Efficacy of Duloxetine on Painful Physical Symptoms in Major Depressive Disorder for Patients With Clinically Significant Painful Physical Symptoms at Baseline: A Meta-Analysis of 11 Double-Blind, Placebo-Controlled Clinical Trials

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ABSTRACT

Objective: To review efficacy of duloxetine for physical symptoms and depressive illness in patients with at least mild to moderate major depressive disorder (MDD; *DSM-IV*) and clinically significant painful physical symptoms at baseline.

Data Sources: Global database of duloxetine clinical trials (Eli Lilly and Company).

Study Selection: All 11 acute, double-blind, placebo-controlled studies of duloxetine (7 with duloxetine 60-mg doses and 4 with non–60-mg doses) in the database that used a scale to measure painful physical symptoms and were completed before March 17, 2011.

Data Extraction: For each study, patients with clinically significant pain levels at baseline (Visual Analog Scale overall pain rating ≥ 30, Numerical Rating Scale score ≥ 3, or Brief Pain Inventory 24-hour average pain rating ≥ 3) were selected in order to determine the effect sizes of duloxetine (compared with placebo for each trial) on the pain and depression measures. Overall effect sizes for both painful physical symptoms and MDD were obtained from the mean of individual-trial effect sizes, and each effect size was weighted relative to the number of patients within each study.

Data Synthesis: The overall mean effect sizes were as follows: painful physical symptoms—60-mg trials, 0.29 (95% CI, 0.06 to 0.52); non–60-mg trials, 0.13 (95% CI, –0.19 to 0.45); MDD—60-mg trials, 0.29 (95% CI, 0.18 to 0.40); non–60-mg trials, 0.16 (95% CI, 0.00 to 0.32). Across the 11 studies, the weighted effect size for painful physical symptoms was 0.26 (95% CI, 0.00 to 0.51) and for MDD, 0.25 (95% CI, 0.16 to 0.34).

Conclusions: According to this meta-analysis, duloxetine 60 mg once daily is as effective in improving painful physical symptoms as it is for depression in patients with MDD and clinically significant painful physical symptoms. The results of this meta-analysis indicate that duloxetine has small effect sizes in reducing painful physical symptoms and depressive symptoms in patients with MDD and clinically significant pain levels at baseline. Thus, the results of the study permit one to conclude that duloxetine has a clinically significant impact on painful physical symptoms and in reducing the severity of depressive symptoms. However, the results do not address its efficacy compared to other alternatives, as in all studies the comparator was placebo.

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Although the diagnosis of major depressive disorder (MDD) is based on a number of core symptoms, painful physical symptoms are increasingly recognized as frequently associated symptoms that have clinical relevance for the patient's outcome.[1] 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%.[2] In the Re-Engineering Systems for Primary Care Treatment of Depression (RESPECT) study, 405 patients with depression were followed in primary care settings while receiving either treatment as usual or enhanced intervention.[3] At baseline, painful physical symptoms of sufficient severity to impact daily activities, at least moderately, were present in 42% of the patients. Although there was some improvement in pain, the degree of severity was at least moderate for 32% of the patients at 6 months, and the severity of pain negatively impacted both response and remission rates with treatment.[3] Similarly, Leuchter and colleagues[4] found that, among patients in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, 80% of patients reported having painful physical symptoms, and these symptoms were associated with lower remission rates and with longer time to remission. However, in the STAR*D trial, painful physical symptoms were no longer predictive of depression outcomes after adjustment for race, medical comorbidity, and severity of depression.[4] Other studies have demonstrated a negative impact of painful physical symptoms on outcome measures such as increase in treatment costs,[5] decrease in productivity,[6] and poor quality of life.[7] Thus, painful physical symptoms associated with depression present an important target for therapeutic intervention.

