Efficacy and Safety of Duloxetine 60 mg Once Daily in the Treatment of Pain in Patients With Major Depressive Disorder and At Least Moderate Pain of Unknown Etiology: A Randomized Controlled Trial

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Objective: Experience of pain in major depressive disorder (MDD) can complicate diagnosis and impair treatment outcomes. This study evaluated the efficacy and safety of duloxetine in the treatment of patients with moderate pain associated with depression.

Method: In this double-blind, placebo-controlled, 8-week study, conducted from May 2005 to May 2006, outpatients 18 years of age or older, presenting with major depressive disorder (DSM-IV criteria; Montgomery-Asberg Depression Rating Scale [MADRS] score ≥ 20), moderate pain (Brief Pain Inventory-Short Form [BPI-SF] average pain score ≥ 3), and Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 4 were randomly assigned to either placebo (N = 165) or duloxetine 60 mg (N = 162) once daily. Primary outcome was change in item 5 score (average pain in the last 24 hours) of the BPI-SF from baseline. Secondary measures were MADRS total score, other BPI-SF items, CGI-S, CGI-Improvement scale, Patient Global Impressions-Improvement scale, Symptom Checklist-90-Revised, response and remission rates, safety, and tolerability.

Results: Duloxetine, compared with placebo, significantly reduced pain and improved depression with significant mean changes at endpoint in both BPI-SF average pain scores (–2.57 vs. –1.64, p < .001) and in MADRS total scores (–16.69 vs. –11.31, p < .001). Remission of MDD and response rates in pain and MDD were significantly (p ≤ .001) higher in duloxetine-treated patients. Duloxetine separated from placebo on most secondary outcome measures including the BPI-SF interference with daily life due to pain. Treatment-emergent adverse events (≥ 10%) in duloxetine-treated patients were nausea, hyperhidrosis, and dry mouth.

Conclusion: These results support duloxetine's efficacy and tolerability in the treatment of pain and depression in patients with at least moderate pain associated with depression.

Trial Registration: ClinicalTrials.gov identifier NCT00191919 (http://www.clinicaltrials.gov).

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Somatic or physical symptoms, often painful, are associated with major depressive disorder (MDD).[1,2] Depression is generally diagnosed through the core mood symptoms and a variety of associated emotional and physical symptoms that are persistent during a 2-week period. In primary care, the diagnosis of depression is complicated due to the combination of core mood symptoms and associated symptoms such as painful physical symptoms.[1,3–5] Among primary care patients, 65% of patients with MDD were shown to have some type of painful physical symptoms.[6,7] A greater severity of painful physical symptoms, including back pain, gastrointestinal pain, and headache, is associated with increased severity of depression and reduces quality of life.[8] The presence of painful physical symptoms in patients with depression impairs treatment outcome,[6,7] decreases remission rates,[9] and creates loss of productivity and quality of life.[3,4,10] Patients with residual symptoms, including painful symptoms, are more likely to relapse.[11] Pain in depression receives inadequate attention for treatment due to poor diagnosis.[12] Treatment of depression ideally should include both core mood symptoms and associated symp-

toms such as pain to achieve adequate remission and prevention of frequent relapse.

It has been suggested that the neurobiological pathways of depression and painful physical symptoms are associated with imbalance of serotonin (5-HT) and norepinephrine.[13,14] The treatment of depression and associated pain may be optimized with therapeutic agents such as tricyclic antidepressants, venlafaxine, and duloxetine as these have been shown to modulate both 5-HT and norepinephrine pathways by inhibiting the reuptake of these neurotransmitters (serotonin-norepinephrine reuptake inhibitors [SNRIs]) at the synapse. Potentiating the activity of 5-HT and norepinephrine is believed to result in central pain inhibition through descending modulatory pain pathways.[15–18]

Duloxetine hydrochloride, an SNRI, is approved for the treatment of MDD, as well as for the management of diabetic peripheral neuropathic pain, in Europe, the United States, and many other countries. Duloxetine treatment improved not only core depressive symptoms but also associated painful physical symptoms as was documented in the pain assessment in secondary[19–21] or primary[22] outcome measures. Duloxetine exerts a substantial direct analgesic effect over and above its antidepressant effects.[23]

If 5-HT and norepinephrine are involved in depression and pain modulation, then a reuptake inhibitor of both neurotransmitters should treat pain effectively in depressed patients with associated pain. Therefore, the underlying hypothesis of this study was to evaluate the efficacy of duloxetine in comparison with placebo on pain (as measured by the Brief Pain Inventory-Short Form [BPI-SF]) in the treatment of patients with at least moderate pain associated with depression. Other outcome measures focused on reduction of depression severity (Montgomery-Asberg Depression Rating Scale [MADRS]), bodily symptoms of psychological distress (Symptom Checklist-90-Revised [SCL-90-R]), general improvement as seen by patients and investigators (Patient Global Impressions [PGI] and Clinical Global Impressions [CGI]), response and remission, as well as tolerability and safety.

