosing groups were not performed due to confounding of dose and protocol, it is interesting to note that the incidence of discontinuations due to nausea, dizziness, and somnolence on the 60 mg QD dose were less than half the rate seen on any other dose. Differences between duloxetine (0.8%) and placebo (1.0%) in the incidence of serious adverse events (eg, those involving hospitalization or life-threatening experience) were not significant ($P=.793$), and no serious adverse event was reported with a frequency greater than 0.1%.

Treatment-emergent adverse events are summarized in Table 5. Adverse events for which the incidence for duloxetine was greater than 5.0%, and twice the rate of placebo, were nausea (21.8%), dry mouth (16.1%), fatigue (11.0%), dizziness (10.7%), constipation (10.6%), somnolence (7.8%), decreased appetite (6.5%), and increased sweating (5.4%).

Nausea was the most frequent treatment-emergent adverse event reported by duloxetine-treated patients. Approximately 70% of these cases were first reported within 2 days of initiating duloxetine dosing,

FIGURE 3

PERCENT MEAN CHANGE FROM BASELINE IN VAS MEASURES OF PAIN SEVERITY IN STUDY 1



* *P*<.05 versus placebo.
† *P*≤.005 versus placebo.
VAS=visual analog scales.

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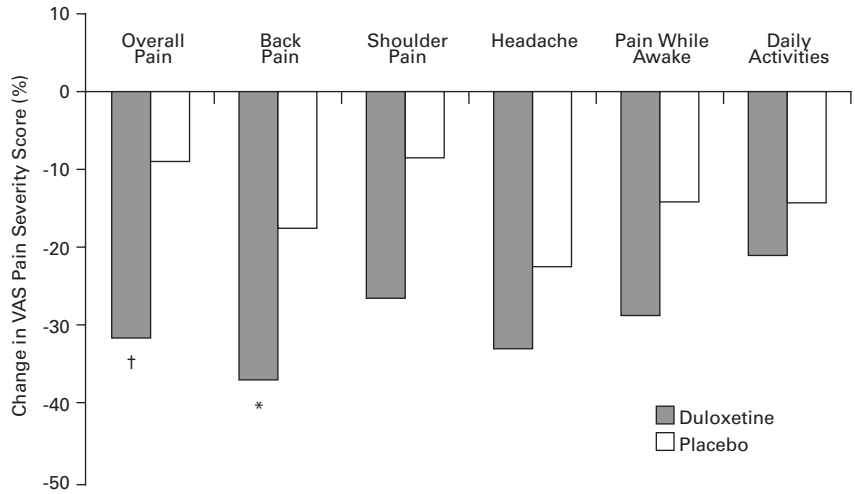
FIGURE 4

PERCENT MEAN CHANGE FROM BASELINE IN VAS MEASURES OF PAIN SEVERITY IN STUDY 2



* *P*<.05 versus placebo.
† *P*≤.005 versus placebo.
VAS=visual analog scales.

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while the median duration of nausea for duloxetine-treated patients was 5 days. Furthermore, in over 90% of all reported cases the nausea was rated as mild or moderate in severity. Given the early onset and typically rapid resolution, the prevalence of nausea declined rapidly over time. In studies where duloxetine was compared with fluoxetine (Studies 3 and 4) the incidence of nausea was nearly identical (duloxetine 17.1% versus fluoxetine 15.7%, *P*=.849), while in those studies where paroxetine was the active comparator (Studies 5 and 6) the incidence of nausea was again not significantly different across treatment groups (duloxetine 21.0% versus paroxetine 15.3%; *P*=.128).

This comparison was noteworthy in that patients treated with fluoxetine and paroxetine were administered 20 mg QD, which is at the lower end of their respective labeled dose ranges, whereas patients treated with duloxetine were administered doses that spanned a wide range (40–120 mg total daily dose). Although the incidence of nausea was somewhat higher for the 60 mg QD duloxetine dose (37.8%) than for the other studied doses, the discontinuation rate due to nausea at 60 mg QD (0.8%) was actually less than half of the observed rate for any other dose.

