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REVIEW

FULL TEXT ARTICLE

Efficacy and safety of duloxetine 60 mg once daily in major depressive disorder: a review with expert commentary

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Abstract

Objective: Major depressive disorder (MDD) is a significant public health concern and challenges health care providers to intervene with appropriate treatment. This article provides an overview of efficacy and safety information for duloxetine 60 mg/day in the treatment of MDD, including its effect on painful physical symptoms (PPS).

Design: A literature search was conducted for articles and pooled analyses reporting information regarding the use of duloxetine 60 mg/day in placebo-controlled trials.

Setting: Placebo-controlled, active-comparator, short- and long-term studies were reviewed.

Participants: Adult (≥18 years) patients with MDD.

Measurements: Effect sizes for continuous outcome (change from baseline to endpoint) and categorical outcome (response and remission rates) were calculated using the primary measures of 17-item Hamilton Rating Scale for Depression (HAMD-17) or Montgomery–Åsberg Depression Rating Scale (MADRS) total score. The Brief Pain Inventory and Visual Analogue Scales were used to assess improvements in PPS. Glass estimation method was used to calculate effect sizes, and numbers needed to treat (NNT) were calculated based on HAMD-17 and MADRS total scores for remission and response rates. Safety data were examined via the incidence of treatment-emergent adverse events and by mean changes in vital-sign measures.

Results: Treatment with duloxetine was associated with small-to-moderate effect sizes in the range of 0.12 to 0.72 for response rate and 0.07 to 0.65 for remission rate. NNTs were in the range of 3 to 16 for response and 3 to 29 for remission. Statistically significant improvements ($p \leq 0.05$) were observed in duloxetine-treated patients compared to placebo-treated patients in PPS and quality of life. The safety profile of the 60-mg dose was consistent with duloxetine labeling, with the most commonly observed significant adverse events being nausea, dry mouth, diarrhea, dizziness, constipation, fatigue, and decreased appetite.

Conclusion: These results reinforce the efficacy and tolerability of duloxetine 60 mg/day as an effective short- and long-term treatment for adults with MDD. The evidence of the independent analgesic effect of duloxetine 60 mg/day supports its use as a treatment for patients with PPS associated with depression. This review is limited by the fact that it included randomized clinical trials with different study designs. Furthermore, data from randomized controlled trials may not generalize well to real clinical practice.

Keywords: duloxetine, major depressive disorder, painful physical symptoms, quality of life, effect size, safety and tolerability

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Introduction

Major depressive disorder (MDD) is a disabling condition, which is often underrecognized and undertreated. Often a chronic condition, MDD is associated with a reduction in quality of life, functional impairment, poor physical health, increased mortality, and increased use of health care resources [1–4]. The deleterious impact of MDD worldwide is disconcerting; in 2004 it was the third leading cause of disease burden and an important reason for disability in developed countries. By 2020, MDD could become an even greater cause of disease burden, predicted to be second only to cardiovascular diseases [4,5]. About 121 million people worldwide are affected by MDD [5]. In the United States, the 12-month prevalence rate has been estimated at 6.7% of the adult population, and 30.4% of these patients have severe depression [6]. In Europe, the prevalence of MDD varies among countries and between urban and rural areas, but in general, it is estimated that 9% and 17% of European men and women, respectively, are affected by MDD [7].

Somatic manifestations of MDD often accompany emotional symptoms and are not infrequently the primary complaint of patients presenting to their health care provider. For example, pain is one of the main complaints of patients who seek medical care at primary care centers and are eventually diagnosed with MDD [8]. Although the diagnosis of MDD is based on a number of core symptoms, painful physical symptoms (PPS) are increasingly recognized as frequently associated symptoms that have clinical relevance for patient outcomes [9,10]. In a naturalistic study of 573 outpatients with MDD, pain was reported by more than two-thirds of depressed patients at baseline, with the severity of pain rated as mild in 25% of patients, moderate in 30%, and severe in 14% [11]. PPS, when added to core emotional symptoms, increase the illness burden in patients, and patients who have PPS associated with their MDD have been found to have worse treatment outcomes, impaired functioning, and a higher risk of treatment resistance and relapse [12,13]. Other negative consequences of PPS in patients with MDD are a lower likelihood of remission, increased treatment costs, decreased productivity, and poor quality of life [9,10,14–16].

MDD has been shown to be frequently associated with other chronic medical and psychiatric conditions, such as chronic insomnia, eating disorders, cancer, arthritis, obesity, and cardiovascular disease [17,18]. The challenge that MDD presents to health care providers is clear, as is the need to intervene with appropriate treatment.

Background

Duloxetine hydrochloride, a serotonin-norepinephrine reuptake inhibitor (SNRI), was approved by the United States Food and Drug Administration (FDA) for the treatment of MDD in 2004, supported by four short-term and one maintenance trial in the adult population. The subsequent approval by the Committee for Medicinal Products for Human Use (CHMP) in Europe for the treatment of MDD was based on seven Phase III trials in the adult population, which have been published in several articles [19–23]. Duloxetine inhibits the neuronal uptake of serotonin and norepinephrine, with negligible affinity for other neuronal receptors, and this dual inhibition mechanism is believed to underlie its therapeutic effects [24–28]. The pharmacokinetic characteristics of duloxetine include a plasma elimination half-life of 12.5 hours, extensive hepatic metabolism by the P450 enzymes CYP1A2 and CYP2D6, a delay to reach maximum concentration from 6 to 10 hours when taken with food, and moderate inhibition of CYP2D6 [27,29–32].

Several preclinical studies that evaluated the effect of duloxetine on animal models of depression and pain suggested the potential usefulness of duloxetine for the treatment of MDD, anxiety, and diabetic peripheral neuropathic pain [33–39]. Subsequent clinical trials led to the approval of duloxetine for MDD, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain in a number of countries [38,39]. In addition, duloxetine was also approved for the treatment of stress urinary incontinence in Europe [38].

In the literature, a number of studies report the efficacy, tolerability, and safety outcomes of duloxetine treatment associated with different dosing regimens, including both fixed and flexible titration regimens as well as different dose ranges and indications [40–42]. For MDD, a previous review summarized the available evidence for the most commonly prescribed dose of duloxetine, 60 mg once daily (QD), in the treatment of MDD from short- and long-term studies [43]. The purpose of the present review is to update the efficacy, tolerability, and safety data for the fixed 60-mg QD dose to include outcomes from all placebo-controlled trials as of June 15, 2011. This present review is based on a significantly expanded duloxetine database that includes ten short-term acute therapy studies (one of which included only Japanese patients), two long-term studies, comparator studies, and post hoc analyses of special populations [44].

Analysis methods for primary and secondary efficacy measures

In previously published analyses of the efficacy of duloxetine, methods for handling missing data have been either analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation or mixed-model repeated measure (MMRM) analysis; however, MMRM has become the preferred method as it is less likely to overestimate efficacy [45]. Thus, for the purposes of this review, the authors will note the method of analysis to allow for appropriate interpretation of the data. When possible, the published MMRM results will be presented, but for some studies that were undertaken earlier in the development program, the published findings may have been undertaken using LOCF methods. In the MMRM analyses, the change from baseline to post-baseline visit in each primary efficacy measure was analyzed based on the restricted maximum likelihood (REML) method and used all continuous, longitudinal observations from each post-baseline visit. The method used for pain outcomes was also the MMRM analysis. An unstructured covariance structure was used to model the within-patient errors. Kenward–Rogers correction was used to estimate denominator degrees of freedom [46]. In the Japanese study, the change from baseline to endpoint based on LOCF was analyzed by ANCOVA because of the study design.