METHOD

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study conducted in 5 European countries in outpatients with MDD and at least moderate pain. The duration of the study was 10 weeks, consisting of an 8-week treatment period and a 2-week tapering period. The treatments were placebo or duloxetine 60 mg per day, escalated from 30 mg per day after the first study week, followed by tapering after 7 weeks of treatment at 60 mg to 30 mg per day for 2 weeks. This study,

conducted from May 2005 to May 2006, was sponsored by Eli Lilly and Company and Boehringer Ingelheim GmbH (Clinical Trial Registration #NCT00191919).

Patients

All patients were male or female outpatients 18 years of age or older with a diagnosis of MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[24] The diagnosis was confirmed by the Mini-International Neuropsychiatric Interview (MINI, version 5.0.0), a standardized diagnostic interview based on DSM-IV criteria.[25] At baseline, all patients had a depression severity with a total score of 20 or higher on the MADRS and at least moderate pain based on a BPI-SF score of 3 or higher for the "24-hour average pain" item. In addition, all patients had to be at least moderately ill as measured by a score of 4 or higher on the Clinical Global Impressions-Severity of Illness scale (CGI-S) at screening and at baseline. Study participants were devoid of any diagnosed pain syndrome as per medical history, and no further differential diagnostic work-up was performed.

Patients were excluded if they had been taking pain medication on a regular basis for the last 6 months. Furthermore, patients must have had 1 previous depressive episode in their medical history. Reasons for study exclusion included the following: current Axis I disorder (other than MDD); anxiety disorder as a primary diagnosis within the past 6 months; an Axis II disorder that could interfere with compliance with the study protocol; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy (in the opinion of the investigator); serious medical illness; history of bipolar disorder, schizophrenia, or other psychotic disorders; history of suicide attempt or judged to be at serious suicidal risk on the basis of MADRS item 10 scoring; a history of substance abuse or dependence within a year of study entry; or a positive urine drug screen for drug abuse. To provide for patient safety in this placebo-controlled depression study, per protocol patients were discontinued from the study if their depression deteriorated during the observation period (as judged by the investigator). This study was approved by the institutional ethical review boards according to the national legislation of Belgium, Germany, France, Finland, and Slovakia. Before their enrollment, all patients signed an informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Primary Efficacy Measure

The primary objective of this study was to assess the efficacy of duloxetine 60 mg per day compared with placebo in outpatients with MDD and at least moderate pain as measured by 24-hour average pain, BPI-SF item 5.[26] The BPI-SF is a patient-rated instrument that measures

the pain intensity, as well as other pain aspects, on an 11-point Likert scale ranging from 0 (no pain or interference) to 10 (most severe pain or complete interference). The patients completed item 5 of the BPI-SF at screening, baseline, and at all other study visits. The primary outcome measure was the mean change in the score for item 5 (average pain in the last 24 hours) of the BPI-SF from baseline during 8 weeks of treatment.

Secondary Efficacy Measures

Pain and pain-related outcomes. The patients were asked to assess the complete BPI-SF, including information about the severity of pain as worst pain and least pain in last 24 hours and pain "right now." The BPI-SF interference questions ask patients, via 7 items, how much they are limited by pain in their daily functioning. Per protocol, an analysis of the BPI-SF interference subscale total score was described; analyses of the 7 single items of the BPI-SF interference subscale were done post hoc. Response in pain severity was defined as a decrease of 30% or more from the individual average pain baseline score after 8 weeks of treatment. A patient was considered a sustained responder at a certain visit if he or she was a responder at this visit and at all following visits until week 8.

Depression-related outcomes. The secondary efficacy measures included the assessment of depression by the MADRS[27,28] at screening and all visits. The scale includes 10 items that assess the core symptoms of depression. The items are scored from 0 to 6 with a maximum total score of 60. Reduction in score is a measure of symptom improvement. Response was defined as a decrease of 50% or more of the individual baseline MADRS total score at endpoint. A patient was considered a sustained responder at a certain visit if he or she was a responder at this visit and at all following visits until week 8. A total MADRS score of 12 or less was defined a priori as achieving remission.[29,30]

General outcomes. The CGI-S and the CGI-Improvement (CGI-I) were used to evaluate the overall disease severity and improvement of patients as judged by investigators.[31] The severity of the disease was assessed by the same evaluator throughout the study using the CGI-S item on a scale of 1 (normal) to 7 (most extremely ill) from screening to the endpoint visits; the CGI-I was used to assess the patient's overall condition on a scale of 1 (very much improved) to 7 (very much worse) from week 1 through week 8.

The PGI-Improvement (PGI-I) scale was used to assess the patient's overall condition, ranging from 1 (very much better) to 7 (very much worse). The patient self-rated this instrument at weeks 3 through 8.

The SCL-90-R was designed to characterize the global symptomatology and psychological distress of psychiatric outpatients.[32–34] This self-report clinical rating scale was administered from baseline through week 8. The statistical analysis plan specified that mean changes from baseline to endpoint between the duloxetine and placebo groups were to be investigated only on SCL-90-R total score (general symptomatic index) and somatic symptoms subscale.

Tolerability and safety. Tolerability and safety measures included incidence of adverse events, discontinuations due to adverse events, treatment-emergent adverse events, changes in vital signs, and changes in standard laboratory parameters, including blood count, electrolytes, and liver function tests.

