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Duloxetine compared with fluoxetine and venlafaxine: use of meta-regression analysis for indirect comparisons

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Abstract

Background: Data comparing duloxetine with existing antidepressant treatments is limited. A comparison of duloxetine with fluoxetine has been performed but no comparison with venlafaxine, the other antidepressant in the same therapeutic class with a significant market share, has been undertaken. In the absence of relevant data to assess the place that duloxetine should occupy in the therapeutic arsenal, indirect comparisons are the most rigorous way to go.

We conducted a systematic review of the efficacy of duloxetine, fluoxetine and venlafaxine versus placebo in the treatment of Major Depressive Disorder (MDD), and performed indirect comparisons through meta-regressions.

Methods: The bibliography of the Agency for Health Care Policy and Research and the CENTRAL, Medline, and Embase databases were interrogated using advanced search strategies based on a combination of text and index terms. The search focused on randomized placebo-controlled clinical trials involving adult patients treated for acute phase Major Depressive Disorder. All outcomes were derived to take account for varying placebo responses throughout studies. Primary outcome was treatment efficacy as measured by Hedge's $g$ effect size. Secondary outcomes were response and dropout rates as measured by log odds ratios. Meta-regressions were run to indirectly compare the drugs. Sensitivity analysis, assessing the influence of individual studies over the results, and the influence of patients' characteristics were run.

Results: 22 studies involving fluoxetine, 9 involving duloxetine and 8 involving venlafaxine were selected. Using indirect comparison methodology, estimated effect sizes for efficacy compared with duloxetine were 0.11 [-0.14;0.36] for fluoxetine and 0.22 [0.06;0.38] for venlafaxine. Response log odds ratios were -0.21 [-0.44;0.03], 0.70 [0.26;1.14]. Dropout log odds ratios were -0.02 [-0.33;0.29], 0.21 [-0.13;0.55]. Sensitivity analyses showed that results were consistent.

Conclusion: Fluoxetine was not statistically different in either tolerability or efficacy when compared with duloxetine. Venlafaxine was significantly superior to duloxetine in all analyses except dropout rate. In the absence of relevant data from head-to-head comparison trials, results suggest that venlafaxine is superior compared with duloxetine and that duloxetine does not differentiate from fluoxetine.
Background
Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) that claims greater affinity for the serotonin and norepinephrine transporters compared with venlafaxine [1,2]. The efficacy and safety of duloxetine in the treatment of major depressive disorder (MDD) in adults (18–65 years) has been evaluated in 9 phase II and III clinical trials [3-5]. All were randomized, double blind, placebo-controlled studies with doses ranging from 40 to 120 mg/day in the acute treatment of MDD. Results have shown that duloxetine provided relief from psychological symptoms of depression compared with placebo. Six of the above studies used an active comparator: either fluoxetine or paroxetine. None, however, was designed and powered for direct head-to-head comparison between duloxetine and the active comparator. Inclusion of a selective serotonin reuptake inhibitor (SSRI) was intended only to show non-inferiority of duloxetine. No trial has used venlafaxine, the other marketed SNRI, as an active comparator.

The amount of data comparing duloxetine with existing antidepressant treatments is quite limited. The lack of direct comparisons between the recommended daily dose (60 mg) and an active comparator was criticised in a recent evaluation of duloxetine by the Committee for Medicinal Products for Human Use (CHMP) [6]. Assessments of the benefit/risk ratio of a new drug compared with a standard drug at an adequate dose are generally required and it is recommended that clinical trials be conducted not only against placebo, but also against active comparators [7]. The aim of such studies may be to show superiority over the active comparator or to demonstrate that at least a similar balance between benefit and risk exists when the drug of interest is compared with another acknowledged standard antidepressant.

In the absence of head-to-head randomized studies, indirect comparisons can be made between molecules. Clinical trials frequently compare efficacy of a drug versus placebo in the treatment of MDD. Less frequent, however, are head-to-head comparisons. Indirect comparisons taking into account all available placebo-controlled studies are capable of obtaining an effect size and a confidence interval of the difference between two compounds. The algorithm used gives results adjusted for discrepancies in sociodemographics, settings and designs.

After conducting a systematic review of the efficacy of duloxetine, fluoxetine and venlafaxine versus placebo in the treatment of MDD we performed an indirect comparison of the benefits of duloxetine versus fluoxetine and venlafaxine. We used meta-regression analysis to test whether or not differences in effectiveness (which cannot be explained by the differences in settings only) exist between fluoxetine and duloxetine on one hand and venlafaxine and duloxetine on the other.

Methods
The analyses sets
We used advanced search strategies based on a combination of text and index terms to interrogate the CENTRAL, Medline and Embase databases as well as the bibliography of the US Agency for Health Care Policy and Research (AHCPR). The bibliography from the AHCPR is an exhaustive literature search (both published and non-published) of trials in depression up to 1999.