In published studies, the categorical outcomes for comparing response and remission rates were based on either LOCF or categorical MMRM. On the basis of recent work by Frank et al., a marginal model with pseudo-likelihood approach implemented using SAS PROC GLIMMIX, thereafter referred to as a categorical MMRM approach, was considered to be the best approach for analyzing the incomplete longitudinal binary data in the clinical trial setting [47]. In this review, therefore, the response and remission rates are presented using the categorical MMRM method where possible; for some post hoc analyses and for those studies with special populations, however, MMRM could not be utilized because of variability in the study schedules. Response was defined as at least 50% improvement in total score on the 17-item Hamilton Depression Rating Scale (HAMD-17) or Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to endpoint, while remission was defined as an endpoint score ≤7 on the HAMD-17 or ≤12 on the MADRS.

Methods for calculation of effect size in MDD studies

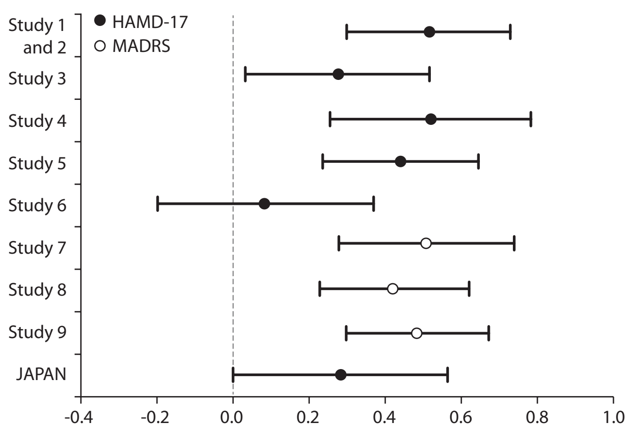
For this review paper, additional analyses for effect size were undertaken to provide an overall summary of the published literature. For these analyses, MMRM methodology was used for determining the effect size. For change in HAMD-17 total score or MADRS total score from baseline to last visit, the least-squares (LS) mean and standard deviation (SD) from primary MMRM analyses were used to calculate effect size based on Glass estimation [48]. Effect size, that is, Cohen's d, for each individual study was calculated as the difference in mean (LS mean or raw mean) change between the duloxetine and the placebo group divided by the SD. For the Japanese study, effect size was calculated using LS mean and SD from the ANCOVA method with LOCF.

For the categorical outcome of proportions (response rate and remission rate estimated using categorical MMRM analysis, or LOCF method for the Japanese study), the variance stabilizing transformation was applied to create the effect size [49,50]. In summary, for the response rate and remission rate from categorical MMRM method, the effect size was calculated based on estimated proportion and effective sample size at last visit from categorical MMRM analysis. The effect size calculations for each study are presented in Figure 1. The effect size for estimated response and remission rates used HAMD-17 total score in all studies except for Studies 7, 8, and 9, where the MADRS total score was used. The data are presented graphically in Figures 2 and 4 for HAMD-17 total score and in Figures 3 and 5 for MADRS total score.

Methods for calculation of NNT for MDD studies

For response and remission rates at endpoint based on the categorical MMRM (CAT_MMRM) method for each individual study, numbers needed to treat (NNTs) were estimated as the inverse of the difference of estimated probability at endpoint from CAT_MMRM model. Then the delta method was used to calculate the 95% confidence interval (CI) of the NNT [51]. For the Japanese study, NNTs were simply calculated as the inverse of the risk difference.

Figure 1. Effect size based on mean change in MMRM analysis at last visit using HAMD-17 total score for Studies 1 to 6 (closed circles). MADRS was utilized for Studies 7 to 9 (open circles). For the Japanese study, effect size for the 60-mg dose was based on change from baseline to 6 weeks (LOCF), which was the secondary efficacy analysis of the study.



Abbreviations
HAMD-17, 17-item Hamilton Rating Scale for Depression; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-model repeated measure.
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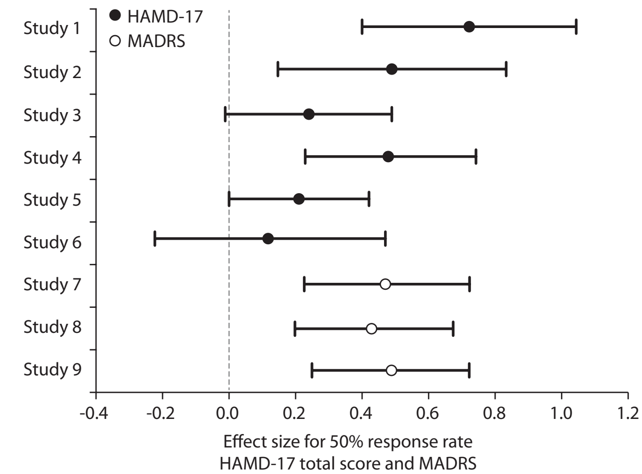
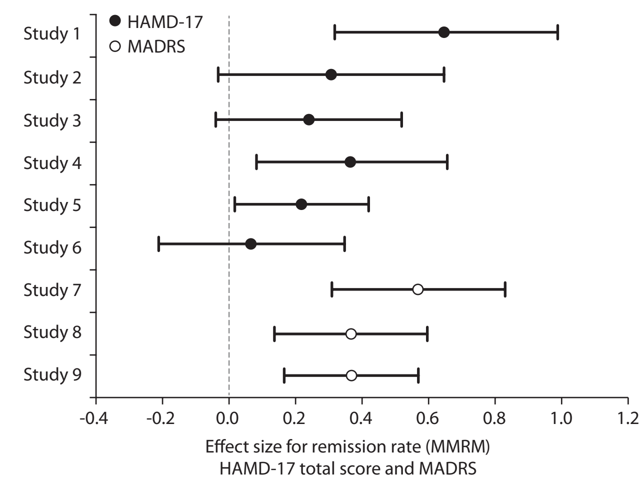
Figure 2. Effect size for 50% response rate based on CAT_MMRM analysis at last visit using HAMD-17 total score, Studies 1 to 6 (closed circles). MADRS total score was used for Studies 7 to 9 (open circles).



Abbreviations
CAT_MMRM, categorical MMRM; HAMD-17, 17-item Hamilton Rating Scale for Depression; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-model repeated measure.
doi: 10.7573/dic.212245.f002

Figure 3. Effect size for remission rate based on CAT_MMRM analysis at last visit using HAMD-17 total score, Studies 1 to 6 (closed circles). MADRS total score ≤12 was used for Studies 7 to 9 (open circles).



Abbreviations
CAT_MMRM, categorical MMRM; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-model repeated measure.
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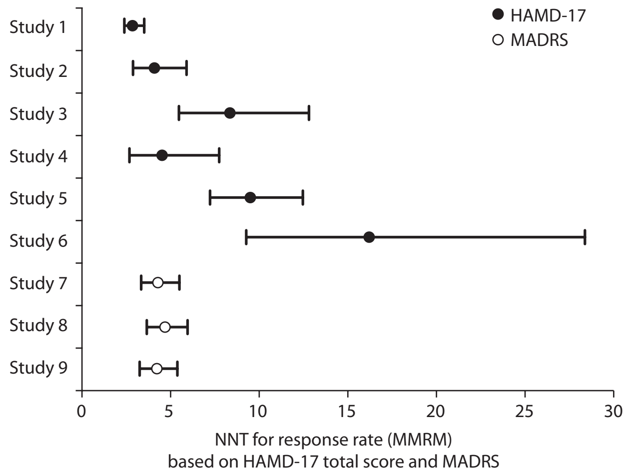
Figure 4. NNT with 95% CI for response rates based on CAT_MMRM using HAMD-17 total score for Studies 1 to 6 (closed circles). MADRS total score was used for Studies 7 to 9 (open circles).