Statistical Analyses

All efficacy analyses were conducted in all patients who had received at least 1 dose of study medication and had at least a baseline and a postbaseline value available for efficacy evaluation. The safety analyses included all patients who had received at least 1 dose of treatment.

The sample size calculation for the primary variable was made on the basis of a 2-sided t test for the difference in means between the 2 independent groups with a significance level of .05. A total sample size of 310 patients (155 in each treatment group) was considered sufficient to detect a difference in BPI-SF average pain change from baseline of 0.8 between duloxetine and placebo with at least 80% power, assuming a common standard deviation of 2.5. Power calculations also were computed for the MADRS, a key secondary variable. This sample size provided 85% power to detect a difference of 2.0 in the MADRS between the treatment groups at a 5% level of significance, assuming a common standard deviation of 5.8. The sample size was increased by 20% to account for screening failures (388 patients needed to be screened).

As primary analysis, the difference in BPI-SF average pain between the treatment groups was assessed using a maximum likelihood-based mixed-effects repeated-measures analysis using all the observations at each postbaseline visit over 8 weeks.[35,36] The model included the fixed categorical effects of treatment, center, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline score-by-visit interaction. The covariance structure to model the within-patient errors was unstructured; the Kenward-Roger method was used to estimate denominator degrees of freedom, and Type III sum-of-squares for the least squares mean were used.

The α level was fixed at 5% for the secondary analyses, and no adjustment was made for multiple comparisons. Further, maximum likelihood-based mixed-effects repeated-measures analyses were done to compare the treatment groups with regard to the change from baseline to endpoint in MADRS total score (with last observation carried forward [LOCF] as predefined secondary analysis), the BPI-SF average pain, and the other pain items of the BPI-SF.

The BPI-SF interference scale (item 9 of the BPI-SF) and the 7 subitems of the BPI-SF interference scale were

Table 1. Baseline Demographic and Clinical Characteristics of All Treated Patients With Major Depressive Disorder and At Least Moderate Pain

Characteristic	Duloxetine (N = 162)	Placebo (N = 165)
Gender, N (%)		
Female	123 (75.9)	118 (71.5)
Male	39 (24.1)	47 (28.5)
Age, mean (range), y	48.1 (18.0–80.0)	52.3 (18.0–82.0)
Ethnicity, Caucasian, N (%)	161 (99.4)	162 (98.2)
BPI-SF score, mean (SD)		
Average pain	5.7 (1.6)	5.7 (1.6)
Least pain during the last 24 hours	3.8 (2.1)	4.0 (2.0)
Pain right now	5.4 (2.1)	5.6 (1.9)
Worst pain during the last 24 hours	7.0 (1.7)	7.0 (1.6)
Interference (mean score)	5.5 (1.9)	5.5 (1.7)
MADRS total score, mean (SD)	29.9 (4.5)	29.2 (4.5)
CGI-Severity of Illness, N (%)		
Moderate	134 (82.7)	137 (83.0)
Severe	27 (16.7)	27 (16.4)
Missing	1 (0.6)	1 (0.6)

Abbreviations: BPI-SF = Brief Pain Inventory-Short Form, CGI = Clinical Global Impressions, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 1. Mean Change From Baseline to Endpoint in Brief Pain Inventory-Short Form Average Pain (primary efficacy measure), Worst Pain, Least Pain, Pain Right Now, and Interference in Patients Treated With Duloxetine or Placebo for 8 Weeks[a]

[a]Maximum likelihood-based mixed-effects repeated-measures analysis (full analysis set, observed cases). All results are statistically significant with LOCF also.
[b]LOCF only.
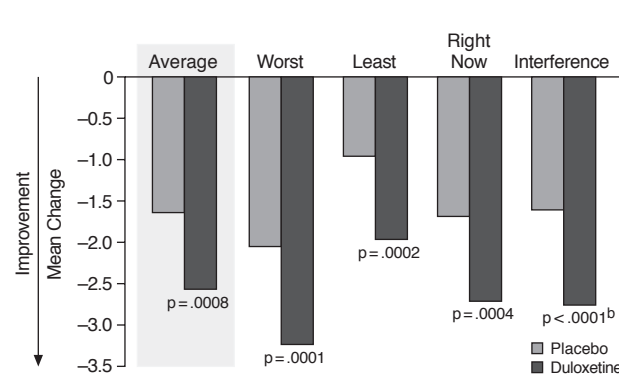Abbreviation: LOCF = last observation carried forward.

analyzed with analysis of covariance, including the main explanatory factor treatment and the factor center, as well as the covariate baseline BPI-SF average pain. The LOCF method of estimation for missing data was used.

For percentage change from baseline and results at intermediate visits, only descriptive analyses were computed. The treatment groups were compared regarding the number of responders and nonresponders (BPI-SF average pain and the MADRS score) at endpoint (week 8, LOCF) and at week 4 (LOCF) using the Cochran-Mantel-Haenszel test with stratification by center (pooled, if necessary). The same analysis was carried out for the MADRS remitters and for the CGI-S, the CGI-I, and the PGI-I at endpoint (week 8, LOCF) and at week 4. The treatment effect for time to sustained response (BPI-SF average pain and MADRS) and time to sustained MADRS remission was examined with the log-rank test and displayed using Kaplan-Meier survival curves.