The neurobiological pathways underlying depression and pain suggest commonalities in the activity of serotonin and norepinephrine transmission.[8] Duloxetine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) that has demonstrated both antidepressant and analgesic efficacy within different conditions including MDD, fibromyalgia, diabetic peripheral neuropathic pain, osteoarthritis, and chronic low back pain.[9] With regard to studies of MDD, duloxetine showed an analgesic effect on painful physical symptoms that was partially independent of the improvement in MDD.[10,11] In a pooled analysis of 2 identical studies, duloxetine 60 mg once daily significantly improved painful physical symptoms compared with placebo treatment.[11] Other pooled analyses of duloxetine trials also indicated efficacy on painful physical symptoms associated with MDD, suggesting analgesic activity.[12,13] Duloxetine's efficacy was demonstrated on painful physical symptoms in elderly patients with MDD[14] and in patients with MDD with at least moderate pain.[15] However,

Clinical Points

- Many patients with depression also experience painful physical symptoms.
- In patients with painful physical symptoms, duloxetine 60 mg once daily had a clinically significant impact on those symptoms and in reducing the severity of depressive symptoms.

there have also been other analyses that have questioned whether duloxetine does effectively reduce painful physical symptoms associated with depression. One meta-analysis of duloxetine trials, based on 5 studies, did not support the analgesic efficacy for painful physical symptoms in MDD.[16] Another meta-analysis, based on 8 studies, compared duloxetine, paroxetine, or both with placebo in patients with MDD.[17] Results of that meta-analysis of pain outcomes from those trials suggested that both duloxetine and paroxetine significantly improved painful physical symptoms compared with placebo, but there was not a significant difference between paroxetine and duloxetine.

Given the heterogeneity of the above analyses with regard to studies and outcomes, and the differences in analytic methods used to evaluate the efficacy of painful physical symptoms associated with MDD, the current meta-analysis was undertaken to examine the efficacy of duloxetine for both painful physical symptoms and depressive illness based on the Eli Lilly and Company global database of duloxetine clinical trials, with 11 double-blind, placebo-controlled studies selected for the analyses. Because the majority of these studies were not designed to specifically address painful physical symptoms, patients with MDD in these studies were generally not required to have these symptoms at baseline, which would necessarily limit conclusions about efficacy for painful physical symptoms in the absence of the symptoms. Therefore, the present meta-analysis also specifically examined the efficacy of duloxetine for painful physical symptoms in patients with MDD who had clinically significant painful physical symptoms at baseline.

METHOD

Trials

The 11 clinical trials used in this individual trial–level meta-analysis are listed in Table 1 along with the study codes, citations, and clinical trial registry information (if available). The dosing groups examined included duloxetine 40 mg (20 mg twice daily), 60 mg once daily, 80 mg (40 mg twice daily), and 120 mg (60 mg twice daily). For convenience and clarity, hereafter, total daily doses will be expressed throughout the article. All studies were randomized, double-blind, and placebo-controlled, with a duration of 8 to 12 weeks for the acute therapy. Baseline demographic and clinical characteristics of the patients in each trial were described in the respective publications listed in Table 1. These 11 studies were selected as they each used a scale to measure painful physical symptoms. The cutoff to include these studies in this meta-analysis was its first submission date of March 17, 2011. As such, the unpublished data from 2 other recently concluded studies (HMGR and HMGU) were not included.

Table 1. Duloxetine Clinical Trials and Pain Measures Used in the Effect Size Analysis[a]

Study Code[b]	Pain Measure	Reference and ClinicalTrials.gov Identifier (if available)
60-mg/d dose		
HMBH-A	VAS	Detke et al[18]
HMBH-B	VAS	Detke et al[19]
HMBV	VAS	Raskin et al,[14] NCT00062673
HMCB	BPI	Brannan et al,[20] NCT00036335
HMDH	BPI	Brecht et al,[15] NCT00191919
HMFS-A	NRS	NCT00536471
HMFS-B		
Non–60-mg/d dose[c]		
HMAT-A	VAS	Nemeroff et al[21] and Mallinckrodt et al[12]
HMAT-B	VAS	Goldstein et al[22]
HMAY-A	VAS	Detke et al[23]
HMAY-B	VAS	Perahia et al[24]

[a]For major depressive disorder effect sizes, the 17-item Hamilton Depression Rating Scale total score was used.
[b]These are the company study codes.
[c]Doses include 40 mg/d, 80 mg/d, and 120 mg/d.
Abbreviations: BPI = Brief Pain Inventory, NRS = Numerical Rating Scale, VAS = Visual Analog Scale.