Abbreviations
CAT_MMRM, categorical MMRM; CI, confidence interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-model repeated measure; NNT, numbers needed to treat.
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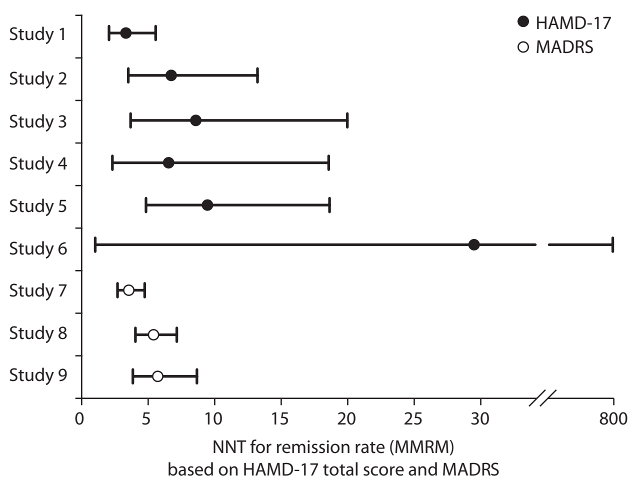
Figure 5. NNTs for remission rate based on CAT_MMRM using HAMD-17 total score for Studies 1 to 6 (closed circles). MADRS total score ≤12 was used for Studies 7 to 9 (open circles).



Abbreviations
CAT_MMRM, categorical MMRM; HAMD-17, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-model repeated measure; NNT, numbers needed to treat.
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Description of studies, patients, and efficacy measures

Refer to Table 1 for overall description of short-term studies (non-pain enriched and pain-enriched), long-term studies, and analyses from special populations. In pain-enriched studies (Studies 6–9), a defined level of pain severity was included as an entry criterion for the studies along with a diagnosis of MDD (see page 7 for additional information).

Short-term acute therapy studies

The short-term studies analyzed were nine 8- to 9-week and one 12-week randomized, double-blind, placebo-controlled studies in patients with MDD that included a duloxetine 60-mg QD treatment arm (Table 1) [21,22,52–58]. All of these studies enrolled adults (≥18 years old) who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, revised (DSM-IV-TR) criteria for MDD [59]. Although the Japanese study was also a short-term study, it will be described in the "Efficacy of duloxetine for the treatment of MDD in special populations" section.

The efficacy of duloxetine 60 mg QD in the treatment of MDD was assessed either by changes in the HAMD-17 or MADRS total score, which were either the study's primary or secondary efficacy measure [60,61]. For study entry, the specific threshold for illness severity (HAMD-17 or MADRS total score) varied for inclusion, but the criteria were sufficient to ensure that patients had at least mild or moderate illness severity. Also, a patient's illness severity was required to meet a score of 4 or greater (moderate severity) on the Clinical Global Impression Severity rating (CGI-S) at screening and baseline visits [62]. Studies 5a and 5b were identical double-blind, placebo-controlled trials that were conducted under the same protocol [58]. The primary outcome for these two studies was mean improvement on the HAMD Work/Activities item 7 at treatment Week 8. All secondary efficacy measures in these two studies were assessed at Week 12 except for the HAMD Maier subscale, which was assessed at Week 8.

Also included within the review of acute studies were four studies (Studies 6–9) that required patients to have a specified minimum severity of PPS at baseline as measured by the Brief Pain Inventory (BPI) [63]. In these studies, patients were required to have a BPI average pain score 2 or 3 at entry as well as at least mild or moderate depressive illness severity as evidenced by a HAMD-17 score of ≥15 or a MADRS score of ≥20 and a CGI-S score of ≥4 at study entry [52,53,55,56].

Other efficacy measures from the acute studies included Visual Analogue Scales (VAS) for pain [64] and the Patient Global Impression-Improvement (PGI-I) scale [62].

Long-term treatment studies

One study included in this analysis specifically examined the efficacy of duloxetine 60 mg QD during long-term treatment, consistent with current recommendations for continuation treatment of 4 to 9 months for the prevention of relapses [65–67]. Perahia et al. conducted a relapse prevention study that demonstrated the efficacy of duloxetine 60 mg QD for continuation treatment of MDD [65]. After 12 weeks of open-label treatment with duloxetine 60 mg QD, responders were randomly assigned to receive duloxetine 60 mg or placebo for an additional 26 weeks; the primary efficacy measure was the time to relapse (TTR). Fava et al. subsequently examined the efficacy of reinstating duloxetine 60 mg QD in patients randomized to placebo in the above study who experienced a relapse of MDD [68].

Table 1. Studies and analyses of duloxetine 60 mg QD in the treatment of MDD.

Reference	Study No./ description	No. of patients	Duration (wk)	Regimens	Primary outcome measure	Secondary outcome measure	Results on HAMD-17 total score/MADRS total score
Acute Studies: Non-pain enriched							
Detke et al. [21]	1	245	9	DLX 60 mg QD vs PBO	HAMD-17 total score	HAMD-17 subscales, CGI-S, PGI-I, VAS, QLDS	DLX>PBO
Detke et al. [22]	2	267	9	DLX 60 mg QD vs PBO	HAMD-17 total score	HAMD-17 subscales, CGI-S, PGI-I, VAS, QLDS	DLX>PBO
Nierenberg et al. [54]	3	410*	8 + 24-wk extension	DLX 60 mg QD vs escitalopram 10 mg QD vs PBO	Onset of antidepressant efficacy	HAMD-17 total score, HAMD-17 subscales, CGI-S, PGI-I	DLX>PBO
Raskin et al. [57]	4**	311	8	DLX 60 mg QD vs PBO	Composite cognitive score	Geriatric Depression Scale, HAMD-17, VAS, CGI-S	DLX>PBO
Oakes et al. [58]	5[a]	384	12	DLX 60 mg QD vs PBO	HAMD Work/ Activities	HAMD-17, SDS, SASS	Not significant
Oakes et al. [58]	5[b]	392	12	DLX 60 mg QD vs PBO	HAMD Work/ Activities	HAMD-17, SDS, SASS	DLX>PBO
Acute Studies: Pain enriched[b]							
Brannan et al. [52]	6	282	9	DLX 60 mg QD vs PBO	BPI average pain	HAMD-17 total score, CGI-S, PGI-I, VAS	Not significant
Brecht et al. [53]	7	327	8	DLX 60 mg QD vs PBO	BPI-SF	CGI-S, PGI-I, MADRS	DLX>PBO
Gaynor et al. [55]	8	528	8	DLX 60 mg QD vs PBO	BPI average pain and MADRS	SDS, PGI-I, C-SSRS	DLX>PBO
Gaynor et al. [56]	9	527	8	DLX 60 mg QD vs PBO	BPI average pain and MADRS	SDS, PGI-I, C-SSRS	DLX>PBO
Long-term Studies							
Perahia et al. [65]	–	278	26	DLX 60 mg QD vs PBO	Time to relapse	HAMD-17, CGI-S, PGI-I, SQ-SS, VAS, QLDS, SDS	DLX>PBO
Fava et al. [68]	–	278	26	DLX 60 mg QD vs PBO	HAMD-17	CGI-S, PGI-I, VAS, SQ-SS, QLDS, SDS	DLX>PBO
Kelin et al.*** [75]	–	124	52	DLX 60 mg QD vs PBO	Time to depressive recurrence	HAMD-17, CGI-S, VAS, SDS	DLX>PBO
Special Populations							
Dunner et al. [70]	Patients with anxiety	512	9	DLX 60 mg QD vs PBO	HAMD anxiety/ somatization item	–	DLX>PBO
Perahia et al. [71]	Patients with milder MDD[c]	159	9	DLX 60 mg QD vs PBO	HAMD-17	CGI-S, PGI-I, SSI	DLX>PBO
Higuchi et al. [44]	Japanese patients	219	6	DLX 60 mg QD vs PBO	HAMD-17	VAS, CGI-I	DLX>PBO
Burt et al. [72]	Females	117	9	DLX 60 mg QD vs PBO	HAMD-17 total score	HAMD-17 subscales, CGI-S, PGI-I, VAS, QLDS	DLX>PBO

*The number of patients taken into account was made up of those in the duloxetine and placebo groups only.
**These are considered part of the special population studies also.
***The results reported here are from the 60-mg only data in the post hoc analysis. The primary study by Perahia et al. reported 60- to 120-mg data [68].
[a]This study by Myers et al. (Trial Registration NCT00536471) reported the primary outcomes from two trials conducted under the same protocol.
[b]These are also considered part of the special population studies.
[c]Milder MDD is defined as patients with HAMD-17 of 15–18.