RESULTS

Baseline Characteristics

A total of 393 patients were screened, and 327 were included in this study. The baseline demographic and clinical characteristics of all 327 randomly assigned outpatients (duloxetine = 162; placebo = 165) are presented in Table 1. A total of 38 investigators participated in this study and treated outpatients in France, Belgium, Finland, Germany, and Slovakia. The mean patient age was 48.1 years in the duloxetine group and 52.3 years in the placebo group, and most patients were Caucasian (duloxetine = 99.4%, placebo = 98.2%) and female (dulox-

etine = 75.9%, placebo = 71.5%). In general, the treatment groups were not different from each other at baseline with regard to either the clinical or demographic characteristics examined except the age difference, which was not considered clinically relevant. A post hoc sensitivity analysis performed on the primary endpoint, adjusting for age, did not result in different outcomes than provided here according to the prespecified statistical analysis plan.
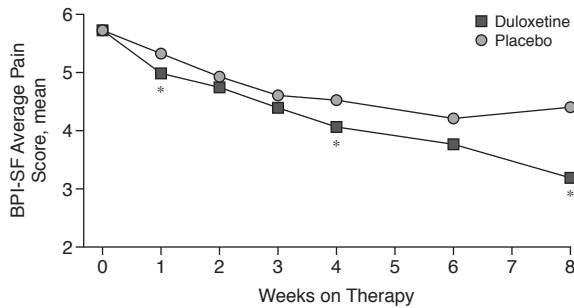
Patient Disposition

Of the total randomly assigned and treated patients, 121 of 162 (74.7%) in the duloxetine group and 128 of 165 (77.6%) in the placebo group completed the study. The main reason for discontinuation in the duloxetine group (17/41) was due to adverse events, and in the placebo group, it was lack of efficacy (14/37).

Efficacy

Pain. The primary efficacy endpoint was the baseline-to-endpoint change in the 24-hour average pain score (item 5) of the BPI-SF as determined by maximum likelihood-based mixed-effects repeated-measures analysis. The p value for the interaction between treatment and time was .0468, which indicates that the response over time differed between the treatment groups.
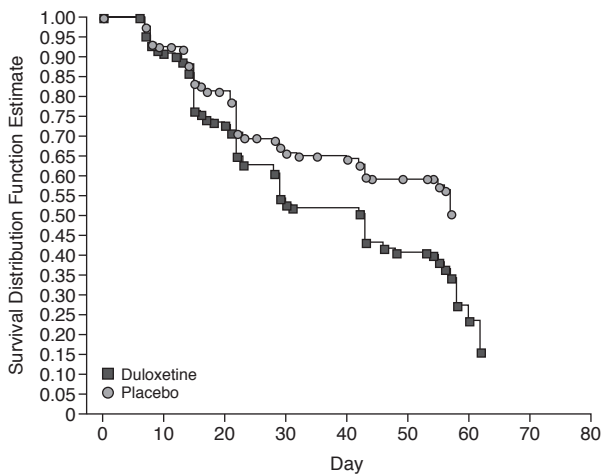
At week 8, the mean change in BPI-SF average pain was –2.57 in patients treated with duloxetine 60 mg and –1.64 in patients treated with placebo, resulting in a significant improvement with duloxetine (p = .0008). Patients receiving duloxetine also experienced a significant reduction at endpoint compared with placebo in the worst pain (p = .0001), least pain (p = .0002), and pain

Figure 2. Time Course of Adjusted Mean Scores of Brief Pain Inventory-Short Form (BPI-SF) Average Pain in Patients Treated With Duloxetine or Placebo for 8 Weeks[a]

[a]Maximum likelihood-based mixed-effects repeated-measures analysis (full analysis set, observed cases).
*p ≤ .05 versus placebo.

Figure 3. Median Time to Sustained Response as Estimated by Kaplan-Meier Survival With Log-Rank Test for Brief Pain Inventory-Short Form for 24-Hour Average Pain

Table 2. Adjusted Mean Changes (SE) From Placebo With 95% Confidence Intervals of Brief Pain Inventory-Short Form (BPI-SF) Average Pain Subscales of Interference (Health Outcomes) in Patients Treated With Duloxetine

Outcome Measure	Mean Change (SE)[a]	95% CI	p Value
BPI-SF average pain	–0.79 (0.26)	–1.30 to –0.27	.0027
General activity	–1.18 (0.29)	–1.76 to –0.60	< .0001
Mood	–1.28 (0.30)	–1.87 to –0.69	< .0001
Walking ability	–0.90 (0.26)	–1.41 to –0.38	.0007
Normal walk	–1.20 (0.28)	–1.76 to –0.65	< .0001
Relations with people	–1.05 (0.28)	–1.59 to –0.50	.0002
Sleep	–1.02 (0.30)	–1.61 to –0.43	.0007
Enjoyment of life	–1.32 (0.31)	–1.93 to –0.70	< .0001

[a]Adjusted for baseline and investigation site.

was significant (p ≤ .001), indicating that duloxetine patients achieved sustained response for the BPI-SF average pain score faster than placebo patients. The time to reach a sustained responder rate of 50% of patients was 43 days in the duloxetine group and more than 56 days in the placebo group.

