

Duloxetine Does Not Relieve Painful Physical Symptoms in Depression: A Meta-Analysis

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Key Words

Duloxetine, analgesic properties · Painful physical symptoms · Depression · Advertising · Data reporting

Abstract

Background: Duloxetine inhibits both serotonin and norepinephrine reuptake and is marketed as a treatment for both the core emotional symptoms and painful physical complaints that often accompany depression. Some studies have found that duloxetine is efficacious in treating painful symptoms associated with depression but these findings have been inconsistent. Several narrative review articles have reached positive conclusions about the efficacy of duloxetine as an analgesic in depression but there has been no quantitative systematic review regarding the impact of duloxetine on pain among this population. A meta-analysis of data pertaining to duloxetine's purported analgesic effects on depressed patients was thus undertaken. **Methods:** Studies were selected through searching Medline and Cochrane Trial databases as well as examining Lilly's public clinical trial

database. A random effects model was used. **Results:** Across five trials, the results indicate a very small ($d = 0.115$) and statistically nonsignificant ($p = 0.057$) analgesic effect for duloxetine. Additionally, some of the relevant data on duloxetine's effects have not been reported fully, making it likely that the obtained results reflect an overestimate of its true impact on painful physical symptoms in depression. **Discussion:** The current analysis is based on a small number of studies; further trials may yield significant results favoring duloxetine. Based upon the currently available evidence, the marketing of duloxetine as an antidepressant with analgesic properties for people with depression does not appear to be adequately supported.

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Increasingly, researchers have noted a relationship between depression and painful physical symptoms [1–3]. The severity of pain in depressed individuals is significantly higher than the pain severity in people who are not depressed. Indeed, a recent survey suggested that patients with depression suffered from a much higher rate of chronic painful physical conditions in comparison to people without depression [4]. Additionally, pain may negatively impact depressive symptoms [5], and treatment response in depression appears inversely proportional to patients' reported pain levels [6]. Given that

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painful symptoms often relate to depression, there is a need for treatments that can alleviate both depressive and pain symptoms.

Duloxetine, a serotonin and norepinephrine reuptake inhibitor has shown efficacy in alleviating symptoms of major depressive disorder [7]. Some researchers have suggested that drugs which exhibit inhibitory effects on both serotonin and norepinephrine reuptake should impact painful physical symptoms in a more notable manner than drugs that target only one of these neurotransmitter systems [8, 9]. Thus, given duloxetine's dual inhibitor profile, it is hoped that it may possess analgesic properties in depression. Based on finding statistically significant results favoring duloxetine over placebo in a small number of trials on some pain measures (though failing to achieve significance on many other pain measures), some researchers have opined that duloxetine does indeed possess analgesic properties for depressed patients [10–12].

Duloxetine is currently marketed in line with the aforementioned reviews which concluded that it is a potent analgesic. For example, on Lilly's website devoted to duloxetine [13], one can view a brief animated presentation on the medication. One slide in the animation states 'Cymbalta [duloxetine], a selective serotonin and norepinephrine reuptake inhibitor offers relief from both the emotional and painful physical symptoms associated with depression' [14; emphasis added]. Two brief case studies are also presented on the site. One of the individuals, Chris, writes that 'After I started taking Cymbalta, I noticed almost immediately that my physical pain had diminished greatly' [15]. There are several other references to duloxetine in relation to painful symptoms of depression on the website. A direct to consumer television advertisement for duloxetine states that 'there are treatments that work on both the emotional and painful physical symptoms of depression, which is thought to be caused by an imbalance of serotonin and norepinephrine' followed by referring consumers to duloxetine's consumer website [13].

At this point, there have been only a handful of studies which have examined the impact of duloxetine on the painful physical symptoms often associated with depression. One study pooled data from three trials and concluded that duloxetine was associated with a significant decrease in painful symptoms in comparison to placebo [16]. However, this pooled analysis did not analyze data in a standardized format such as effect size; rather, it reported p values from some comparisons between duloxetine and placebo, focusing nearly exclusively on statistically significant findings, despite many comparisons at

varying time points apparently not yielding significant benefit for the medication. Thus, although the authors concluded that duloxetine is effective in reducing painful physical symptoms for depressed patients, data were not reported in such a format that could validate their claim.

Sales of duloxetine have been strong. One analyst noted that they reached 348.6 million USD in the third quarter of 2006. The analyst further stated that duloxetine 'continues to show exceptionally strong growth in 2006, and new prescription levels are currently more than 40% above late 2005 levels' [17]. Clearly, duloxetine is becoming a popularly prescribed antidepressant and it is possible that some of this popularity can be attributed to its marketing as a treatment for pain in depressed patients, yet there is no systematic data across trials to examine the purported pain-relieving properties of duloxetine in depression. Thus, the present study was conducted in order to systematically evaluate the potential analgesic effects of duloxetine in depression.