Abbreviations

DLX, duloxetine; PBO, placebo; QD, once daily; HAMD-17, 17-item Hamilton Rating Scale for Depression; CGI-S, Clinical Global Impression-Severity; PGI-I, Patient Global Impression-Improvement; VAS, Visual Analog Scale; QLDS, Quality of Life in Depression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; BPI, Brief Pain Inventory; C-SSRS, Columbia-Suicide Severity Rating Scale; SASS, Social Adaptation Self-evaluation Scale; SQSS, symptom questionnaire-somatic subscale; SSI, Somatic Symptom Inventory.

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For patients who are particularly vulnerable to the development of new MDD episodes (i.e., patients who have experienced at least three episodes), another study was undertaken to examine the efficacy of duloxetine 60 mg to prevent the recurrence of new depressive episodes. In this study by Perahia et al., patients received open-label duloxetine treatment for up to 34 weeks; patients who met response criteria were then randomly assigned to 52 weeks of maintenance treatment with duloxetine or switched to placebo in a double-blind fashion [69]. The primary outcome for this study was the time to recurrence of an MDD episode.

Special population: anxiety in patients with MDD

In a post hoc analysis from Studies 1 and 2, the efficacy of duloxetine 60 mg QD was evaluated for alleviating anxiety symptoms in patients with MDD [70]. Analyses of the mean change in HAMD item 10 (anxiety-psychic) and HAMD anxiety subfactor score were undertaken to examine the effect of duloxetine on anxiety.

Special population: patients with milder MDD

Perahia et al. conducted a pooled analysis of Studies 1 and 2 that included the subset of patients with milder MDD (defined as a HAMD-17 baseline total score of 15 to 18) in order to examine the efficacy, safety, and tolerability of duloxetine 60 mg QD in the treatment of milder MDD [71].

Special population: Japanese patients

Higuchi et al. conducted a comparative study in Japanese patients to assess the efficacy of duloxetine 40 mg and 60 mg versus placebo and paroxetine in patients with MDD [44].

Special population: women aged 40-55 years

Burt et al. conducted a post hoc analysis of pooled data from Studies 1 and 2 to examine the efficacy of duloxetine 60 mg QD in female patients aged 40–55 years with MDD [72].

Special population: elderly patients

The efficacy of duloxetine 60 mg QD was evaluated in a study with elderly patients with MDD (Study 4) [57]. In this 8-week, double-blind, placebo-controlled study, patients were required to be aged ≥65 years; have MDD based on DSM-IV-TR diagnostic criteria; a HAMD-17 total score ≥18 at screening and baseline; and at least 1 previous episode of MDD. Efficacy of duloxetine in MDD was determined by secondary measures that included the Geriatric Depression Scale and HAMD-17 total score [73].

Outcomes from short-term acute therapy studies: non-pain-enriched studies

Study 1 (Detke et al. 2002) [21]

Significant differences favouring duloxetine were seen between duloxetine-treated patients and placebo-treated patients in the primary efficacy measure (change from baseline in HAMD-17 total score) and in all secondary efficacy measures except for five of six VAS pain items (VAS overall pain, VAS headache, VAS shoulder pain, VAS interference with daily activities, and VAS time in pain while awake). The rates of response, calculated using categorical MMRM analyses, were 42% and 65% (p=0.004) for placebo-treated and duloxetine-treated groups, respectively; and the corresponding rates of remission were 28% and 34.2% (p=0.064) (Table 2).

Study 2 (Detke et al. 2002) [22]

Patients treated with duloxetine had significantly greater improvements in the primary outcome (change from baseline in HAMD-17 total score) and in most of the secondary efficacy measures (PGI-I, VAS overall pain, Quality of Life in Depression Scale [QLDS], and in three of five HAMD-17 subscales) compared to patients treated with placebo (Table 2) [74]. By MMRM, all six VAS outcomes were not significant compared to placebo. The rates of response, calculated using categorical MMRM analyses, were 29% and 62% (p<0.001) for placebo-treated patients and duloxetine-treated patients, respectively, and the corresponding rates of remission were 16% and 44% (p<0.001).

Study 3 (Nierenberg et al. 2007) [54]

When compared to the patients treated with placebo, patients who received duloxetine showed significant improvement in the HAMD-17 total score, in three out of five HAMD-17 subscales, and in the CGI-S and PGI-I endpoint scores. Response and remission rates, calculated using categorical MMRM analyses, were greater in the duloxetine group compared to the placebo group; however, the difference did not reach statistical significance (response: 49% *vs* 37%; remission 40% *vs* 28%).

Study 4 (Raskin et al. 2007) [57]

This study included only elderly patients and will be described in the section "Efficacy of duloxetine for the treatment of MDD in special populations."

Studies 5a and 5b (Oakes et al. 2012) [58]

In Study 5a, there were no significant differences between treatment groups in mean change from baseline in the HAMD Work/Activities item (the primary outcome measure) at Week 8 (p=0.051). In Study 5b, patients treated with duloxetine showed significantly greater improvement in HAMD Work/Activities item at Week 8 compared to patients treated with placebo (p<0.001). Duloxetine-treated patients in each study showed significant improvement in HAMD Maier subscale (Study 5a: p=0.002; Study 5b: p<0.001), HAMD-17 total score (Study 5a: p=0.013; Study 5b: p<0.001), and CGI-S (study 5a: p=0.032; Study 5b: p<0.001) compared to placebo-treated patients. In Study 5a, response and remission rates when calculated using the CAT_MMRM were not significantly different between duloxetine- and placebo-treated patients, whereas in Study 5b, response and remission rates using the CAT_MMRM were statistically significantly greater in the duloxetine group compared to the placebo group (response: p=0.016 and remission: p=0.022) (Table 2).

Table 2. Outcomes of comparisons (duloxetine 60 mg QD versus placebo) from ten acute-treatment studies in patients with MDD.

Measure	Study 1 [21]	Study 2 [22]	Study 3 [54]	Study 4 [57]	Study 5[a] [58]	Study 6 [52]	Study 7 [53]	Study 8 [55]	Study 9 [56]	Japanese [44]
HAMD-17 total score	<0.001*	0.024*	≤0.05	<0.001	Study 5a: 0.013 Study 5b: <0.001	NS	NA	NA	NA	0.044
HAMD Work/Activities	NA	NA	NA	NA	Study 5a: NS* Study 5b: 0.019	NA	NA	NA	NA	NA
HAMD-17 subscales										
Anxiety	0.004	NS	NS	NA	NA	NA	NA	NA	NA	NA
Core	<0.001	<0.001	≤0.01	NA	NA	NA	NA	NA	NA	NA
Retardation	<0.001	0.003	≤0.01	NA	NA	NA	NA	NA	NA	NA
Maier	<0.001	0.003	≤0.01	NA	Study 5a: 0.026 Study 5b: <0.001	NA	NA	NA	NA	NA
Sleep	0.001	NS	NS	NA	NA	NA	NA	NA	NA	NA
CGI-S	<0.001	NS	≤0.01	<0.001	Study 5a: 0.032 Study 5b: <0.001	NS	≤0.001	NA	NA	NA
PGI-I	<0.001	0.014	≤0.05	NA	NA	NS	≤0.05	≤0.021	≤0.01	NA
BPI average pain	NA	NA	NA	NA	NA	NS*	<0.001	≤0.001*	<0.001*	NA
VAS overall pain	0.019	0.037	NA	NS	NA	0.006	NA	NA	NA	NS
Headache	NA	NA	NA	NA	NA	NA	NA	NA	NA	NS
Back pain	<0.001	NA	NA	<0.01	NA	0.006	NA	NA	NA	NS
Shoulder pain	NA	NA	NA	NA	NA	NA	NA	NA	NA	NS
Interference with daily activities	NA	NA	NA	NA	NA	NA	NA	NA	NA	NS
Time in pain while awake	NA	NA	NA	<0.05	NA	NA	NA	NA	NA	NS
QLDS	0.001	0.032	NA	NA	NA	NA	NA	NA	NA	NA
MADRS	NA	NA	NA	NA	NA	NA	≤0.0001	<0.001*	<0.001*	NA
Response	0.004	<0.001	NS	<0.001	Study 5a: NS Study 5b: 0.016	NS	<0.001	<0.001	<0.001	NS
Remission	NS	<0.001	NS	<0.02	Study 5a: NS Study 5b: 0.022	NS	<0.001	0.001	<0.001	<0.05

Significance of duloxetine versus placebo in change from baseline to endpoint given.
*Primary efficacy measure.
[a]The publication by Myers et al. (Trial Registration NCT00536471) reported the primary outcomes from two trials conducted under the same protocol. The primary endpoint data were collected at 8 weeks and the secondary endpoint data were collected at 12 weeks except for the HAMD Meier, which had an 8-week endpoint.