Safety: Cardiovascular Assessments

Mean changes in supine systolic and diastolic blood pressure for duloxetine-treated patients were approximately 1.5 mm Hg, and did not increase markedly by dose. The incidences of treatment-emergent elevated systolic and diastolic blood pressure at endpoint for duloxetine-treated patients compared with placebo-treated patients were 6.9% versus 3.3% (*P*=.003) for systolic pressure and 4.4% versus 2.3% (*P*=.027) for diastolic pressure, respectively. Differences between duloxetine and placebo treatment groups in the incidence of sustained (at least three consecutive visits) hypertension were not significant (sustained systolic blood pressure: duloxetine 0.5% versus placebo 0.2%, *P*=.395; sustained diastolic pressure: duloxetine 0.3% versus placebo 0.2%, *P*=1.00; either systolic or diastolic pressure: duloxetine 0.7% versus placebo 0.4%, *P*=.706). Duloxetine-treated patients exhibited a mean increase in supine heart rate of approximately 1.5 beats per minute (bpm), compared with a mean decrease of 0.5 bpm in heart rate in the placebo-treated group.

Duloxetine did not increase QTc intervals or other cardiac intervals and the incidence of abnormal increases in QTc (≥30 msec) were 4.2% and 5.3% for duloxetine- and placebo-treated patients, respectively.

Safety: Laboratory Values

Although statistically significant mean changes from baseline were seen for some laboratory analytes, including alkaline phosphatase, creatine

phosphokinase, alanine aminotransferase, and uric acid, these changes were well within the normal reference range[54] and thus not considered clinically relevant. No significant differences between duloxetine and placebo existed in the incidence of treatment-emergent abnormal laboratory values at endpoint.

Safety: Sexual Functioning

No significant differences between duloxetine and placebo groups were observed for mean change in ASEX total scores. The only significant difference on mean change in ASEX individual items was noted for the response to Question 4 ("How easily can you reach an orgasm?") where the mean change was greater for duloxetine-treated patients (0.33 versus –0.02 for duloxetine and placebo, respectively; *P*=.001). Analysis by gender indicated that the significant difference was due to a difference in the responses of male patients. For female patients, no significant differences were seen between the treatment groups for any of the individual questions.

The rate of occurrence of adverse events related to sexual function was generally low. Thus the rate of decreased libido was 3.1% among all duloxetine-treated patients compared with 0.7% for placebo (*P*<.001), while the incidence of loss of libido did not differ significantly from the placebo rate (0.2% versus 0.1% for duloxetine and placebo, respectively; *P*=1.00). Analyzed separately by gender, the rate of decreased libido among male patients receiving duloxetine was 7.7% (versus 2.1% for placebo, *P*=.011) while the rate in female MDD patients was 1.7% (versus 0% for placebo, *P*=.01). The incidence of anorgasmia was 3.7% in male and 2.3% in female patients treated with duloxetine (both *P*<.01

TABLE 5

TREATMENT-EMERGENT ADVERSE EVENTS* FROM ALL PLACEBO-CONTROLLED STUDIES

ADVERSE EVENT	PLACEBO (N=723)	DULOXETINE (N=1,032)	*P* VALUE
Nausea	50 (6.9%)	225 (21.8%)	<.001
Dry mouth	47 (6.5%)	166 (16.1%)	<.001
Fatigue	33 (4.6%)	114 (11.0%)	<.001
Insomnia	41 (5.7%)	113 (10.9%)	<.001
Dizziness	38 (5.3%)	110 (10.7%)	<.001
Constipation	27 (3.7%)	109 (10.6%)	<.001
Diarrhea	45 (6.2%)	92 (8.9%)	.046
Somnolence	21 (2.9%)	80 (7.8%)	<.001
Decreased appetite	15 (2.1%)	67 (6.5%)	<.001
Increased sweating	11 (1.5%)	56 (5.4%)	<.001

* Adverse events reported by 5.0% or more of duloxetine-treated patients.

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versus placebo), while the rates of sexual dysfunction (not otherwise specified) for duloxetine did not differ significantly from placebo among either male or female patients.

Safety: Discontinuation Emergent Events

Treatment-emergent discontinuation symptoms that were most frequently reported (≥2%) upon abrupt cessation of duloxetine therapy were dizziness (9.9%), nausea (4.7%), headache (4.3%), paraesthesia (2.4%), and insomnia (2.0%).

Safety: Other Findings

Duloxetine had a relatively small effect upon body weight during the studies of 8–12-weeks' duration. Duloxetine-treated patients exhibited a mean decrease of 0.54 kg (1.18 lbs) in weight, significantly different (P<.001) from placebo-treated patients, who gained an average of 0.25 kg (0.56 lbs).