Patients

The entry criteria were similar across all the studies. Study participants were outpatients, including men and women at least 18 years of age who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[25] criteria for MDD. Patients must have signed an informed consent form prior to participating in the respective study. To be eligible for enrollment, patients must have scored ≥ 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S)[26] and had a total score of at least ≥ 15 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[27] or a total score of ≥ 20 on the Montgomery-Asberg Depression Rating Scale (MADRS)[28] when appropriate. In addition, for studies HMDH and HMCB, patients were required to have pain ratings of at least mild to moderate on the average pain item of the Brief Pain Inventory[29] (BPI; score of ≥ 2 in HMCB; ≥ 3 in HMDH). Exclusion criteria included the following: primary Axis I disorder (other than major depression), an Axis II disorder that could interfere with study compliance, treatment-resistant depression, serious medical illness, substance abuse or dependence within the prior year or positive drug screen test, and current use of central nervous system medication.

Measures

Overall pain was assessed using different tools, including a Visual Analog Scale (VAS) for overall pain, BPI average pain severity, and a Numerical Rating Scale (NRS) for average pain. For the current effect size analysis, only the subset of patients from each of the trials that met the threshold for

clinically significant pain were included for both analyses of painful physical symptoms and MDD. For each study, patients with clinically significant levels of pain at baseline (a VAS overall pain rating ≥ 30, an NRS score ≥ 3, or a BPI 24-hour average pain rating ≥ 3) were selected to determine the individual trial effect sizes on the pain outcome measure. For MDD assessment, $HDRS_{17}$ total score was used in all studies with the exception of study HMDH, in which MADRS total score was used.

Analysis of Effect Size

The effect sizes for change in pain and depression scales were determined using the Glass estimation methods.[30,31] Briefly, least squares means and standard errors for main effect of treatment (each individual dose of duloxetine vs placebo) were calculated using the mixed-model repeated-measures (MMRM) analysis method. An unstructured covariance structure was used to model the within-patient errors. Kenward-Roger correction[32] was used to estimate denominator degrees of freedom. In the MMRM analysis, the model included the fixed categorical effects of treatment, pooled investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of the baseline value of the variable being analyzed and baseline value of the variable being analyzed–by-visit interaction. The baseline value of the variable being analyzed and the baseline-by-visit interaction are included to account for the differing influence over time of the baseline score on the postbaseline scores.

Effect size of each duloxetine dose compared with placebo for each individual study and weighted effect size from several studies were calculated using least squares means and standard deviations for main effect of treatment.[30] Effect size for each individual study was calculated as the difference in least squares mean change between the duloxetine group (each dose group) and the placebo group divided by the standard deviation and effect size:

$$\sigma = \frac{m_1 - m_2}{S}$$

where m_1 and m_2 are the least squares means and S is the standard deviation from the MMRM analysis. Hedges[33] showed that if both the experimental and the control population distributions are normal and N_1 and N_2 are moderate to large (at least equal to 10), the sampling distribution of effect size is approximately normal under null hypothesis with the mean of zero and variance of

$$\sigma^2 = \frac{N_1 + N_2}{N_1 N_2} + \frac{\sigma^2}{2\,(N_1 + N_2)}$$

To estimate the effect size for pooled duloxetine doses across different studies, a meta-analysis approach was applied.[34] In this approach, the weighted effect size is computed as a weighted mean of the effect sizes from all studies. The weight for each study is equal to the precision, which is the inverse of the variance of the effect size for each study divided by the sum of the inverse of the variance of effect size for each study. It is shown that the asymptotic variance of this pooled effect size is 1/(sum of [1/variance of effect size of each study]).