Abbreviations

QD, once daily; HAMD-17, 17-item Hamilton Rating Scale for Depression; CGI-S, Clinical Global Impression-Severity; PGI-I, Patient Global Impression-Improvement; VAS, Visual Analog Scale; QLDS, Quality of Life in Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NA, not applicable; NS, not significant; MMRM, mixed-model repeated measures; LOCF, last observation carried forward.

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Short-term studies: pain enriched

In these below-described Studies 6 to 9, as previously noted, a defined level of pain severity was included as an entry criterion for eligibility into the trial along with a diagnosis of MDD. Pain outcomes from these studies will be reviewed in the section entitled "Impact of duloxetine treatment on pain in MDD." See Table 2 for a summary of outcomes.

Study 6 (Brannan et al. 2005) [52]

Based on primary MMRM analyses of continuous measures at last visit, patients in the duloxetine treatment group did not show a significant improvement in the HAMD-17 total score compared to patients in the placebo group (p=0.544), and the two treatment groups did not differ in their response or remission rates based on CAT_MMRM analyses. Response rates were 51% for placebo-treated patients and 56% for duloxetine-treated patients (p=0.506), and remission rates were 32% for placebo-treated patients and 35% for duloxetine-treated patients (p=0.715). Similarly, no significant differences were found between the treatment groups on the CGI-S and PGI-I ratings at study endpoint (Table 2).

Study 7 (Brecht et al. 2007) [53]

Depression severity was significantly reduced after 8 weeks of treatment in duloxetine-treated patients compared to placebo-treated patients, as measured by the mean change in MADRS total score (secondary efficacy measure) (p<0.05) based on MMRM analysis method. The secondary measures of CGI-S and PGI-I scores also showed significantly greater mean improvement for duloxetine-treated patients compared to placebo-treated patients. Response rates, calculated using the CAT_MMRM analysis, were significantly higher (p<0.001) in duloxetine-treated patients (61%) compared to placebo-treated patients (38%). Remission rates (MADRS ≤12) calculated using the CAT_MMRM analysis, were also significantly higher in duloxetine-treated patients than placebo-treated patients (57% and 29%, respectively; p<0.001) (Table 2).

Study 8 (Gaynor et al. 2011a) [55]

Compared to the placebo-treated group, patients treated with duloxetine showed significantly greater improvement in the co-primary outcome of change in MADRS total score from baseline at 8 weeks (p<0.001) and had a significantly higher remission rate at the 8-week endpoint using the CAT_MMRM analysis (duloxetine: 53% *vs* placebo: 35%) (p=0.001). Using CAT_MMRM analysis for a 50% response rate based on MADRS total score, patients treated with duloxetine showed significant improvement compared to those treated with placebo (63.0% *vs* 42.0%, respectively; p<0.001). Duloxetine significantly improved overall PGI-I scores (p≤0.021, MMRM) and Sheehan Disability Scale (SDS) global functional impairment score (p=0.019, MMRM) compared to placebo.

Study 9 (Gaynor et al. 2011b) [56]

Study 9 assessed the same co-primary outcomes described above for Study 8. Compared to patients treated with placebo, those treated with duloxetine showed significantly greater improvement in MADRS total score from baseline at 8 weeks (p<0.001) and had a higher remission rate (MADRS total score ≤12) at the 8-week endpoint using the CAT_MMRM methodology (duloxetine: 42% *vs* placebo: 24%; p<0.001). Using CAT_MMRM analysis for 50% response rate based on MADRS total score, patients treated with duloxetine showed significant improvement compared to those treated with placebo (56.0% *vs* 32.0%, respectively; p<0.001). Duloxetine significantly improved overall PGI-I scores (p≤0.01, MMRM) and SDS global functional impairment score (p<0.001, MMRM) compared to placebo.

Summary of efficacy of duloxetine for the treatment of MDD in short-term studies

The efficacy outcomes reported in the nine short-term studies are summarized in Table 2. In these studies, the primary outcome measure was predominantly mean change from baseline on the HAMD-17 or the MADRS total score, and in eight out of nine studies, patients who received duloxetine 60 mg QD showed a statistically significant improvement on these measures compared to those who received placebo.

The effect size obtained for the change in HAMD-17 total score using MMRM analysis ranged from 0.08 to 0.52 (Figure 1). For the Japanese study, as mentioned in the methods section, the change in HAMD-17 total score is only analyzed by ANCOVA method with LOCF. The effect size for mean change in HAMD-17 total score at LOCF endpoint in the Japanese study is 0.28 with 95% CI (0.002, 0.564).

The effect size for 50% response rate (CAT_MMRM) based on HAMD-17 total score ranged from 0.12 to 0.72 for Studies 1 to 6 and, based on MADRS, ranged from 0.43 to 0.49 for Studies 7 to 9 (Figure 2). For the Japanese study, based on LOCF method, effect size for remission is 0.29 (95% CI, 0.01, 0.57); effect size for response is 0.26 (95% CI, -0.02, 0.54).

The effect size for remission rate (CAT_MMRM) based on HAMD-17 total score ranged from 0.07 to 0.65 for Studies 1 to 6. For Studies 7 to 9, the effect size for remission rate (CAT_MMRM) based on MADRS total score ≤12 ranged from 0.37 to 0.57 (Figure 3). For the Japanese study, based on LOCF method, NNT for remission is 7.7; NNT for response is 7.8.

The NNTs for response rate based on HAMD-17 total score ranged from 2.86 (95% CI, 2.33, 3.51) to 16.29 (95% CI, 9.33, 28.45) for Studies 1 to 6 and, based on MADRS, ranged from 4.19 (95% CI, 3.24, 5.43) to 4.64 (95% CI, 3.62, 5.95) for Studies 7 to 9 (Figure 4).

The NNTs for remission rate based on HAMD-17 total score ranged from 3.49 (95% CI, 2.12, 5.75) to 29.57 (95% CI, 1.09, 803.8) for Studies 1 to 6 and, based on MADRS, ranged from 3.59 (95% CI, 2.72, 4.76) to 6.29 (95% CI, 3.71, 10.68) for Studies 7 to 9 (Figure 5).

Efficacy of duloxetine for the treatment of MDD in long-term studies

In the relapse prevention study by Perahia et al., patients receiving duloxetine showed a statistically significantly longer time to relapse of MDD compared to patients receiving placebo (p=0.004). This difference was noticed as early as 1 month after withdrawal of treatment [65]. Fewer patients treated with duloxetine relapsed compared to patients who received placebo (17.4% *vs* 28.5%, respectively; p≤0.05). Overall probability of relapse was 19.7% in duloxetine-treated patients versus 38.3% in patients treated with placebo.

