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# Duloxetine 60 mg once daily in the treatment of milder major depressive disorder

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## SUMMARY

There is ongoing debate regarding the effectiveness of antidepressants in patients with milder major depressive disorder (MDD). This post-hoc analysis evaluated the efficacy and tolerability of duloxetine in the subset of 159 (75 duloxetine and 84 placebo) patients with milder MDD (baseline $HAMD_{17}$ total score $\geq$15 and $\leq$18) who were treated once daily with duloxetine 60 mg or placebo in two identical, 9-week, randomised, double-blind trials. At endpoint, change from baseline on $HAMD_{17}$ was greater in the duloxetine group (−7.0) than in the placebo group (−4.1) ($p = 0.005$). Response and remission rates, and improvement on the Clinical Global Impressions-Severity (CGI-S) scale, the Patient Global Impressions-Improvement (PGI-I) scale, and measures of painful symptoms were also significantly better in the duloxetine group ($p < 0.05$). Tolerability was consistent with that seen in previous studies of duloxetine in patients with more severe depression. In conclusion, duloxetine 60 mg/day is effective and well tolerated in milder MDD.

**Keywords:** Milder major depressive disorder; duloxetine; pooled analysis; severity



## INTRODUCTION

Considerable evidence supports the efficacy of antidepressants in the treatment of moderate and severe major depressive disorder (MDD), yet there are relatively few data to support the use of newer antidepressants in treating patients with milder MDD (1,2). It has been suggested that antidepressants should not be used for the initial treatment of mild depression, because the risk/benefit ratio is unfavourable (3). As many patients presenting with MDD in the primary care setting have milder disease (4), there is a need to more closely examine the efficacy, safety and tolerability of antidepressant treatment in patients with milder MDD.

Attempts to draw conclusions about the usefulness of antidepressants in milder MDD are hampered by inconsistencies in the terminology used to describe disease and disease severity. The term 'mild depression' has been used by commentators and investigators to describe a number of different disease states. Whereas MDD is characterised by relatively well-defined, accepted and recognised criteria [i.e. *Diagnostic and statistical manual of mental disorders* (DSM-IV-TR) (5), Research Diagnostic Criteria (RDC) (6)], the term 'mild depression' means different things to different people. This term has been interpreted to mean minor depressive disorder, subsyndromal depression, dysthymia and other states, all of which are diagnostic entities in their own right; these entities differ from MDD in that they are characterised by fewer symptoms, different durations and lower functional impact than MDD (7–10). The term milder depression has also been used to refer to milder cases of depression that meet the diagnostic criteria for MDD but have few, if any, symptoms beyond the minimum required and result in only minor functional impairment (5). In clinical practice, where few physicians use a structured clinical interview when making a clinical diagnosis, some patients are diagnosed with MDD even though they do not meet the full diagnostic criteria (11).

Despite the disability associated with milder depressive states (8,12,13), some treatment guidelines maintain that treatment with antidepressants in such cases may be associated with a poor risk–benefit ratio and that this precludes recommending the use of antidepressants in such circumstances (3). In the past, the substantial side effects associated with the tricyclic antidepressants (TCAs) may have justified such a recommendation. However, with the advent of newer antidepressants with efficacy similar to that of the TCAs but with considerably better tolerability (14,15), the risk/benefit ratio of antidepressant treatment is arguably now improved. In

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light of this, the question of whether to treat patients with milder MDD with antidepressants should be revisited.

Duloxetine hydrochloride (Cymbalta®) is a dual inhibitor of serotonin (5HT) and norepinephrine (NE) reuptake. It has a high and relatively balanced (i.e. ratio of binding affinities) affinity for 5HT and NE reuptake transporters (16,17). Moreover, duloxetine has negligible affinity for muscarinic, cholinergic, histamine$_1$ and other receptors (16,18). Duloxetine has been shown to be an effective treatment for MDD at doses ranging from 40 to 120 mg daily (19–22), including cases of severe depression (23). Duloxetine is licensed for the treatment of MDD in the US at a daily dose of 40–60 mg, and in Europe and elsewhere at a daily dose of 60 mg, the dose received by the patients in this analysis.