Response rates in average pain reduction were significantly higher for patients treated with duloxetine than for patients treated with placebo at week 8 (60.3% versus 44.0%, p = .0045).

In the BPI-SF interference scale after 8 weeks of treatment, duloxetine was significantly (p ≤ .0001) better than placebo in improving daily functioning affected by pain (Figure 1). Furthermore, duloxetine significantly reduced pain interference on functioning versus placebo on all 7 items of the BPI-SF interference (Table 2).

Depression. Treatment with duloxetine resulted in a significant reduction in depression severity after 8 weeks of treatment compared with placebo, as measured by the mean change in MADRS total score (–16.69 vs. –11.31, p ≤ .0001). A time-course analysis of the MADRS total score is shown in Figure 4; the treatment-by-time interaction was highly significant (p = .0001). Starting from week 2, duloxetine separation from placebo was significant (p < .05) at all time points to the endpoint. The results remained significant when LOCF was used.

Response rates after short-term treatment of depression for 8 weeks were significantly higher for patients treated with duloxetine compared with patients treated with placebo (55.1% vs. 35.2%, p < .005).

At week 8, 52.6% and 28.9% of the patients in duloxetine and placebo groups, respectively, reached remission criteria (MADRS total score ≤ 12, p ≤ .001). Similarly, with post hoc, more stringent definitions of remission using MADRS total score of 10 or less and of 8 or less, more patients in the duloxetine treatment group (44.2% and 36.5%, respectively) remitted compared with the placebo group (21.4% and 15.7%, respectively).

The time to sustained depression response was examined by Kaplan-Meier survival analysis with a log-rank

right now (p = .0004) categories as assessed by maximum likelihood-based mixed-effects repeated-measures analysis (Figure 1). The tests of the treatment-by-time interaction resulted in significant results in favor of duloxetine for all 3 pain categories including worst pain (p = .0048), least pain (p = .0054), and pain right now (p = .0264).

The BPI-SF average pain was assessed as a function of time on a weekly basis (Figure 2). Duloxetine treatment effect separated from placebo as early as week 1 with significant (p ≤ .05) differences between the treatment groups at the 1-, 4-, and 8-week time points (Figure 2). The baseline-to-endpoint analysis on the BPI-SF pain items remained significant when LOCF was used.

The time to sustained pain response as examined by Kaplan-Meier survival analysis is shown in Figure 3. The log rank between the duloxetine and placebo treatments

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Figure 4. Time-Course Analysis of Montgomery-Asberg Depression Rating Scale (MADRS) Total Score in Patients Treated With Duloxetine or Placebo for 8 Weeks[a]
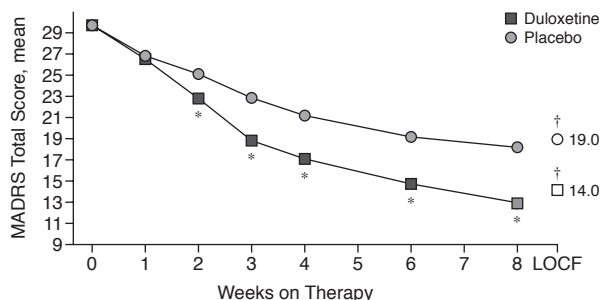
[a]Maximum likelihood-based mixed-effects repeated-measures analysis (full analysis set, observed cases).
*p < .05 for placebo versus duloxetine.
†p < .05 at week 8 for the change from baseline for both placebo and duloxetine in the last-observation-carried-forward analysis (LOCF).

Figure 5. Median Time to Sustained Response as Estimated by Kaplan-Meier Survival With Log-Rank Test for Montgomery-Asberg Depression Rating Scale Total Score
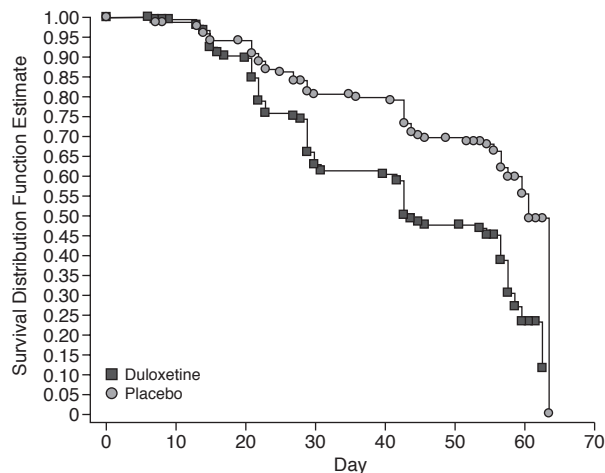
test for the treatment group differences (Figure 5). The time required to reach a sustained responder rate of 25% of patients (first quartile corresponding to a nonresponder rate of 75%) was 26 days for duloxetine and 43 days for placebo; the p value for the log-rank test was < .0001.