Fava et al. further described outcomes for 278 patients who entered the continuation phase of the relapse prevention study described above [68]. A total of 88 patients experienced a relapse of their MDD during this phase of the study, and of the patients who relapsed, 29 (10%) had received duloxetine 60 mg QD and 58 (21%) had received placebo (one patient discontinued the study). Nearly three-quarters of the patients (74%) in the placebo group who relapsed responded to reinstatement of duloxetine 60 mg QD.

After completion of the continuation phase of treatment for MDD, maintenance treatment is generally recommended for those patients at a higher risk of depressive recurrence, for instance those patients who have experienced more than three episodes of MDD, have residual symptoms, had an early age of onset, have a family history of mood disorders, and/or have ongoing psychosocial stressors [67]. One study has been conducted on the efficacy of duloxetine for the prevention of new depressive episodes [69]. A post hoc analysis from this study was undertaken with the subsample of patients who were only treated with duloxetine 60 mg QD during the continuation and maintenance phases [75]. Duloxetine 60 mg QD-treated patients had a longer time to the emergence of a new depressive episode compared to placebo-treated patients (p=0.001). Recurrence rate at any time favored duloxetine over placebo (12.5% *vs* 31.7%; p=0.004) [75]. These results are consistent with the primary analysis of the study, which indicated greater efficacy of duloxetine compared to placebo in preventing new episodes of MDD [69].

Efficacy of duloxetine for the treatment of MDD in special populations

The efficacy of duloxetine 60 mg QD has also been evaluated for the treatment of MDD in special populations, including older/elderly patients, females, patients with milder MDD, Japanese patients, and patients with comorbid anxiety symptoms as well as patients with a predetermined level of pain as described previously in the section "Short-term studies: pain enriched" [44,52,53,55–57,70,72,76].

Special population: anxiety in patients with MDD

In a post hoc pooled analysis from Studies 1 and 2, the efficacy of duloxetine 60 mg QD was evaluated for its effects on anxiety symptoms in patients with MDD [70]. Although patients were not originally included in the study based on anxiety symptoms, analyses of the HAMD item 10 (anxiety-psychic) and the HAMD anxiety subfactor score (Items 10–13, 15, and 17) were undertaken to examine the effect of duloxetine on anxiety symptoms. At baseline, no significant differences were present between treatment groups in the Hamilton Anxiety Rating Scale (HAMA) total score and HAMD anxiety subfactor score. Based on the main effect of treatment using MMRM method (data from all visits), there was a significant advantage of duloxetine 60 mg QD compared to placebo in regard to improvement in the HAMD item 10 (p<0.0001) and in the HAMD anxiety subfactor score (p=0.0003). Significance in visit-wise differences between treatment groups was first reached within 2 weeks and was maintained until endpoint.

Another examination of the efficacy of duloxetine 60 mg QD for the treatment of anxiety symptoms associated with MDD was conducted using data from Study 3. During the acute treatment phase, anxiety measures included the anxiety/somatization subscale of the HAMD-17 scale, the HAMA total score, and the Hospital Anxiety and Depression Scale (HADS) anxiety subscale. All mean changes were analyzed based on an MMRM approach. After 8 weeks of treatment, there was no difference in the improvements in anxiety symptoms between treatment groups. During the extension phase, similar outcomes were observed, with no statistically significant differences in any of the anxiety measures between duloxetine or placebo.

Special population: patients with milder MDD

A post hoc analysis by Perahia et al. pooled data from Studies 1 and 2, which included only patients with milder MDD, defined as a score of 15 to 18 on the HAMD-17 total score at study baseline [71]. A total of 159 patients meeting this definition were randomly assigned to receive placebo (n=84) or duloxetine 60 mg QD (n=75). Patients treated with duloxetine 60 mg QD showed significantly greater improvement from baseline to endpoint in the HAMD-17 total score and a number of secondary efficacy measures. Response rates, calculated using LOCF method, for the placebo-treated patients and duloxetine-treated patients were 29.3% and 47.9%, respectively (p=0.020); remission rates were 24.4% for the placebo-treated patients and 40.8% for the duloxetine-treated patients (p=0.037).

Special population: Japanese patients

Change in the HAMD-17 total score was significantly greater in the duloxetine 60-mg group (-10.0 ± 6.4) compared to the placebo group (-8.3 ± 5.8) at Week 6 after randomization (p=0.0440). Secondary efficacy measures included the HAMD-5 total score, VAS score for overall pain, and response and remission rates [44]. For change in the HAMD-5 total score, there was a statistically significant difference between the duloxetine 60-mg and placebo groups (-0.95 with 95% CI of -1.72, -0.18). For change in the VAS total score for overall pain, there was a statistically significant difference between the duloxetine 60-mg and placebo groups (-1.259 with 95% CI of -2.020, -0.498). The difference between response rates in the duloxetine and placebo groups was not significant. However, the difference in remission rates between both groups did reach significance (duloxetine: 35.1%, placebo: 22.1%; p<0.05).

Special population: women aged 40–55 years

Burt et al. conducted a post hoc analysis that pooled data from female patients participating in Studies 1 and 2 [72]. Women receiving duloxetine 60 mg QD had significantly greater improvement in the primary efficacy measure (HAMD-17 total score) and key secondary efficacy measures (CGI-S, PGI-I, VAS overall pain, QLDS, and HAMD-17 subscales) at study

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endpoint compared to women treated with placebo. The response rates were 32% and 58% (p=0.008) for placebo-treated patients and duloxetine-treated patients, respectively; the corresponding rates of remission for these two groups were 19% and 35% (p=0.06).

Special population: elderly

Study 4 included only older (≥65 years) patients with MDD. At baseline, patients in the duloxetine group had a higher Geriatric Depression Scale total score than the patients in the placebo group (p=0.006). Compared to placebo-treated patients, duloxetine-treated patients showed a significantly greater improvement in the Geriatric Depression Scale total score (p<0.001) and the HAMD-17 total score (p<0.001) from baseline to endpoint as well as higher response rates (duloxetine: 37.3%, placebo: 18.6%; p<0.001) and remission rates (duloxetine: 27.4%, placebo: 14.7%; p<0.02) [57].

In addition, Nelson et al. conducted a post hoc analysis of data from 90 patients aged ≥55 years (mean age: 63.5 years; 60% female) who participated in Studies 1 and 2 (placebo: n=43; duloxetine: n=47) [76]. Patients aged ≥55 years who were treated with duloxetine 60 mg QD showed significantly greater improvement (p=0.014) in the HAMD-17 total score from baseline to endpoint compared to placebo-treated patients. Regarding the secondary efficacy measures, duloxetine-treated patients exhibited significantly greater improvements in three of five HAMD-17 subscales (core factor: p=0.006; retardation: p=0.027; Maier: p=0.017) and CGI-S scale score (p=0.016) compared to the placebo-treated patients. Response rate determined by LOCF method was not significantly greater for the duloxetine group (41.3%) compared to the placebo group (23.8%, p=0.112); remission rate using LOCF was 30.4% for duloxetine treatment and 14.3% for placebo treatment (p=0.080).

Impact of duloxetine treatment on pain in MDD

A recently published review article by Robinson et al. assessed the efficacy of duloxetine for the management of painful symptoms associated with MDD. Data were pooled from Studies 1, 2, 4, and 6, and a main effect of treatment analysis showed that duloxetine 60 mg QD was statistically superior to placebo on all VAS assessments, except for headaches [77].

As noted earlier, Studies 6 to 9 specifically examined the efficacy of duloxetine in patients with MDD who had higher levels of pain at study entry, as defined a priori in the protocol.

In Study 6, the primary efficacy outcome measure was improvement in the BPI 24-hour average pain score [52,63]. Baseline BPI scores for both groups were similar (4.62 for duloxetine and 4.85 for placebo; p=0.259). Early improvement was observed in patients treated with duloxetine compared to placebo (p≤0.005 at Week 1 and p≤0.05 at Week 2), but the difference was not statistically significant at study endpoint (MMRM analysis). When treatment effects were pooled for all visits, patients treated with duloxetine showed significantly greater mean improvement compared to those receiving placebo on all BPI pain severity measures and on six of seven BPI pain interference items. The findings of this particular study support the theory of a direct analgesic effect of duloxetine, since compared to placebo the drug reduced PPS in the absence of significant improvement in depressive symptoms.