Mania and suicide are major areas of interest in patients undergoing antidepressant treatment for MDD. Although patients with bipolar disorder were excluded from all of the duloxetine studies, the number of duloxetine-treated patients who reported treatment-emergent mania was zero, compared with one case (0.1%) in the placebo-treated group. Furthermore, no patients attempted suicide. The occurrence rates of suicidal or self-injurious ideation were 0.2% and 0.1% for duloxetine-treated patients compared with 0.3% and 0% for placebo-treated patients, respectively (P=1.00 for both events). On HAMD-17 Item 3 (suicide), the duloxetine-treated groups had a significantly greater mean reduction (advantage) over the placebo groups in four of the six trials. Furthermore, no cases of suicide attempt, suicidal ideation, or self-injurious ideation were reported in the fluoxetine- or paroxetine-controlled databases. Analyses of HAMD-17 Item 3 revealed that both duloxetine-treated groups (40 mg/day and 80 mg/day) had a significant advantage over the paroxetine-treated group in Study 6. Paroxetine (20 mg QD) did not differ significantly from placebo on HAMD-17 Item 3 in this study (P=.508).

Discussion

Definitive evidence for the efficacy of duloxetine in the treatment of MDD (duloxetine was significantly superior to placebo on the primary efficacy measure) was observed in four of the six studies. In addition, duloxetine within the range 40–120 mg/day exhibited no significant safety risks and good tolerability, as indicated by discontinuation rates similar to fluoxetine and paroxetine in the active comparator-controlled studies, and also comparable to reported SSRI discontinuation rates.[55]

A distinction exists between the presentation of safety data and efficacy data within this report. While all of the safety analyses were

performed on a pooled patient database drawn from seven individual duloxetine studies, efficacy analyses were carried out primarily on individual studies (the only analyses for which efficacy data were pooled by dose are the effect-size calculations described above). Each study was designed a priori to detect an effect with a given power, and thus pooling of efficacy data could potentially result in inappropriate magnification of these effects. Furthermore, specific design differences existed between protocols. Thus the protocol employed for Studies 1 and 2 had a 9-week exposure to duloxetine 60 mg QD, while Studies 3, 4, 5, and 6 employed a duloxetine treatment period of 8 weeks. In addition, Studies 5 and 6 employed a duloxetine dosage of 20 mg or 40 mg twice-daily, while in Studies 3 and 4 duloxetine was administered in a forced-titration regimen up to 120 mg/day. For these reasons, detailed statistical analyses of pooled efficacy data across different doses were not performed.

In addition to demonstrating significant superiority on the HAMD-17 total score in four of the six studies, duloxetine also demonstrated significant superiority to placebo on a number of secondary measures across five of the trials. It should be noted that Khan and colleagues[56] recently reported that less than half of the Phase II and III trials of effective antidepressant medications produce positive results. Keeping their discussion in mind, duloxetine does indeed exhibit evidence of a robust efficacy profile.

Relief of the severity of core symptoms of MDD, as measured by dimensional rating scales such as the HAMD-17, is a critical foundation for the demonstration of efficacy in the treatment of this condition. However, MDD is a complex illness defined by multiple domains of emotional symptom distress along with functional consequences, such as impairment of daily activities and reduction in overall quality of life. In the clinical development of duloxetine, a variety of symptom domains were assessed in several ways. Several subscales of the HAMD-17 were employed to reflect more specific areas of symptomatic distress (core symptoms, anxiety/somatization, sleep, retardation).[39] Duloxetine-treated patients exhibited statistically significant improvement in many of these subscale measures (Table 4), especially when receiving doses of 60 mg/day or higher.

Categorical improvement in a patient's illness is typically described using changes in HAMD-17 scores to classify patients into meaningful patterns of clinical change, including response (defined as a 50% reduction from baseline to endpoint score) and remission (defined as an endpoint score ≤7). Remission is an especially important goal in antidepressant therapy, and thus the probabilities of remission of 56.1%, 57.2%, 44.2%, and 43.0% observed for duloxetine-treated patients in Studies 1, 2, 3, and 6, respectively, were most noteworthy. In Study 1 the

duloxetine remission probability was almost three times that observed for placebo (44.2% versus 15.7%, respectively), while in Study 6 the probability of remission with duloxetine (80 mg/day) was 1.68 times greater than that observed for the paroxetine-treated (20 mg QD) group. These results are consistent with recently published studies suggesting that higher probabilities of remission are achieved with dual-reuptake inhibitor antidepressants than with SSRI medications,[10] especially when SSRI doses are at the lower end of the dose range.