We performed post-hoc analyses of pooled data to evaluate the efficacy and tolerability of duloxetine 60 mg once daily in patients who met the criteria for MDD but whose depression was of milder severity as defined by a baseline total score of 15–18, inclusive, on the 17-item Hamilton Depression Rating Scale (HAMD$_{17}$) (24,25).

## METHODS

### Study Design

This analysis combined data from two identical, 9-week, randomised, multicentre, double-blind, placebo-controlled, parallel-group Phase III trials in adults with MDD (19,20). The study design included double-blind variable-duration placebo lead-in and lead-out periods to blind the patients and investigators to the beginning and end of active treatment. Patients received placebo or duloxetine 60 mg daily for up to 9 weeks. Both studies were performed according to the Declaration of Helsinki and approved by the appropriate ethics committees. All patients gave written informed consent. Further details regarding study design, patients and methods are described elsewhere (19,20).

### Patients

The two studies enrolled 245 and 267 patients, respectively, across 39 centres in the US. Patients were male or female adults at least 18 years of age who met the diagnostic criteria for MDD as defined in the DSM-IV (26), based on the Mini International Neuropsychiatric Interview (MINI) (27). Site personnel administering the MINI were required to have had substantial previous experience using either this instrument or the SCID (28). To be enrolled in these studies, patients were required to score $\geq$15 on the HAMD$_{17}$ (24,25) and $\geq$4 on the Clinical Global Impressions-Severity (CGI-S) scale (29) at screening and before the start of treatment.

Patients were excluded from the studies if they had a current Axis I disorder other than MDD, including but not limited to dysthymia; an anxiety disorder as a primary diagnosis within a year of study entry; or an Axis II disorder that could interfere with compliance with the study protocol. Patients were also excluded if they had a serious medical illness, a history of substance abuse or dependence within a year of study entry, or a positive urine drug screen. Additional exclusion criteria included a lack of response of the current depressive episode to two or more adequate courses of antidepressant therapy, treatment-resistant depression, initiation or stoppage of psychotherapy within 6 weeks before enrolment or starting psychotherapy at any time during the study. Concomitant medications with primarily central nervous system activity were not permitted, with the exception of chloral hydrate (up to 1000 mg) or zolpidem (up to 10 mg) for insomnia for no more than six nights during the study.

### Measurements

Patients were evaluated at a screening visit approximately 1 week before the start of treatment, at the start of treatment (week 0), once a week for the first 3 weeks of active treatment and every other week thereafter. The primary efficacy measurement was the HAMD$_{17}$ total score. Response and remission rates based on the HAMD$_{17}$ were secondary efficacy measures. Response was defined as a decrease from baseline to endpoint of $\geq$50% on the HAMD$_{17}$ total score. Remission was defined as an endpoint HAMD$_{17}$ total score $\leq$7. Additional secondary efficacy measurements included the physician-assessed CGI-S scale (29), the Patient Global Impression-Improvement (PGI-I) scale (29) and the Somatic Symptom Inventory (SSI) (30). Severity of overall pain, shoulder pain, back pain, headache, pain while awake, and daily interference due to pain were measured via visual analogue scales (VAS) (31).

Safety and tolerability assessments were performed at each visit and included spontaneously reported adverse events, serious adverse events, and measurement of supine blood pressure and heart rate. Tolerability was also assessed through comparisons of rates of discontinuation due to adverse events. Sustained elevation in blood pressure was defined as supine diastolic blood pressure of $\geq$90 mmHg with an increase from baseline of 10 mmHg or supine systolic blood pressure of $\geq$140 mmHg with an increase from baseline of 10 mmHg for at least three consecutive visits.

### Statistical Analysis

All randomised patients with milder MDD, defined as an HAMD$_{17}$ score of 15–18, inclusive, at baseline, were included in the safety analysis, while patients with milder MDD and at least one postbaseline assessment were included in the efficacy analysis, as required to determine change from baseline. Baseline was defined as the most recent observation

 

prior to the start of treatment, and endpoint was defined as the last, postbaseline observation obtained during the 9-week treatment period.