An estimated 95% confidence interval (CI) for the effect size and weighted effect size was created using these estimators and the critical values from a standard normal distribution. If the lower bound of 95% of the effect size is greater than zero, it indicates that duloxetine is statistically significantly superior to placebo. The approach described here for calculating weighted effect size across studies is a fixed-effect meta-analysis approach, where we assume that the true effects investigated in the set of studies are regarded as the effects of interests that may not be generalized to the larger population.

RESULTS

Trial Characteristics

The 11 selected clinical trials were conducted by Eli Lilly and Company, Indianapolis, Indiana, and/or Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany. All were placebo-controlled, double-blind, multicenter studies investigating the efficacy of duloxetine for the treatment of MDD with treatment duration of 8 to 12 weeks. All of the studies (except HMDH) used $HDRS_{17}$ total score as the primary endpoint for assessing MDD. In study HMDH, MADRS total score was the primary endpoint for measuring MDD. Except in studies HMDH and HMCB, the patients were not required to have clinically significant pain as an entry criterion at baseline. Most of these studies were disclosed and/or registered on ClinicalTrials.gov (Table 1). Additional details of the trials and patients can be found in the publications and clinical trials registry links listed in Table 1.

Frequency of Clinically Significant Painful Physical Symptoms

The proportions of patients with clinically significant painful physical symptoms at baseline in these trials are presented in Table 2. For trials that used the VAS measure, the proportions of patients ranged from 29% to 55% with ≤ 7% difference between duloxetine and placebo groups in these 7 trials. In the 2 trials that used BPI average pain measure, and in the 1 trial that used NRS, frequency of pain was much higher than that in the trials that used VAS, ranging between 70% and 96% (Table 2). However, because the 2 trials that used the BPI required patients to have a BPI score ≥ 2 or ≥ 3 at baseline, these higher rates are not unexpected.

Effect Size by Individual and Pooled Trials

Analyses of the effect sizes (95% CI), or the treatment effectiveness, of duloxetine in each trial in comparison with placebo (for both painful physical symptoms and depression outcomes) are presented in Figure 1. For convenience, identical trials with the same protocol (such as studies HMBH-A and HMBH-B) were pooled. As shown in Figure 1, individually, most of the studies had effect sizes significantly different from zero, ranging from 0.21 to 0.44 for painful physical symptoms and 0.20 to 0.47 for depression. The

Table 2. Frequency of Clinically Significant Painful Physical Symptoms in Clinical Trials by Treatment and Dose[a]

Frequency-of-Pain Measure and Study Code[b]	Treatment and Dose	n/N	%
VAS overall pain rating ≥ 30			
HMBH-A and HMBH-B	Duloxetine 60 mg/d	91/249	37
	Placebo	92/254	36
HMAT-A and HMAT-B	Duloxetine 40 mg/d	64/172	37
	Duloxetine 80 mg/d	57/166	34
	Placebo	51/175	29
HMAY-A and HMAY-B	Duloxetine 80 mg/d	101/185	55
	Duloxetine 120 mg/d	97/195	50
	Placebo	92/192	48
HMBV	Duloxetine 60 mg/d	90/207	43
	Placebo	48/104	46
BPI 24-hour average pain item ≥ 3			
HMCB	Duloxetine 60 mg/d	103/141	73
	Placebo	107/141	76
HMDH[c]	Duloxetine 60 mg/d	152/162	94
	Placebo	159/165	96
NRS score ≥ 3			
HMFS-A and HMFS-B	Duloxetine 60 mg/d	348/500	70
	Placebo	176/247	71