The time to sustained remission was estimated using the Kaplan-Meier survival curves with a log-rank test (Figure 6). The time course of treatment effect showed a significant log-rank p value (< .0001) favoring duloxetine. A separation of duloxetine treatment from placebo occurred from day 20 as shown in Kaplan-Meier curves (Figure 6).

Other outcomes. Disease severity was further assessed by the investigator using the CGI-S and analyzed by Cochran-Mantel-Haenszel test at week 8. Of patients in

Figure 6. Median Time to Sustained Remission as Estimated by Kaplan-Meier Survival With Log-Rank Test for Montgomery-Asberg Depression Rating Scale Total Score
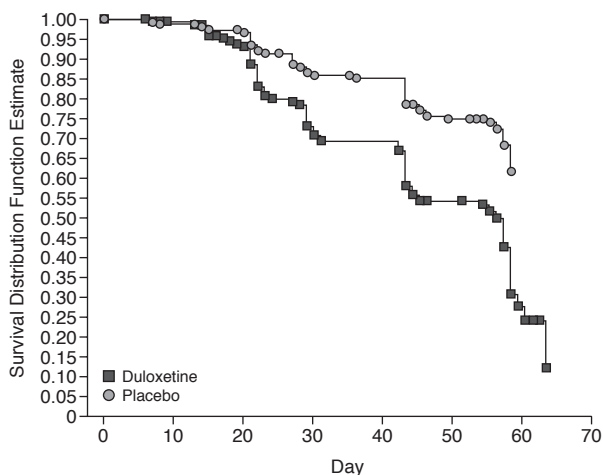
the duloxetine treatment group, 46.1% were rated as normal (scoring 1 or 2 on the CGI-S) compared with 27.7% in the placebo group (p ≤ .001). Only 3.9% and 6.9% in the duloxetine and placebo groups, respectively, were severely ill at week 8. Also at week 8, a significant difference in CGI-I in favor of duloxetine was found (p = .002); 62.6% in the duloxetine group and 42.1% in the placebo group improved (scoring 1 or 2) in the opinion of the investigator, and less than 1.3% in the placebo group and 2.6% in the duloxetine group were severely ill (scoring 6 or 7) at week 8. At week 8, 51.3% of patients in the duloxetine group compared with 31.4% of patients in placebo group improved on the PGI-I scale (scoring 1 or 2, p ≤ .05). The percentages of patients with a worsening condition, scoring 6 or 7 on the PGI-I, were 5.8% in the duloxetine group and 5.1% in placebo group.

Furthermore, duloxetine treatment for 8 weeks resulted in significantly better treatment effects on the SCL-90-R questionnaire. Patients treated with duloxetine scored significantly better on the general symptomatic index (p = .0008) and on the somatic subdomain of the SCL-90-R (p = .0011) (Table 3).

Tolerability and Safety

Of the 327 randomly assigned patients, treatment-emergent adverse events were more frequently reported during the treatment period (excluding the tapering phase) by patients receiving duloxetine compared with placebo. Ninety of 162 patients (55.6%) in the duloxetine group as compared to 75 of 165 patients (45.5%) in the placebo group reported at least 1 treatment-emergent adverse event. The most frequent treatment-emergent adverse events with an incidence of 2% or greater in any treatment group are listed in Table 4. Nausea, hyperhidrosis, and dry

Table 3. Mean Changes From Baseline to Endpoint in Symptom Check List-90-Revised (SCL-90-R) for Somatic Average Score (SAS) and General Symptomatic Index (GSI) in Patients Treated With Duloxetine or Placebo for 8 Weeks

	Duloxetine		Placebo		Difference From Placebo[a]		
SCL-90-R	N	Mean (SE)	N	Mean (SE)	Mean (SE)	95% CI	p Value[b]
SAS	155	−0.74 (0.06)	151	−0.50 (0.06)	−0.25 (0.08)	(−0.40 to −0.10)	.0011
GSI	149	−0.65 (0.04)	143	−0.45 (0.05)	−0.21 (0.06)	(−0.33 to −0.09)	.0008

[a]Adjusted for baseline and country.
[b]p Value for the treatment-group difference from placebo at week 8.

Table 4. Most Frequent (> 2% in any group) Treatment-Emergent Adverse Events in Patients Treated With Duloxetine or Placebo for 8 Weeks

Adverse Event	Duloxetine (N = 162), N (%)	Placebo (N = 165), N (%)
Nausea	40 (24.7)	13 (7.9)
Hyperhidrosis	19 (11.7)	4 (2.4)
Dry mouth	17 (10.5)	6 (3.6)
Fatigue	13 (8.0)	3 (1.8)
Headache	12 (7.4)	15 (9.1)
Nasopharyngitis	10 (6.2)	9 (5.5)
Dizziness	9 (5.6)	6 (3.6)
Constipation	9 (5.6)	2 (1.2)
Diarrhea	7 (4.3)	3 (1.8)
Vomiting	7 (4.3)	2 (1.2)
Insomnia	6 (3.7)	3 (1.8)
Influenza	4 (2.5)	2 (1.2)
Vertigo	4 (2.5)	4 (2.4)
Stomach discomfort	4 (2.5)	1 (0.6)

mouth were the most frequently reported treatment-emergent adverse events (> 10%) in patients treated with duloxetine.