Method

Selection of Studies

Eli Lilly, manufacturer of duloxetine, has released a statement indicating that it 'discloses publicly all medical research results that are significant to patients, health care providers or payers – whether favorable or unfavorable to a Lilly product – in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products' [18]. Thus, Lilly's online trial database [19] was searched for studies in which duloxetine was used to treat depressed patients. In addition, a search of the Medline database was undertaken on October 19, 2006, using the keyword 'duloxetine'. Likewise, a search of the Cochrane Central Register of Controlled Trials was performed using duloxetine as a keyword. The Medline search yielded 336 studies, while the Cochrane search netted 91 hits, and www.lilly-trials.com yielded 12 reports. Four of the studies were available as both a journal article and from www.lillytrials.com, whereas one study was only available on www.lillytrials.com. In the four studies for which data were available both in Lilly's database and in a published journal format, the data were reported identically. There were no published studies found that did not report data in Lilly's public database. After reviewing abstracts and obtaining studies, a total of five studies were included, based upon their meeting the following criteria:

- 1 Participants must have been diagnosed with depression according to the study investigators.
- 2 Only double-blind studies were included.
- 3 Studies were published in English.
- 4 Sufficient statistical information was provided to calculate effect sizes.
- 5 Participants were aged 18 or older.
- 6 Trials which predominantly included patients due to the presence of a comorbid diagnosis (e.g. fibromyalgia) were excluded.

ed, as the present analysis was designed to assess the impact of duloxetine on symptoms of pain in depression, not in other conditions.

- 7 Studies may have included a randomized controlled design or a crossover design, provided that a sufficient washout period was provided in the crossover design to minimize discontinuation effects. No crossover trials were found in the present search; thus, only randomized controlled trials were included.
- 8 Selective reporting of data must be minimized. Trials which reported data only on measures that were statistically significant were excluded, as such reporting clearly overestimates the treatment effect by excluding data which fail to show a treatment effect. Given the small number of trials included, one trial was included in which data were clearly reported selectively, though data reporting in this trial was not limited exclusively to measures that yielded statistical significance.

Outcome Measures

Data were reported on the following measures: Visual Analogue Scales (VAS), Somatic Symptoms Inventory, and the Brief Pain Inventory. Given the variety of pain measures employed by investigators and that none of the employed measures seems related to a compellingly more valid assessment of pain than the others [20–22], the data across all pain measures in each study were pooled to create a single omnibus effect size.

Data Extraction

Two independent reviewers extracted data, which were checked for inconsistencies. No inconsistencies were noted.

Study Quality

While the design of all included studies included random assignment and double-blinding, data were not reported fully in several of the trials, which will be discussed later.

Statistical Analysis

Calculation of Effect Sizes

Outcomes across all pain measures were pooled within studies to provide one omnibus effect size for each study. Each study's overall effect size was weighted by its inverse variance in order to provide a pooled effect size estimate (d_p) that most accurately represented the true population effect size [23].

Level and detail of data reporting varied across primary studies. Standardized mean difference effect sizes (Cohen's d) were computed from means and standard deviations when possible. In their absence, effect sizes were calculated from the combination of p values and sample sizes. After all effect sizes were calculated, they were converted to Hedges' d , which corrects for a small bias in Cohen's d [23]. No study presented data in terms of dichotomous outcomes. All effect sizes were calculated using Comprehensive Meta-Analysis software [24].

The main analysis involved the comparison of effect sizes between duloxetine, pooled across doses, and placebo. In some studies, three or more treatment groups were evaluated. If two duloxetine doses (40 and 80 mg) were compared to placebo in the same study, then both the 40 mg versus placebo and 80 mg versus placebo effects were computed versus the same placebo group, which creates a structural dependency that may result in inaccurate analyses [25], though a much larger meta-analysis found that fail-

ing to correct for dependencies made little difference in the final results [26]. Thus, analyses were conducted in which dependencies were eliminated through pooling the average effect (i.e. pooling 40 mg duloxetine vs. placebo and 80 mg duloxetine vs. placebo into a single average effect size in the same study) and where the assumption of independence was violated through including both effects separately.

Homogeneity

Tests of homogeneity examine whether studies within a particular classification are all estimating the same effect. Therefore, a test of homogeneity, using Q , was performed for each analysis. Significant heterogeneity implies that moderator variables are influential and should be examined in follow-up analyses. Given that the Q test lacks power when a meta-analysis includes a small number of studies [27, 28], an alternative measure of heterogeneity that is not dependent on sample size (I^2) was also used. Guidelines suggest that an I^2 value greater than 50% indicates significant heterogeneity [29].

Statistical Model

Meta-analysts differ regarding the appropriateness of fixed versus random effect models [30]. Fixed effect models account for variance that arises due to each study sampling a set of subjects, while random effect models add the additional variance component which arises from sampling studies from a universe of possible studies which could have been conducted or may be performed at a later date. Incorporation of the additional variance component allows for greater generalization than the fixed effects model, which only allows generalization across the studies included in the meta-analysis. When heterogeneity is low, the results of random and fixed effect analyses converge, while their results become somewhat divergent as heterogeneity increases [30]. In order to maximize the generalizability of the findings, random effect analyses were used.