[a]For major depressive disorder effect sizes, the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score was used.
[b]These are the company study codes.
[c]This is the only study that required that all patients have clinically significant pain at baseline. All patients included in the analysis had clinically significant pain at baseline and had nonmissing baseline and postbaseline measures for $HDRS_{17}$ total score or MADRS total score; patient numbers differ from the overall N due to exclusion of randomized patients without postbaseline values.
Abbreviations: BPI = Brief Pain Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, NRS = Numerical Rating Scale, VAS = Visual Analog Scale.

pooled weighted effect size for all duloxetine doses was significant for efficacy in MDD (Figure 1). Although the pooled weighted effect size for efficacy of duloxetine across all doses on painful physical symptoms associated with MDD was not significant, it was closer to significance with a lower bound of 95% CI equal to −0.002 (Figure 1); this observed effect size was similar in magnitude to that of depression.

Effect Size by Dose

Because the doses varied across trials, a meta-analysis was also undertaken to examine the effect sizes based on dose. Figure 2 presents the results of the effectiveness of duloxetine in comparison with placebo by dose across multiple studies as assessed by pooled effect sizes (95% CIs). The dose showing the greatest effect size was 60 mg/d. The overall weighted effect sizes for the duloxetine 60-mg dose for painful physical symptoms and depression were similar (0.29) and both were statistically significant, whereas the overall weighted effect size for non–60-mg doses of duloxetine for painful physical symptoms (0.13) was slightly lower than that for depression (0.16).

DISCUSSION

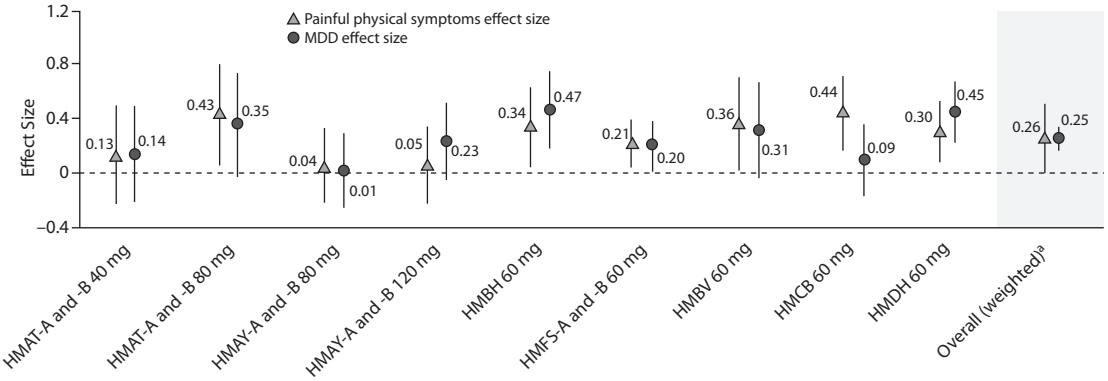
In this trial-level meta-analysis of 11 placebo-controlled trials, patients who had mild or moderate baseline painful physical symptoms associated with MDD demonstrated a clinically meaningful reduction as assessed by effect size in both depression symptoms and painful physical symptoms. Similar findings were reported earlier in the pooled analyses of similarly designed placebo-controlled duloxetine trials.[11,21] The effect sizes for both painful physical symptoms and MDD were similar for most trials. The weighted effect sizes for overall studies were 0.26 for painful physical symptoms and 0.25 for MDD, suggesting that duloxetine is equally effective on both painful physical symptoms and MDD.