Differences between the treatment groups in the change from baseline to endpoint in continuous variables were assessed using an analysis of covariance (ANCOVA) model which included the main effects for treatment group and study, with baseline value included as a covariate. Comparisons were based on least squares adjusted mean change. Categorical outcomes were assessed using the Cochran-Mantel-Haenszel test for general association or Fisher exact test when cell sizes were very small. Adjustments for multiple comparisons were not made, and missing data were not imputed. Statistical significance was determined at the $p < 0.05$ level. Consistent with the protocols for the individual studies, the primary outcome for assessing efficacy in this work was the change from baseline in $HAMD_{17}$ total score. Additional efficacy outcomes are presented as supportive evidence. Change from baseline was evaluated using the approach of last observation carried forward (LOCF) for all patients with at least one postbaseline observation.

To assess the consistency of the treatment response across the population, we performed linear regression on the change in $HAMD_{17}$ total score and logistic regression on response and remission rates. Consistency of treatment effect was assessed via the baseline $HAMD_{17}$ score-by-treatment group interaction. Models included terms for treatment group, study and baseline score, and interactions were considered statistically significant at the $p < 0.10$ level.

## RESULTS

### Demographics and Disposition

A total of 159 (84 placebo and 75 duloxetine) patients had milder MDD as defined by a score of 15–18, inclusive, on the $HAMD_{17}$ at baseline, and were included in the safety analysis; 153 patients (82 placebo and 71 duloxetine) had at least one postrandomisation visit and were included in the efficacy analyses. The treatment groups were similar with respect to demographic characteristics and depression history (Table 1). The mean $HAMD_{17}$ scores at baseline were 16.9 for the placebo group and 16.7 for the duloxetine group.

**Table 1** Baseline demographics and depression history of patients with milder major depressive disorder (MDD)

| *Characteristic* | *Placebo (n = 84)* | *Duloxetine 60 mg (n = 75)* | *p-value** |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 41.8 (15.7) | 39.6 (13.1) | 0.687 |
| Range | 18–82 | 19–75 | |
| **Sex (%)** | | | |
| Female | 52 (61.9) | 48 (64.0) | 0.870 |
| **Origin (%)** | | | |
| Caucasian | 68 (81.0) | 61 (81.3) | 0.257 |
| African descent | 7 (8.3) | 8 (10.7) | |
| Hispanic | 8 (9.5) | 3 (4.0) | |
| Other | 1 (1.2) | 3 (4.0) | |
| **Weight (kg)** | | | |
| Mean (SD) | 82.5 (19.8) | 86.0 (27.4) | 0.327 |
| Range | 49.9–131.7 | 46.3–168.9 | |
| **$HAMD_{17}$ total** | | | |
| Mean (SD) | 16.9 (1.1) | 16.7 (1.0) | 0.056 |
| Median | 17 | 17 | |
| Range | 15–18 | 15–18 | |
| **CGI-S** | | | |
| Mean (SD) | 4.1 (0.3) | 4.1 (0.2) | 0.511 |
| Range | 4–5 | 4–5 | |
| **Age at first depressive episode** | | | |
| Mean (SD) | 28.8 (15.6) | 28.2 (13.2) | 0.953 |
| Range | 5–72 | 6–69 | |
| **Duration of current depressive episode (weeks)** | | | |
| Mean (SD) | 108.0 (310.7) | 116.8 (202.1) | 0.619 |
| Range | 2–2392 | 3–1211 | |
| **Number of previous depressive episodes** | | | |
| Mean (SD) | 5.8 (16.8) | 5.4 (16.5) | 0.903 |
| Range | 0–141 | 0–99 | |

CGI-S, Clinical Global Impressions-Severity; $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; SD, standard deviation. *The p-values for continuous measures are based on a main effects ANOVA model including treatment and study. The p-values for categorical outcomes are based on the Cochran-Mantel-Haenszel test for general association controlling for study.