Results

Study Characteristics

The five included studies [31–35] comprised a total of 1,448 participants of whom 562 received placebo, 714 received duloxetine, and 172 received paroxetine.

Outcomes

As can be seen in table 1, duloxetine, when pooled across doses, was not efficacious to statistically significant degree ($p = 0.057$) in treating painful physical symptoms of depression in comparison to a placebo, and the effect size of $d = 0.115$ was very small. The analysis including dependent observations yielded nearly identical results, also showing a lack of statistically significant superiority for duloxetine. Effect sizes were similar across all doses of duloxetine. In comparison to paroxetine, there was no sign of superiority for duloxetine. The dis-

Table 1. Composite effect sizes and homogeneity of effects for duloxetine in treating painful symptoms of depression

Comparison	k	d ₊	Z	p	Q	p	I ² , %
Duloxetine versus placebo ^a	5	0.115	1.90	0.057	1.81	0.770	0
Duloxetine versus placebo ^b	7	0.101	1.92	0.055	2.75	0.840	0
Duloxetine 60 mg versus placebo	3	0.142	1.94	0.052	1.08	0.58	0
Duloxetine 40 mg versus placebo	2	0.019	0.181	0.856	0.07	0.795	0
Duloxetine 80 mg versus placebo	2	0.095	0.879	0.379	0.70	0.402	0
Duloxetine versus paroxetine 20 mg ^c	2	-0.033	-0.31	0.760	0.56	0.453	0
Duloxetine 40 mg versus paroxetine 20 mg	2	-0.069	-0.65	0.518	0.18	0.673	0
Duloxetine 80 mg versus paroxetine 40 mg	2	0.004	0.04	0.971	1.16	0.283	13.4

^aAll doses combined, no dependent comparisons. ^bAll doses combined, including dependent comparisons. ^cAll doses combined.

tribution of effects within each comparison appeared homogeneous. Only one study used the Brief Pain Inventory, so meta-analytic comparisons are not reported on this measure in comparison to other measures. The VAS measures, when pooled, showed about as much change on average ($d = 0.103$) as did the Somatic Symptoms Inventory items ($d = 0.051$), so the type of measure did not appear to moderate the effect.

Discussion

In summary, available data indicate that, in depression, the analgesic effects of duloxetine over placebo are statistically nonsignificant and of a very small magnitude [36]. Further, there is no evidence of any effect favoring duloxetine over paroxetine.

Even these small effects may be inflated due to reporting bias. For example, study 6353, subsequently published as [37], indicated that three measures would be used to assess pain, yet data on two of these measures were not reported. Compared to other studies, this study showed a relatively strong effect favoring duloxetine ($d = 0.192$), yet it is possible that the unreported measures yielded less positive effects and were thus not reported. Data were also selectively reported in studies 4298a and 4298b, published as [38, 39], respectively. The study 4298a and 4298b protocols at www.lillytrials.com reported that two measures would be utilized to assess pain in each trial. Detke et al. [38] reported statistically significant results on selected subscales of one measure for duloxetine compared to placebo, though means and standard deviations were not reported. In study 4298b, the journal report [39] not-

ed a lack of significant change compared to placebo on one measure, whereas it reported one statistically significant result on a single subscale of the other pain measure. Again, means and standard deviations were not reported for the pain measures. Given the presence of selective data reporting, studies 4298a and 4298b were not included in the analysis. Study 6353 was included while 4298a and 4298b were not because 6353 included all subscales of a particular measure, which is likely less biased than studies which only reported significant results. Given the selective reporting of results in study 6353, it is possible that the overall effect of duloxetine versus placebo is actually smaller than the very small and statistically nonsignificant effect found in the present analysis.

A limitation of the present analysis is the size of the sample. As only five studies were included, it is certainly possible that additional research will yield data indicating that duloxetine does indeed possess an analgesic effect for patients with depression.

It bears comment that several review articles have touted duloxetine's analgesic properties despite the evidence to the contrary. For example, one review stated that '... the current [set of] results ... suggests that the dual reuptake inhibition of duloxetine yields improvement on both the core emotional symptoms and physical symptoms associated with depression' [11]. Two other reviews also made similarly positive comments [10, 12]. It is important to note that these favorable review articles were written by company authors or were supported by grants from Lilly.

The present analysis provided several examples of incomplete data reporting. In order to facilitate dissemination of the most accurate information, researchers should

fully disclose data across all dependent variables used in clinical trials. The claims made in advertisements regarding duloxetine's purported analgesic properties in depression do not rest on a solid evidentiary foundation, which suggests that regulatory agencies should more closely evaluate claims made in such commercial promotions.

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