This finding is different from the meta-analysis results reported by Spielmans,[16] as described earlier in this article. In the meta-analysis by Spielmans, only 5 studies were used (HMBH-A, HMBH-B, HMAT-A, HMAT-B, and HMCB). In addition to these 5 studies, 6 more studies were included in the current analysis. Spielmans' analysis included the patients with or without clinically significant painful physical symptoms at baseline from Eli Lilly's online database. Data on painful physical symptoms published in Eli Lilly's online database included all randomized patients with baseline and nonmissing postbaseline measures of painful physical symptoms; for studies HMBH-A, HMBH-B, HMAT-A, and HMAT-B, the VAS results from both analysis of covariance (ANCOVA) with the last observation carried forward (LOCF) and MMRM at endpoint were presented. In study HMCB, the BPI results from MMRM at endpoint were presented. The meta-analysis by Spielmans[16] does not clearly state whether the LOCF or MMRM results from the first 4 studies were used for calculating the effect size. However, in the present analysis, we had selected the subset of patients with clinically significant painful physical symptoms at baseline, and we also used the MMRM analysis method. The MMRM method has been recognized in the literature as a method with key theoretical advantages over LOCF.[35–39] The LOCF method imputes the endpoint using the last nonmissing observation, thus assuming that the last nonmissing observation will remain unchanged up to study endpoint; MMRM uses all the data across all the time points and extrapolates the information from observed data to infer the missing data mechanism. Based on the research conducted by Siddiqui et al,[35] the MMRM analysis appears to be a superior approach in controlling Type I error rates and minimizing biases, as compared with the LOCF ANCOVA analysis. In addition, within our MMRM analysis method, the results were summarized using the main effect of treatment averaged across all the time points, instead of using the treatment effect at the last visit.

Main effect of treatment was deemed most appropriate because it evaluates the overall treatment effect across all time points. In addition, pain improvement is often characterized by rapid onset, with drug versus placebo differences remaining fairly constant over the course of treatment.

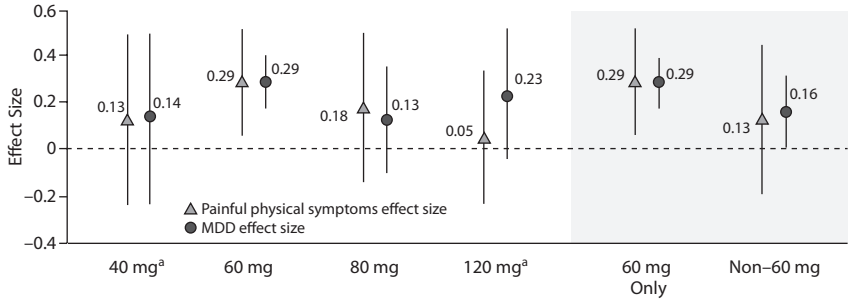
In the current meta-analysis, the effect sizes did not follow a pattern of dose-response in the efficacy of duloxetine on either painful physical symptoms or MDD. However, there was a greater increase in effect sizes from 40 mg/d to 60 mg/d followed by decrease at 80 mg/d or 120 mg/d. The lack of a

Figure 1. Effect Size Summary With 95% Confidence Intervals for Painful Physical Symptoms and Major Depressive Disorder (MDD) in Patients With Mild to Moderate MDD and Clinically Significant Painful Physical Symptoms



[a]All other effect sizes shown are nonweighted.

Figure 2. Summary of Weighted Effect Sizes With 95% Confidence Intervals by Dose for Painful Physical Symptoms and Major Depressive Disorder (MDD) in Patients With Mild to Moderate MDD and Clinically Significant Painful Physical Symptoms



[a]Effect size is based on only 1 study dose arm in 2 studies and is unweighted.

dose-response may be due to lack of enough power at 40 mg/d, 80 mg/d, and 120 mg/d as compared with 60 mg/d because 7 of 11 studies were conducted to assess the efficacy of duloxetine 60 mg/d relative to placebo, whereas duloxetine 40 mg/d and 120 mg/d treatment were represented in only 2 studies and 80 mg/d was represented in only 4 studies. Similar findings were observed with our earlier effect-size analysis for the dose-response relationship for duloxetine efficacy in depression.[40] Antidepressants, in general, have a relatively flat dose-response relationship on improvement in depression.[41] The lack of dose-response may also be due to high variability in duloxetine pharmacokinetics, in that different dose levels may be required to maintain blood levels.[42,43] Antidepressant therapy is also challenged by high rates of placebo response in randomized controlled trials, a phenomenon that has been shown to influence the clinical outcomes.[44,45] Higher placebo response is associated with lower effect size and vice versa.[46]