During the treatment period, 10.5% of patients in duloxetine group and 5.5% of patients in the placebo group discontinued from the study due to adverse events (p = .094). Depression (N = 2, 1.2%), diarrhea (N = 2, 1.2%), and nausea (N = 2, 1.2%) were the most frequent reasons for discontinuation in patients treated with duloxetine. Depression (N = 3, 1.8%), diarrhea (N = 2, 1.2%), and nausea (N = 2, 1.2%) were the most frequent reasons for discontinuation in placebo group. No patient died during this study. Three patients in the duloxetine group had serious adverse events during this study, including car accident, knife cut, and worsening of depression, none of which were considered drug-related. All 3 patients recovered from the events.

With regard to vital signs during this study, small mean increases of pulse rate (2–3 bpm) were observed in the duloxetine group. One patient in placebo group and 6 patients in duloxetine group had increases of pulse rate of greater than 10 bpm from baseline. No clinically relevant mean changes were observed in blood pressure. While there were some differences between duloxetine and placebo in laboratory evaluations, none of these were considered clinically relevant.

DISCUSSION

Summary of Findings

In the current study, duloxetine was compared with placebo in the treatment of patients with major depressive disorder and associated pain of at least moderate severity. The primary outcome measure was relief of pain based on the understanding that both 5-HT and norepinephrine neurotransmitters are involved in pain modulation. The data demonstrated that duloxetine 60 mg once daily was significantly superior to placebo in reducing BPI-SF average pain after 8 weeks of treatment. Furthermore, duloxetine was effective on other important pain measures, including the BPI-SF interference score addressing impairment of daily functioning by pain, and in producing a response to pain treatment, as defined by a decrease of 30% or greater from the baseline pain severity. Duloxetine also reduced the depressive symptom severity significantly in comparison with placebo, resulting in significantly higher response and remission rates as measured by the MADRS. Better overall improvement with duloxetine was observed by investigators and patients as assessed by CGI-I and PGI-I scores. Duloxetine improved the general health symptoms in psychiatric patients as assessed by the SCL-90-R and the somatic symptoms subdomain. Duloxetine was safe and well tolerated during this study of short-term depression treatment.

Pain

The association of pain with depression and its clinical relevance has been described in the recent literature.[1,2,37] The current study is one of the few placebo-controlled studies with the primary focus on pain in patients with depression and associated pain.[22,38,39] The current study has used 3 methodological approaches to investigate pain symptoms associated with depression in the absence of accepted diagnostic criteria or a definition: (1) excluding patients with a diagnosed organic pain syndrome, but requiring at least moderate pain severity at baseline, (2) selecting patients with at least 1 previous episode of depression, and (3) a confirmed diagnosis of major depressive episode using a structured diagnostic interview.

The baseline severity of average pain was surprisingly high (close to 6 out of a range from 0 to 10 on an 11-point

Likert scale) and clinically relevant. These baseline values are comparable to patient populations studied with pain due to diabetic peripheral neuropathy.[40,41] Duloxetine significantly reduced all BPI-SF pain measures compared with placebo including average pain, worst pain, least pain, and pain right now. The magnitude of pain reduction with duloxetine treatment in this pain-burdened patient population is comparable to that seen in studies of duloxetine in diabetic peripheral neuropathic pain[41,42] and similar to other drugs with analgesic properties, such as pregabalin,[43] oxycodone,[44] or tramadol,[45] studied in pain conditions. The mean average pain score after 8 weeks of duloxetine treatment was close to 3 on the BPI-SF average pain measure and can be considered as mild compared to moderate or higher level at baseline. A 30% reduction in pain severity is reported to be clinically significant[46] and the almost 50% reduction at endpoint in the mean BPI-SF average pain in patients treated with duloxetine in this study is therefore highly clinically relevant. In addition, a clinically relevant and significantly shorter period of 26 days for pain response to duloxetine treatment was observed as compared with 43 days in the placebo group. Considering the extent of suffering of patients with moderate pain in depression, the significant reduction of the BPI-SF interference scale and in all of the 7 items of health outcomes is important. The SCL-90-R was used to better understand the psychological distress of patients with depression and pain. For example, a patient treated in this study might have felt relief from unspecific musculoskeletal pain but also might experience some seasonal headache or gastrointestinal side effects resulting in a minimal net change in experiencing average pain. Duloxetine reduced the SCL-90-R general score and the somatic subdomain score indicating improvement in the health outcome–related symptom clusters.