It is becoming increasingly recognized that the emotional symptoms of MDD are only a part of the complex phenomenology of this illness. Among unexplained symptoms, those characterized as painful bodily distress are usually the most common.[20] This group of symptoms can often include diffuse musculoskeletal pain, abdominal pain, headaches, and chest pain, among others.

In addition to their role in mood disorders, 5-HT and NE also act as inhibitory neurotransmitters in descending pain pathways.[25-27] Thus it may be anticipated that an inhibitor of both 5-HT and NE reuptake would normalize the endogenous tone of the pain pathways,[57] and may demonstrate efficacy in the alleviation of painful physical symptoms. Duloxetine is a dual 5-HT/NE reuptake inhibitor, and it was for this reason that steps were taken to gather preliminary data on the reduction in severity of physical symptoms of depression. Patients in the studies described herein were not screened specifically for a predefined severity threshold in symptoms, and these studies were not specifically powered to assess pain outcomes. Studies are in progress where patients are specifically screened and studies adequately powered for efficacy in such outcomes. However, the current results in which duloxetine demonstrated significant improvement in pain severity in patients with low baseline VAS pain scores (Figures 3 and 4) suggests that the dual reuptake inhibition of duloxetine yields improvement on both the core emotional symptoms and physical symptoms associated with depression.

Duloxetine has been shown to be safe and well tolerated in a dose range of 40–120 mg/day. Indeed, the overall discontinuation rate due to adverse events for duloxetine-treated patients over the entire dosing range was only 14.6%. This compares favorably with discontinuation rates for SSRIs (14.9%) and TCAs (19.0%) which were derived from a meta-analysis,[55] and also to the discontinuation rate due to adverse events reported for venlafaxine.[58] Furthermore, discontinuation rates for duloxetine-treated patients were not significantly different from those receiving fluoxetine or paroxetine in the active comparator-controlled arms of Studies 3–6.

The overall incidence of adverse events for duloxetine was similar to that of currently available medications used for the treatment of MDD. The range of adverse events reported was consistent with the known

pharmacology of the molecule, namely its principal action on both serotonergic and noradrenergic neurotransmission. More specifically, adverse events included nausea, dry mouth, fatigue, insomnia, and constipation. Nausea was the most frequently observed treatment-emergent adverse event, occurring at an overall rate of 21.8% within the duloxetine dosing range of 40–120 mg/day studied here. This compares favorably to nausea rates of 21% to 30% observed for sertraline, 15% to 36% for paroxetine, and 31% to 43% for venlafaxine extended release.[59]

Because spontaneous reporting of sexual dysfunction as an adverse event may often underestimate the magnitude of this outcome, the ASEX was specifically included in four of the trials as a solicited measure of sexual function. Though the rates of spontaneous adverse events indicating possible treatment-emergent sexual dysfunction were greater for duloxetine-treated patients than for placebo they were, in general, low. For example, the rate of decreased libido was 3.1% among duloxetine-treated patients compared with 0.7% for placebo.

Duloxetine did not have any significant effect upon the incidence of new cases of "sustained" hypertension, nor did it produce any clinically significant differences in other cardiovascular measures. Thus the data show that duloxetine had no effect on prolongation of the QT interval or any apparent clinically meaningful difference from placebo on hemodynamic indices. In line with its NE enhancement function duloxetine produced a statistically significant, but clinically trivial, increase in heart rate of approximately two bpm compared to placebo. The magnitude of this cardiovascular effect was, however, significantly less marked than that observed for the norepinephrine reuptake inhibitor, desipramine.[60] Further studies will be required to fully understand the detailed mechanism underlying these cardiovascular effects.

In addition to providing data concerning the overall safety and efficacy of duloxetine, the six depression studies described here were also analyzed to evaluate an optimal dosing regimen for duloxetine, based upon efficacy, tolerability, and potential patient compliance. Early studies of duloxetine focused upon twice-daily dosing, but considering the increased patient compliance associated with simpler dosing regimens[61] it was important to determine whether once-daily dosing would prove to be an effective strategy.[62] Although duloxetine has a mean plasma half-life of ~12 hours,[63] medications that penetrate the blood-brain barrier may have much longer half-lives in the central nervous system than in plasma[64] and therefore maintain therapeutic central nervous system levels after plasma levels have decreased.[65] Therefore, Studies 1 and 2 were specifically designed to investigate the efficacy of duloxetine administered in a once-daily dose of 60 mg.