The other three pain-enriched studies (Studies 7, 8, and 9) demonstrated the analgesic effect of duloxetine at 60 mg QD for PPS associated with MDD [53,55,56]. The primary efficacy measure of Study 7 was the mean change from baseline to endpoint in the BPI 24-hour average pain score, which was significantly greater in the duloxetine group compared to the placebo group (p=0.0008) (MMRM analysis) [53]. The relationship between the time course of improvement of the depressive symptoms as measured by the MADRS score, and the time to reduction in painful symptoms as measured by the BPI 24-hour average pain score, suggests that the analgesic effect of duloxetine occurs independently from the improvement in core symptoms of MDD [53]. Regarding the BPI 24-hour average pain score (one of the co-primary outcome measures in Studies 8 and 9), duloxetine was associated with statistically significant improvement (reduction) from baseline to 8 weeks of treatment in the BPI average pain rating (p≤0.001) in both studies. The time course of improvement in depression and pain symptoms in Study 8 showed that analgesic efficacy preceded efficacy in core depressive symptoms, whereas in Study 9, efficacy in core depressive symptoms preceded analgesic efficacy.

To further examine if duloxetine-induced relief in PPS occurs independently from the drug's antidepressant effect, Fishbain et al. conducted a post hoc analysis of six Phase III, double-blind, placebo-controlled studies of patients with MDD [78]. Two of these studies (Studies 1 and 2) evaluated duloxetine 60 mg QD compared to placebo (the population was pooled into a single group named "60 mg QD population"). Only patients with moderate pain (≥30 mm on baseline VAS) were included in this analysis. Onset of antidepressant efficacy was defined as the first occurrence of a ≥50% reduction from baseline in the HAMD-17 total score; onset of analgesic effect was defined as the first occurrence of a ≥50% reduction from baseline on VAS. Time to antidepressant response versus time to analgesic response was compared between treatments through a log-rank test. A faster time to analgesic effect (time to ≥50% reduction in VAS) versus antidepressant effect (time to ≥50% reduction in HAMD-17) was shown for all VAS subscores with a significance of p<0.001 for each one. A linear regression model (to predict the relationship between improvement in pain and depressive symptoms) demonstrated that the change in overall pain from baseline represented less than 10% of the variability in the change in depression severity in the duloxetine 60-mg QD group, demonstrating that the change in pain and core MDD symptoms are independent [78].

Time course of change studies

The time course of first response and sustained response in depressive symptomatology are of major interest to clinicians. Antidepressants that offer a rapid onset of action may reduce the risk of suicide, provide a faster improvement in depressive symptoms and functional well-being, and foster continued treatment compliance [79].

Brannan et al. conducted a pooled analysis from Studies 1 and 2, to analyze the onset of antidepressant effect [80]. Median time-to-onset of sustained improvement of 10%, 20%, and 30% in the HAMD-17 total score for duloxetine was 14 days, 21 days, and 35 days, respectively. For those patients who received placebo, time-to-onset for sustained improvements of 10% and 20% was 34 and 49 days, respectively, and, for the 30% improvement, the median time was non-estimable since fewer than half of the patients met this criterion by the end of the trial. The comparison between duloxetine and placebo in the median times to achieve 10% and 20% improvement in the HAMD-17 favored duloxetine over placebo (p<0.001) [80].

In Study 3, onset of antidepressant efficacy was the primary endpoint and was defined as achieving a 20% decrease from baseline in the HAMD-17 Maier subscale at Week 2 that was maintained or exceeded at all subsequent visits throughout the acute treatment phase. Results from the primary outcome measure showed that duloxetine was non-inferior to escitalopram in onset of efficacy. Probabilities of meeting onset criteria for the duloxetine and escitalopram group were 42.6% and 35.2%, respectively (95% CI, -1.3%, 16.2%, p=0.097). Additional assessments were made to test the robustness of the primary analysis (main effect of treatment and Kaplan–Meier). Using main effect of treatment analysis, a significantly greater proportion of patients treated with duloxetine met onset criteria compared to patients treated with escitalopram (p=0.026). Using the Kaplan–Meier analysis, time-to-onset for duloxetine-treated patients was 23 days (median), which was significantly lower than the time-to-onset for both escitalopram-treated patients (41 days; p=0.032) and placebo-treated patients (55 days; p<0.001). The time-to-onset of antidepressant effect for escitalopram was not different from placebo (p=0.087) [54].

Active comparator studies

A few studies have specifically compared duloxetine 60 mg with active comparators. In Study 3, described earlier, secondary analyses evaluated mean change in the HAMD-17 total score, HAMD-17 subscales, CGI-S, PGI-I from baseline to endpoint, response rates, and remission rates. Duloxetine and escitalopram showed significant improvement in most of the measures described above (mean change from baseline) when compared to placebo. Response rates for duloxetine were significantly greater compared to placebo (p=0.04) (LOCF analysis); however, escitalopram response rates did not differ significantly from placebo response rates. Remission rates did not differ significantly among the three treatment groups (LOCF analysis) [54].

The Japanese study compared the efficacy of duloxetine versus placebo and paroxetine [44]. Patients were randomly assigned to duloxetine 40 mg (n=91), duloxetine 60 mg (n=84), placebo (n=156), and paroxetine (n=164). Improvement in the HAMD-17 total score was numerically, but not statistically, greater in the duloxetine 60-mg group (-10.0 ± 6.4) compared to the paroxetine group (-9.4 ± 6.9).

Third-party studies of duloxetine compared to escitalopram

Separate from the Lilly database of clinical trials for duloxetine, there have been a few other studies that compared treatment with duloxetine to other active pharmacotherapies for MDD. Khan et al. conducted a double-blind comparative study between escitalopram and duloxetine, for the acute treatment of patients with MDD [81]. Patients were randomly assigned to receive duloxetine 60 mg daily or escitalopram 10 to 20 mg daily (10 mg QD for the first 4 weeks) and were followed for up to 8 weeks of treatment. The primary efficacy measure was the mean change in MADRS total score. Treatment with escitalopram resulted in a significantly greater improvement in MADRS total score compared to duloxetine, but the groups did not differ across other efficacy measures [81].

In another comparator study of duloxetine (60 mg, n=151) and escitalopram (20 mg, n=143), the efficacy of both therapies was compared for the acute and continuation treatment of patients with MDD [82]. The primary efficacy measure for both endpoints (8 weeks for the acute phase, and 24 weeks for the continuation phase) was based on the mean change from baseline in the MADRS score. Response rates (≥50% decrease in MADRS) and remission rates (MADRS ≤12) were measured as secondary efficacy measures. Results showed that patients in both groups showed improvements in the mean MADRS total score steadily from baseline to endpoint. However, after 8 weeks of treatment, patients treated with escitalopram showed significantly greater reduction in the MADRS score and a higher response rate (p<0.05 for both outcomes) compared to those who received duloxetine. At Week 24, the proportion of responders and remitters in both treatment groups was comparable and did not significantly differ [82].

Tolerability and safety

For the examination of safety outcomes, data were pooled from the seven short-term, double-blind, placebo-controlled studies (Studies 1–7, Table 3). Data from the other acute therapy studies were not included in these analyses as they were completed after the integration of the pooled dataset; however, there were no additional safety signals observed within these studies compared to the pooled dataset.

Within the pooled dataset, the most common treatment-emergent adverse events (TEAEs) (reported by ≥5% of patients) were nausea, headache, dry mouth, diarrhea, dizziness, constipation, fatigue, insomnia, and decreased appetite. Except for headache and insomnia, these occurred significantly more often in duloxetine treated-patients compared to placebo-treated patients (Table 3).