Depression

In this study, pain and depression have been assessed with almost exclusive scales. The MADRS scale was chosen to assess core symptoms of depression without focusing on physical complaints. A baseline score of 30 on the MADRS scale represents moderate to moderately severe depression, and in this study, the baseline values were 29.9 and 29.2 in the duloxetine and placebo groups, respectively. Duloxetine treatment separated significantly from placebo as early as week 2 on the MADRS scale, and the difference between the treatments continued to grow wider until the end of treatment at week 8. The efficacy and onset of action of duloxetine in this pain-burdened patient population with depression is very similar to previous studies investigating patients with depression irrespective of pain using the 17-item Hamilton Rating Scale for Depression.[47] In the current study, patients were treated with duloxetine 30 mg once daily during the first week of treatment, and the findings showed that in the

first week, duloxetine did not separate from placebo. After 8 weeks of duloxetine 60 mg once daily treatment, a mean difference of 5.4 in MADRS total score was observed between duloxetine and placebo, which is comparable to the efficacy of duloxetine in patients with depression but without associated pain.[20,48] The relevance of changes in MADRS total score in duloxetine-treated patients is corroborated by significant changes in the CGI-S and by improvement of overall health and disease status.

Duloxetine treatment resulted in significantly higher response and remission rates. More conservative definitions of remission with a MADRS score of 10 or less and of 8 or less were used in post hoc analyses, and the remission rates remained significantly higher in duloxetine treatment compared with placebo. The improvement toward remission is further supported by a significant separation of PGI-I scores with duloxetine treatment compared with placebo. Another clinically important aspect of this study was the assessment of the time to achieve sustained remission in the 2 treatment arms (43 days for duloxetine and > 56 days for placebo). After 20 days, the survival curves separated. The faster onset of action in the active treatment arm is accompanied by a faster attainment of clinically relevant improvement.

Depression and Pain

Different retrospective[4,11,37,49] or prospective[22,38,50] approaches have tried to describe or unravel the relationship between pain and depression. Of clinical importance is the question of whether depression is a consequence of pain or vice versa, or if pain is an independent symptom of depression. What can be learned from this study? (1) Patients with nonspecific pain of at least moderate severity associated with depression do exist and have been studied here. The requirement of at least 1 previous episode of MDD in the medical history and the exclusion of pain related to a diagnosed organic pain syndrome were our approach to identify this patient population. Thereby, we aimed to exclude chronic pain patients with some symptoms of depression. (2) The time course of reduction of depressive symptoms (MADRS) and pain (BPI-SF average pain), as well as the time to sustained improvement (response and remission), does not suggest that relief of pain is a consequence of treating depression. (3) Duloxetine, a dual reuptake inhibitor of 5-HT and norepinephrine, treats both (mood and pain) symptom domains better than placebo. All 3 arguments provide additional support for a common neurobiological pathway involving disturbances in 5-HT and norepinephrine in both disease entities, which has been suggested since the introduction of tricyclic antidepressants in clinical practice.[51] Of importance, in patients with diabetic peripheral neuropathic pain, duloxetine did not change electrophysiologic ulnar and peroneal nerve conduction velocity, a finding that

argues against duloxetine's effect on the peripheral sensory nervous system.[40]

Tolerability and Safety

Overall, tolerability and safety of duloxetine in this study was similar to many other published short-term and long-term duloxetine studies.[42,47,48,52,53] The completion rates, the rates for early discontinuation due to adverse events, and the serious and nonserious adverse event frequency and profile were all within the expected range. This was the first fixed-dose study treating all patients randomly assigned to duloxetine for the first week with 30 mg once daily and 60 mg once daily thereafter. Nausea was the most frequently reported treatment-emergent adverse event in duloxetine-treated patients. The reporting frequency of 24.7% appears to be lower than the rate reported in studies in which patients were treated with 60 mg once daily,[22,47,52] but is comparable to the overall nausea rate across duloxetine studies.[54] If a lower starting dose (such as 30 mg once daily for better tolerability) is considered, a delay in efficacy[55] must be considered. However, recent data suggest that taking duloxetine 60 mg with food decreases the nausea rate.[56] Vital signs and laboratory values did not reveal any new findings in this study.

Limitations

Results from this study must be seen within the limitations of the design. (1) To show a treatment effect with pain as the primary endpoint, patients with a predefined pain threshold and depression were selected, which might be seen as an unusual way to study outcome in depression and also may introduce a selection bias. (2) The inclusion and exclusion criteria used may have allowed for the inclusion of some patients with an undiagnosed pain syndrome. (3) Currently, there is no better instrument to address pain symptoms in depression than a "classical" depression scale and a pain scale originally validated for severe organic pain syndromes. Therefore, average pain is not able to unravel the relation of depression and pain, and the disease pattern of "pain associated with depression" does not allow causal conclusions. (4) This was a short-term treatment study; as such, long-term data in such a patient population with depression and pain are missing. (5) No active comparator was included in this study. (6) The fixed-drug dose design might not necessarily reflect the typical clinical setting and might obscure the full potential of the treatment.

CONCLUSION

The results of this study further support the efficacy and tolerability of duloxetine in the treatment of both pain and depression in patients with at least moderate pain associated with depression.

Drug names: duloxetine (Cymbalta), oxycodone (Oxycontin, Roxicodone, and others), pregabalin (Lyrica), tramadol (Ultram and others), venlafaxine (Effexor and others).

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