### Efficacy

Patients in the duloxetine group had significantly greater improvement in $HAMD_{17}$ total scores compared with patients in the placebo group (−7.0 vs. −4.1, $p = 0.005$) (Table 2). Response and remission rates were also significantly higher among duloxetine-treated patients compared with placebo-treated patients. The rate of remission in the duloxetine group was 40.8%, compared with 24.4% in the placebo group ($p = 0.037$), and the rate of response in the duloxetine group was 47.9%, compared with 29.3% in the placebo group ($p = 0.020$).

The results of analyses of other secondary efficacy measures were also indicative of greater improvement in duloxetine-treated patients (Table 2). Global improvement was significantly better in the duloxetine group compared with the placebo group when assessed by both physicians (CGI-S) and patients (PGI-I). When patients rated their pain severity using VAS, improvement was similar in the duloxetine and placebo groups for four of the six measures (headache, shoulder pain, interference with daily activities and time in

 

**Table 2** Summary of primary and secondary efficacy measures for patients with milder major depressive disorder (MDD)

| | *Placebo (n = 82)* | | *Duloxetine 60 mg (n = 71)* | | |
|---|---|---|---|---|---|
| *Measure* | *Baseline** | *Change†* | *Baseline** | *Change†* | *p-value‡* |
| $HAMD_{17}$ total | 16.9 | −4.1 | 16.7 | −7.0 | 0.005 |
| CGI-S | 4.1 | −0.9 | 4.0 | −1.4 | 0.010 |
| PGI-I | – | 3.4 | – | 2.7 | <0.001 |
| VAS | | | | | |
| Overall | 22.2 | −3.5 | 23.7 | −9.9 | 0.045 |
| Headache | 15.9 | −1.7 | 13.6 | −1.1 | 0.854 |
| Back pain | 17.6 | −2.3 | 19.3 | −9.2 | 0.024 |
| Shoulder pain | 13.8 | −3.9 | 14.5 | −6.9 | 0.243 |
| Interference with daily activities | 14.1 | −1.6 | 13.7 | −3.7 | 0.443 |
| Time in pain while awake | 27.4 | −6.6 | 29.3 | −10.7 | 0.272 |
| $SSI_{avg}$ § | 1.7 | −0.2 | 1.7 | −0.3 | 0.042 |
| $SSI_{pain}$ ¶ | 12.9 | −1.4 | 12.7 | −2.3 | 0.075 |

CGI-S, Clinical Global Impressions-Severity of Illness; $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; PGI-I, Patient Global Impressions-Improvement; SSI, Somatic Symptom Inventory; VAS, Visual Analogue Scale for pain. *Mean baseline values. †Least-squares mean change from baseline to last observation. ‡Pairwise comparisons between duloxetine and placebo. §The $SSI_{avg}$ is the average score for all items on the $SSI_{28}$, a 28-item questionnaire on which patients indicate how much various physical complaints (including pain in joints and pain in neck) bothered them over the past week using a rating scale of 1 (not at all) to 5 (a great deal) (30). ¶The $SSI_{pain}$ is the sum of the seven pain-related items (items 2, 3, 9, 14, 19, 27 and 28) of the $SSI_{28}$ (30).

pain while awake), and statistically significant in favour of duloxetine with regard to reductions in both overall pain and back pain.

Regression results demonstrated a consistency in the treatment effect across this population with regard to both change in $HAMD_{17}$ total score ($p = 0.513$) and remission rates ($p = 0.179$). For response rates, duloxetine–placebo differences tended to decrease with increasing baseline $HAMD_{17}$ score within the population studied ($p = 0.087$).

## Safety

Four (4.8%) patients in the placebo group and 10 (13.3%) in the duloxetine group discontinued the study because of adverse events ($p = 0.090$). The adverse events that led to discontinuation were different for each of the 14 patients who discontinued and included ataxia, mania, somnolence and vomiting in the placebo group, and anorexia, anorgasmia, central nervous system stimulation, delayed ejaculation, fatigue, hypertension, insomnia, migraine, nausea and rash in the duloxetine group. Treatment-emergent adverse events reported in 5% or more of duloxetine-treated patients are listed in Table 3. Treatment-emergent adverse events were noted in 61 (72.6%) patients in the placebo group, compared with 70 (93.3%) in the duloxetine group ($p < 0.001$). The most commonly reported treatment-emergent adverse events among duloxetine-treated patients were nausea (34.7%), dry mouth (22.7%), headache (20.0%) and dizziness (18.7%), and except for headache, these were reported significantly more often than in the placebo group ($p \leq 0.006$). No serious adverse events were reported by any patients included in this analysis.