No significant differences were seen in the rate and types of serious adverse events between patients treated with placebo

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Table 3. Treatment-emergent adverse events (TEAEs) reported with ≥5% incidence in patients treated with placebo or 60 mg duloxetine based on Studies 1–7 pooled.

Adverse event, n (%)	Placebo (n=1066)	Duloxetine 60 mg QD (n=1552)	p-value[a]
Patients with ≥1 TEAE	739 (69.3)	1213 (78.2)	<0.001
Nausea	88 (8.3)	387 (24.9)	<0.001
Headache	147 (13.8)	239 (15.4)	0.262
Dry mouth	73 (6.8)	288 (18.6)	<0.001
Diarrhea	78 (7.3)	163 (10.5)	0.006
Dizziness	53 (5.0)	148 (9.5)	<0.001
Constipation	51 (4.8)	145 (9.3)	<0.001
Fatigue	48 (4.5)	131 (8.4)	<0.001
Insomnia	65 (6.1)	111 (7.2)	0.303
Decreased appetite	25 (2.3)	91 (5.9)	<0.001

[a]Fisher's exact test.
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and duloxetine 60 mg QD in the pooled dataset. Of the 2618 patients included in the pooled safety analysis, the rate of serious adverse events was 1.7% for patients in the placebo group and 1.1% for patients in the duloxetine group.

Pooled safety data for the duloxetine 60 mg QD dose regarding blood pressure, heart rate, and weight can be found in Table 4. There was a statistically significant difference between duloxetine- and placebo-treated patients in the LS mean change from baseline for diastolic blood pressure but not for systolic blood pressure. Patients treated with duloxetine had a statistically significant mean increase of 0.95 mm Hg in diastolic blood pressure. There were no significant differences between duloxetine and placebo in the rates of sustained elevation in blood pressure or heart rate (LS mean change [SE]: placebo 0.23 [0.47] *vs* duloxetine 1.24 [0.34]). Patients treated with duloxetine experienced a mean weight loss of -1.06 kg compared to -0.13 kg in patients treated with placebo (p<0.001).

Table 4. Vital signs in patients treated with duloxetine 60 mg QD versus placebo based on Studies 1–7.

Vital sign	Placebo (n=383)	Duloxetine 60 mg QD (n=766)	p-value
Blood pressure, mm Hg			
Systolic	-0.73 (0.58)	0.71 (0.42)	0.089[a]
Diastolic	-0.28 (0.41)	0.95 (0.29)	0.001[a]
Sustained elevation, n (%)			
Systolic	1 (0.3)	8 (1.0)	0.286
Diastolic	2 (0.5)	1 (0.1)	0.259
Heart rate, bpm	0.23 (0.47)	1.24 (0.34)	0.073
Weight, kg	-0.13 (0.12)	-1.06 (0.11)	<0.001

[a]Within 60 mg QD group p-value for baseline increase.
All values are LS mean change (standard error) unless otherwise specified.
Abbreviations
QD, once daily; bpm, beats per minute.
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Treatment with duloxetine 60 mg QD was not associated with significant changes in hematology and blood chemistry laboratory values, except for low cholesterol present in 10.3% of patients in the placebo group and 6.5% of patients in the duloxetine group (p=0.004).

Overall, the safety and tolerability profile for duloxetine 60 mg QD in the treatment of MDD from the seven acute trials are consistent with that reported in the product guidelines (package insert) [83].

Pooled safety analyses have also been conducted for duloxetine treatment utilizing larger datasets across different dose ranges and indications. The interested reader should refer to published analyses of hepatic data, cardiovascular data, and suicidality data for more information [40,84–86].

Expert commentary by Michael Thase

The data presented in this review demonstrate that 60 mg QD of duloxetine is an effective and well-tolerated therapy for MDD, both for the acute phase of treatment and for prevention of relapse and recurrence of new depressive episodes. Indeed, available evidence suggests that the 60-mg QD dose represents the optimal balance of efficacy and tolerability for the average patient with MDD. As most patients can begin therapy with this dose of duloxetine, it can be said that duloxetine has notably simple dosing characteristics, which can be viewed as a strength for patients, providers, and pharmacy benefit managers (i.e., fewer visits and less chance for mistakes during upward titration).

With respect to absolute and relative efficacy, the data presented in this review indicate that the magnitude of depressive symptom reduction and likelihood of benefit (i.e., response and remission rates) observed in placebo-controlled studies of duloxetine are at or above suggested thresholds for clinical significance [87] and – at the least – comparable to other newer-generation antidepressants. For example, about two-thirds of the studies reported effect sizes of at least 0.4 on the primary continuous outcome measure and six of seven placebo-controlled studies of duloxetine 60 mg QD observed NNT values of less than 10. Such consistency of findings is conspicuous in an era in which at least one-half of placebo-controlled studies of known antidepressants fail to observe significant benefit. Similarly, three of four "pain-enriched" studies reported significant relief of PPS associated with depression. Although the clinical significance of these findings is not as well established, it is noteworthy that Fishbain and colleagues [78] found that improvement in painful symptoms was not simply an epiphenomenon of duloxetine's antidepressant effect.

Whereas it is clear that the 60-mg QD dose of duloxetine should be considered the usual target dose for treatment of MDD, it has not yet been demonstrated when and if higher doses (i.e., 90–120 mg QD) should be used. In the United States, where duloxetine has been available since 2004, doses above 60 mg QD are seldom prescribed by primary care providers, though psychiatrists do use higher doses for a significant minority of depressed patients, particularly for treatment of patients with more chronic, severe, or treatment-resistant illnesses [88]. This observation, which is likewise true for the other types of antidepressants, no doubt – at least in part – reflects that specialists have a greater level of comfort with higher doses of antidepressants, as well as wish to help by titrating the dose upwards, particularly when there are very few limiting adverse effects. In practice, when upward titration is temporally associated with the desired clinical response, clinicians invariably attribute the success to their action (i.e., increasing the dose) rather than coincidence and the passage of time.

To date, the findings of only one randomized controlled trial directly address the question of increasing the dose [89]. In this study, 255 patients with MDD who had not remitted following at least 5 weeks of therapy with duloxetine 60 mg QD were randomly assigned to either 8 additional weeks of treatment with duloxetine 60 mg QD (plus an additional placebo) or up-titration to 120 mg QD. Results of this adequately powered and well-controlled trial provided no hint of greater benefit for the patients who received treatment with higher doses of duloxetine, with similar levels of symptom reduction and both groups having final remission rates of about 40% [90]. Whether higher doses might be specifically more useful for patients with unremitting pain symptoms warrants prospective study, particularly since doses above 60 mg QD are routinely indicated for treatment of neuropathic pain.

The findings of the study described above suggest that, for the average patient, any potential therapeutic benefit conveyed by higher doses of duloxetine is essentially offset by increasing side effects and attrition due to intolerable side effects. It could also mean that, for the large majority of patients, duloxetine therapy at 60 mg QD is adequate to occupy at least 80% of the serotonin transporters (SERT) (see, as an example, Meyer et al. 2004) [91]. Less is known about the desired effect of duloxetine and other SNRIs on occupancy of the norepinephrine transporter (NET). Recent identification of radioligands for NET should finally facilitate this important line of research [92,93].

Limitations: In this review article, a majority of the studies included were randomized clinical trials, but the designs of these varied such that the data from them could not be pooled. In addition, data from randomized control trials may not generalize well to "real world" clinical practice.

Conclusions

This review provides evidence that duloxetine 60 mg QD is effective for the treatment of adult patients with MDD in the short- and long-term phases of treatment. Duloxetine 60 mg QD also represents a viable choice of treatment for those patients with painful physical symptoms associated with MDD. The decision to prescribe duloxetine 60 mg QD rather than other pharmacological treatment options should be based on the patient's complete clinical profile, taking into account MDD severity, and the presence of PPS, previous antidepressant use and response, and any previous history of relapse/recurrence, among other factors.

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