The tolerability of duloxetine across its dosing range was assessed by comparing discontinuation rates between the various doses. Statistical tests between dose groups were performed only in Studies 5 and 6, in which duloxetine 40 mg/day and 80 mg/day doses were administered under the same protocol and could therefore be reliably compared. Differences between the group administered 40 mg/day and the group given 80 mg/day in the overall rate of discontinuation due to adverse events were not significant in these studies (11.9% versus 15.4%, respectively; P=.355), and there were also no significant differences in the incidence of discontinuation due to any given adverse event between the dose groups. A side-by-side comparison of discontinuation rates due to adverse events across all duloxetine doses studied in the seven trials yielded values of 12.1% at 40 mg/day, 13.1% at 60 mg/day, 15.2% at 80 mg/day, and 9.9% when titrated from 40 mg/day to 120 mg/day. These results suggested that duloxetine was well tolerated at all studied doses (40–120 mg/day), and indicated that the relative efficacy of differing doses should be the primary method used to determine an optimal dosing regimen.

Further evidence for the superior efficacy of duloxetine doses at 60 mg/day and above was provided by an analysis of secondary efficacy measures. In Studies 5 and 6, a total of 13 secondary efficacy measures were assessed in each trial: five HAMD-17 subfactors, HAMD-17 Item 1, probability of response, probability of remission, Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Anxiety (HAM-A), CGI-S, PGI-I, and Quality of Life in Depression Scale (QLDS). At a duloxetine dose of 40 mg/day, 4 of the 26 secondary measure analyses across the two studies demonstrated superiority over placebo, while at 80 mg/day a total of 15 of the 26 secondary measure analyses achieved significance (Table 4). This comparison may be further extended to Studies 1 and 2 in which 10, rather than 13, secondary measures were analyzed in each trial (MADRS and HAM-A were not collected; QLDS was not analyzed). Across these two trials, duloxetine at 60 mg QD demonstrated significant superiority over placebo in 16 out of the 20 secondary measure analyses (Table 4). These comparisons reinforce the results of the effect-size comparisons, and demonstrate that a robust efficacy profile is associated with a duloxetine dose of 60 mg QD.

Duloxetine has been examined in clinical studies of patients with MDD in doses up to 120 mg/day. Based upon a consideration that once-daily dosing is advantageous, especially with regard to ease of use and associated patient compliance, duloxetine 60 mg QD is found to represent the lowest dose with consistent efficacy while 60 mg QD also has acceptable tolerability and safety. The recommended initial starting dose in the treatment of MDD should be 60 mg once daily. Dose adjustments to a

maximum total daily dose of 120 mg/day, if clinically indicated, appear to be safe based upon assessment of the results of these controlled trials.

Conclusion

The effectiveness of duloxetine in treating the emotional and physical (painful and somatic) symptoms of depression has been established in four randomized, double-blind, placebo-controlled studies. In all four, duloxetine had significantly greater mean changes compared with placebo on the primary outcome measure of the HAMD-17 total score. Estimated probabilities of remission (HAMD-17 total score ≤7) ranged from 43% to 57%. Significant differences from placebo were detected as early as week 1 on measures of the core emotional symptoms of depression (core factor and Maier subscales of the HAMD-17), painful physical symptoms (VAS scales for pain), and on global wellness (CGI-S).

Thus, duloxetine has demonstrated efficacy on both the emotional and physical symptoms associated with MDD. This combined effect may be responsible for a greater probability of remission than that generally seen with SSRIs. However, additional studies designed specifically to address these effects will be required to further assess the efficacy of duloxetine in the resolution of physical symptoms associated with depression, the efficacy of duloxetine in painful conditions independent of depression, and to attempt to understand the extent to which emotional and physical manifestations of this condition are interrelated.

The results presented here support the view that dual 5-HT/NE reuptake inhibitors may be particularly effective for helping patients achieve full symptom resolution.[10-13] Duloxetine's mechanism of action as a potent dual 5-HT/NE reuptake inhibitor is thought to underlie its demonstrated efficacy in treating traditional symptoms of depression as well as its emerging efficacy in the treatment of physical symptoms. In these studies, duloxetine was safely administered and well tolerated at doses up to 120 mg/day, and appears to have a similar safety profile to available SSRIs. Based on the safety data, and considering the improved patient compliance associated with once-daily dosing, the optimal recommended starting dose is 60 mg per day. ✤

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