Adverse events occurring within 2 weeks of abrupt discontinuation of treatment were reported in 9 (16.1%) patients in the placebo group, compared with 19 (41.3%) in the duloxetine group ($p = 0.005$). The discontinuation-emergent adverse events most commonly reported in duloxetine-treated patients were dizziness (15.2 vs. 0% for placebo) and nausea (6.5 vs. 0% for placebo), and only dizziness occurred in significantly more duloxetine-treated patients than in placebo-treated patients ($p = 0.003$).

**Table 3** Number (%) of patients with milder major depressive disorder (MDD) who reported treatment-emergent adverse events*

| *Event* | *Placebo (n = 84)* | *Duloxetine 60 mg (n = 75)* | *p-value* |
|---|---|---|---|
| Nausea | 6 (7.1) | 26 (34.7) | <0.001 |
| Dry mouth | 6 (7.1) | 17 (22.7) | 0.006 |
| Headache | 20 (23.8) | 15 (20.0) | 0.574 |
| Dizziness | 4 (4.8) | 14 (18.7) | 0.006 |
| Appetite decreased | 2 (2.4) | 10 (13.3) | 0.010 |
| Constipation | 3 (3.6) | 10 (13.3) | 0.026 |
| Insomnia | 10 (11.9) | 9 (12.0) | 0.981 |
| Somnolence | 7 (8.3) | 8 (10.7) | 0.616 |
| Vomiting | 2 (2.4) | 8 (10.7) | 0.032 |
| Diarrhoea | 5 (6.0) | 7 (9.3) | 0.429 |
| Fatigue | 3 (3.6) | 7 (9.3) | 0.137 |
| Pharyngitis | 6 (7.1) | 7 (9.3) | 0.619 |
| Upper respiratory tract infection | 4 (4.8) | 7 (9.3) | 0.262 |
| Back pain | 2 (2.4) | 5 (6.7) | 0.183 |
| Dyspepsia | 8 (9.5) | 4 (5.3) | 0.323 |

*Events included in the table are those reported in ≥5% of duloxetine-treated patients.

 

**Table 4** Least squares mean change from baseline in weight and vital signs in patients with milder major depressive disorder (MDD) treated with placebo or duloxetine 60 mg once daily

| | *Placebo* | | *Duloxetine* | | |
|---|---|---|---|---|---|
| *Variable* | *n* | *Mean change ± SE* | *n* | *Mean change ± SE* | *p-value** |
| Body weight (kg) | 82 | −0.5 ± 0.31 | 71 | −0.5 ± 0.34 | 0.954 |
| Heart rate (bpm) | 82 | −1.9 ± 0.90 | 71 | 2.5 ± 0.97 | 0.001 |
| Systolic blood pressure (mmHg) | 82 | −2.6 ± 1.24 | 71 | −2.0 ± 1.33 | 0.723 |
| Diastolic blood pressure (mmHg) | 82 | −0.2 ± 1.00 | 71 | 1.0 ± 1.07 | 0.412 |

bpm, beats per minute; mmHg, millimetres of mercury; SE, standard error.
*Between-group comparison based on ANCOVA model containing treatment, study and baseline value.

Overall, changes from baseline in body weight and vital signs were modest and clinically unremarkable in both treatment groups (Table 4). Although the difference in the mean change in heart rate between the duloxetine and placebo groups was statistically significant, it was not considered clinically meaningful as none of the changes in heart rate resulted in patients' discontinuing the study and none met the criteria for a serious adverse event. No patients exhibited any treatment-emergent sustained elevations in blood pressure.