In this analysis, the overall effect sizes were small for both painful physical symptoms and MDD. However, the individual study effect size was as high as 0.47, suggesting that some patients may benefit from the treatment more than other patients. In addition, the small effect size is also partly due to the fact that the sample size was reduced by the inclusion of only the subset of patients with clinically significant pain level at baseline. When describing effect sizes, we used the terminology suggested by Cohen[47] in his nontechnical guide for interpreting the clinical impact of one of the most commonly expressed types of effect size in the behavioral sciences (ie, the correlation coefficient, or *r*). Per standards used in the behavioral sciences (as described by Cohen[47]), correlation values within the 0.10 to 0.29 ranges were considered "small" effects; values from 0.30 to 0.49, "medium" effects; and correlations exceeding 0.50, "large." These definitions roughly parallel the conversion of correlation value into coefficients of determination (r^2) to represent the approximate *r* values necessary to account for 1%, 10%, and 25% of the variance of the dependent variable, respectively.[48] In a recent review of all Eli Lilly chronic pain studies, effect sizes of 0.2 to 0.6 were reported[49]; these findings are comparable with those reported in the current analysis for painful physical symptoms.

Descending serotonin and norepinephrine pathways have been suggested as modulators of pain perception, and duloxetine has demonstrated efficacy in nondepressed patients with diabetic peripheral neuropathic pain,

osteoarthritis, and chronic low back pain and in both depressed and nondepressed patients with fibromyalgia.[9] The current findings of equal efficacy as evidenced by similar effect sizes for painful physical symptoms and MDD further support the involvement of the dual-reuptake mechanism of serotonin and norepinephrine in depression and pain. However, it should be noted that a meta-analysis of 8 studies (7 studies from Eli Lilly and Company and 1 from GlaxoSmithKline) did not suggest superiority of the SNRI compared with SSRI interventions.[17] Those authors note that their meta-analysis results do not support the hypothesis that SNRIs may have special analgesic effects in addition to their antidepressant effects because of dual-reuptake inhibition. The analysis demonstrated that duloxetine was superior to placebo in treating painful physical symptoms in depression. Although paroxetine was also shown to be effective, this finding does not disprove the potential role for dual-reuptake inhibition actions in treating the painful physical symptoms associated with depression. Regardless of the mechanism, it has been postulated that improvement in both depression and pain improves treatment outcomes for patients with MDD, such as response and long-term remission.[11]

The limitations of this study include the fact that the results are based on a post hoc fixed-effect meta-analysis and thus may not be applicable to the general population. Additionally, the trials did not specifically enroll patients with pain at baseline except in 2 studies. Also, a few studies used non–60-mg doses, and thus our study is underpowered to find differences at different doses of duloxetine on painful physical symptoms. Strengths of the study include the use of the analytically appropriate MMRM method, the use of the main effect of treatment to provide estimate of effect across all time points, and the selection of patients with clinically significant painful physical symptoms at baseline that would warrant clinical intervention.

In summary, the trial-level meta-analysis results presented here further support the efficacy of duloxetine for the treatment of both depressive symptoms and painful physical symptoms associated with MDD. However, the results do not address its efficacy compared to other alternatives, as in all studies the comparator was placebo.

Drug names: duloxetine (Cymbalta), paroxetine (Paxil, Pexeva, and others).

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Potential conflicts of interest: **Drs Ball**, **Desaiah, Russell,** and **Robinson** and **Ms Zhang** are employees of Eli Lilly, and **Drs Ball** and **Desaiah** are stock shareholders in Eli Lilly. **Dr Spann** was an employee of Eli Lilly from March 2006 to March 2010. **Dr Demyttenaere** has been a consultant for, received grant/research support or honoraria from, or been on the speakers/advisory boards of AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Lundbeck, Servier, Takeda, and Wyeth.

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