## DISCUSSION

In this pooled analysis, duloxetine 60 mg once daily was significantly better than placebo in reducing the severity of depressive symptoms in patients with milder MDD. Decrease from baseline in the total $HAMD_{17}$ score, the primary efficacy variable, was significantly greater in the duloxetine group than in the placebo group. Improvement from baseline was also significantly greater in the duloxetine group than in the placebo group on most of the secondary measures, including response and remission rates, the CGI-S, PGI-I, SSI, and the VAS assessments of overall pain and back pain. Duloxetine-associated efficacy, as measured by the $HAMD_{17}$ (the primary efficacy variable) and remission rates, remained consistent across the narrow range of baseline $HAMD_{17}$ scores that defines this population, although there was an unexpected tendency for the treatment effect seen in response rates to decrease as baseline $HAMD_{17}$ scores increased. This finding is likely to be an artefact given the lack of a similar finding for $HAMD_{17}$ mean change or remission rate.

In terms of safety and tolerability, more duloxetine-treated patients than placebo-treated patients discontinued treatment because of an adverse event, although the difference was not statistically significant. Nevertheless, the rate of discontinuation due to adverse events in these mildly depressed patients (13.3%) was similar to that seen in the two studies from which the subset of patients with milder MDD included in this analysis was taken [13.8% (19), 12.5% (20)]. Some adverse events were reported more frequently by duloxetine-treated patients than by placebo-treated patients. Significantly more duloxetine-treated than placebo-treated patients reported adverse events after abrupt discontinuation of treatment. The frequency of discontinuation-emergent adverse events might have been lower had doses been reduced gradually, as directed in the product labelling. No serious adverse events were reported in either treatment group, and the magnitude of observed changes in weight and vital signs was not considered to be clinically significant.

The results of the efficacy and tolerability analyses presented here, including the nature and frequency of treatment-emergent adverse events, in patients with milder MDD are consistent with findings published previously on the efficacy and tolerability of duloxetine in MDD across broader populations of depressed patients (19–22,32). There is a perception that patients with milder depression might be more intolerant of adverse events when treated with antidepressants, a belief which has contributed to concerns that the benefits of antidepressant treatment in patients with milder disease may not outweigh the possible risks, but our findings do not support this.

Findings from our analyses are consistent with those from a number of published studies, although differences in the definition of mild depression and consequent variations in the nature of populations studied make direct comparison difficult. Paykel et al. (4) assessed the benefits of amitriptyline in 141 primary care patients, many of whom had milder depression on the basis of their baseline $HAMD_{17}$ score. The patients studied satisfied the Research Diagnostic Criteria (RDC) for probable or definite major, minor, or intermittent depression (6) and had baseline $HAMD_{17}$ scores from 6 to 24. They received double-blind treatment with amitriptyline (median dose 125 mg) or placebo daily for 4–6 weeks. The authors found that amitriptyline-treated patients with baseline $HAMD_{17}$ scores from 13 to 24 derived benefit from treatment, whereas those with scores of 6–12 did not (4). They concluded that amitriptyline treatment is beneficial in all but the most mildly depressed patients. These results are similar to those of Stewart et al. (33). Stewart and colleagues also studied outpatients who met the RDC for

 

major, minor or intermittent depressive disorder and used baseline HAMD scores as a measure of pretreatment depression severity. They found that the response to desipramine treatment was significantly greater than the response to placebo among patients with pretreatment HAMD scores from 14 to 18, but not among those with pretreatment HAMD scores of $<14$.

The analysis populations studied by Paykel et al. and Stewart et al. (4,33) differed from our analysis population in that they included patients with minor depression and intermittent depression in addition to MDD, whereas all patients in our analyses were required to meet the DSM-IV criteria for MDD. Data from studies of the effect of antidepressants in patients with milder depression who met the RDC or DSM criteria for MDD are sparse. Although the results of such studies have been mixed, generally they are consistent with our findings and those published by Paykel and Stewart. That is, studies in which the populations consisted of MDD patients with pretreatment HAMD scores greater than 13 or 14 demonstrated a significant benefit of pharmacotherapy, whereas patients with pretreatment HAMD scores below that cut-off did not (33–37). A study by Fabre and Putman and a further study by Elkin et al. are exceptions to this generalisation (38,39). These studies found no significant differences in treatment outcomes between the placebo and antidepressant treatment groups in patients who met criteria for MDD and whose pretreatment HAMD scores were between 14 and 19 or 20.

The disparity in the results of studies evaluating the treatment of milder depressive states may be attributable to the lack of consistent diagnostic criteria, sample heterogeneity, differences in the endpoints measured and variability in the definition of 'response', among other factors. Fundamental differences in study design, such as the use of a placebo lead-in period and the timing of baseline assessments, duration of treatment and inclusion of additional supportive treatment can also affect study outcomes. Recognising these difficulties, the UK National Health Service is funding the THREAD (threshold for antidepressants) study, which compares the effectiveness of selective serotonin re-uptake inhibitors (SSRIs) plus supportive care with supportive care alone in primary care patients with HAMD scores $\geq 12$ (40).

In this study, we defined 'milder depression' as a $HAMD_{17}$ score of 15–18. Because there is no 'definitive' or universally accepted definition of milder depression in terms of a range of scores on the $HAMD_{17}$, the range of 15–18 was selected as it is consistent with that used in other published work to represent 'mild' depression (34,36,38). We used the $HAMD_{17}$ to assess depression, because "although its limitations are well documented (41)", it remains the gold standard for evaluating the efficacy of new treatments (41–43).

It is unlikely that improved $HAMD_{17}$ scores in our study were related to pharmacological effects of duloxetine unrelated to antidepressant activity. While it is true that an antidepressant with a predominantly sedative pharmacological profile might improve $HAMD_{17}$ scores relating to insomnia by virtue of its sedative effects alone, duloxetine does not cause sedation in the vast majority of patients. Data to support this contention come from adverse event reporting, where insomnia reported as an adverse event occurred at least as often (in 12.0% of patients) as somnolence (in 10.7% of patients). Further, duloxetine is in fact associated with anorexia and weight loss with short-term treatment rather than increased appetite and/or weight gain (32), strongly suggesting that increased appetite resulting from pharmacological effects of duloxetine is not driving an improvement on the HAMD weight and appetite item (44).

A limitation of this study is that patients in our analysis population had baseline $HAMD_{17}$ scores of 15–18, indicative of milder depression, and CGI-S scores of $\geq 4$, 4 being indicative of 'moderate' depression (29). One explanation for this discrepancy might be that the $HAMD_{17}$ is a multidimensional instrument which yields an overall severity score via the summation of ratings on a selection of items relating to individual depressive symptoms. By contrast, with the CGI-S, the clinician is required to arrive at an overall, global assessment of the patient's disease severity. While a particularly severe symptom would not unduly load the final outcome on the $HAMD_{17}$ as it would be 'watered down' by a lower level of severity of other symptoms rated by the $HAMD_{17}$, the final outcome on the CGI-S might be disproportionately driven by one particularly severe symptom, which would lead to a disconnect between ratings on these two instruments. We would argue that by being a more representative measure of the individual symptoms making up the syndrome of depression, the total score on the $HAMD_{17}$ carries more weight than the one-item CGI-S, although both have their place.

A further limitation is that this is a post-hoc analysis of pooled data from a subgroup of patients from two separate trials. These studies were only 9 weeks in duration, and even patients with milder depression would be expected to be treated for longer periods. Both studies excluded patients with comorbid mental health and severe physical problems, and these are highly prevalent in everyday primary care.

In conclusion, duloxetine 60 mg once daily was effective in the treatment of patients with milder MDD, and the safety and tolerability of duloxetine in this population were consistent with that seen overall in the two published studies from which the subset of patients with milder MDD included in this analysis were taken (19,20). The lack of a demonstrably higher rate of discontinuation due to adverse events in the duloxetine-treated patients in this milder MDD population compared with that in the overall population in the two published studies suggests that patients with milder MDD are not less tolerant of duloxetine treatment than patients

 

with more severe disease. Overall, these findings, together with other published data in patients with milder MDD described previously, are at odds with guidance advising against the use of antidepressants in milder depression. This disparity may be driven by a lack of clarity within such guidelines as to what constitutes milder depression, which itself reflects the confusion and lack of consensus regarding the terminology currently used to describe milder depressive states as a whole.

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## DISCLOSURES

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