Selection criteria were: study reporting HAMD results in randomised trials with a placebo arm, involving adult patients suffering from MDD (as assessed by DSM (III, III-R, IV)) treated in acute phase with either fluoxetine, venlafaxine, duloxetine. Excusion criteria were presence of comorbidities; absence of the HAMD scale; involving adolescents, children or elderly; absence of randomisation and absence of a placebo arm.

These criteria were considered sufficient to retrieve all studies of interest to be included in the analysis set.

Two research assistants independently selected papers by reading the abstract and, if necessary, the entire article to assess eligibility and data extraction. Careful re-reading of the papers resolved differences between each author analysis set and letters were sent to corresponding authors in the attempt to reduce missing data.

Publication bias was assessed drawing funnel plots, and Egger Test was used to test funnel plot asymmetry.

Statistical outcomes
Because different trials do not necessarily use the same scale and/or version for assessing efficacy, an effect size was derived from the primary outcome of each study (either HAM-D 17 21 or 24). This enabled deriving a common effect measure across studies that used different scales. The effect size was Hedge's g (a Standardised Response Mean estimator), which was corrected for small sample size bias. To compute an effect size, both the mean and an estimate of dispersion (variance, standard deviation) have to be present. When the dispersion was missing, data was imputed using the sample size weighted method [8]. If both mean and dispersion were missing, the study was removed from the analysis set.

The computed effect sizes were adjusted for severity at baseline to account for differences in patients' groups (selection bias).
The effect size was defined as the difference between the mean change in depression scale score from baseline to end-of-study in the active arm and the mean change in depression scale score from baseline to end of study in the placebo arm; divided by the standard deviation of the difference.

Other endpoints were response and dropout rates. Response was defined as a reduction of at least 50% in the HAM-D score from baseline. Dropouts were considered regardless of cause, which gave a rough indicator of the tolerability and safety of the treatment. In other words, dropouts were an indicator of failures of the present therapy.

The response and dropouts rates were analysed using log-odds ratios. A log-odds ratio equal to zero indicated that there was no statistical difference between the two compared groups. Considering the response rate, a value greater than zero indicated that more patients in the treatment group were classified as responders, and therefore that the treatment was better compared with the reference (placebo or duloxetine). A value lower than zero indicated that the reference (placebo or duloxetine) was better. Regarding dropouts, a value greater than zero indicated that more patients in the reference group (placebo or duloxetine) withdrew, and therefore that the treatment was better (in terms of efficacy and/or safety) compared with the reference (placebo or duloxetine). A value lower than zero indicated that treatment was less effective or less tolerated than the reference (placebo or duloxetine).

**Statistical methods**

Random-effect meta-analyses were computed for each outcome and each treatment compared with placebo. Mean age, mean percentage of male, mean study duration and range of dosage were computed for each treatment.

Following recommendations by Glenny et al. [9] and van Houwelingen et al. [10], a mixed procedure was run. This enabled handling studies with more than two arms (typically when different dosages are included in the same study), as well as studies presenting two drugs in the same trial (two trials assessed the effectiveness of duloxetine versus placebo and were fluoxetine controlled). The method used is a weighted least squares algorithm which iteratively computes a between-study variance while keeping each within-study variance constant. Therefore, what are modelled by default (when no adjustment is made) are drug effect (an antidepressant effect of the drugs) and drug-specific effect. The drug specific effect is the effect tested between the two treatments compared.

The models were computed under SAS PROC MIXED [11]. This procedure gives also good coverage for confidence intervals according to van Houwelingen et al. [10]. As in van Houwelingen et al., [10] Wald confidence intervals were used.

Sensitivity analyses were planned a priori and included: Performing several adjustments. The variables chosen a priori as having a potential influence over the outcome of a study were age, male percentage, duration of study and dosage. Robustness was then assessed observing the variation in the estimation of the outcome, its corresponding confidence interval, as well as the size of the estimated residual between-study variance [10]. An adjustment over the fact that the effect size was imputed was also run (in case the dispersion had to be imputed to compute an effect size). To assess its influence over the results, studies were removed from the analysis set one at a time. A post hoc sensitivity analysis was run on a subgroup of fluoxetine studies excluding the studies where the number of patients was below 20.

The following rules were applicable for all computed models:

- In case an adjustment factor was missing, it was imputed by the corresponding weighted mean computed with available data.
- Influence of missing data was computed through sensitivity analyses by removing the studies where the data was missing.
- In the event that an outcome was missing and no reply was received from the letters sent, the study was removed from the analysis set for the particular analysis for which the outcome was missing.

**Results**

No precise answers were received from the letters sent to corresponding authors; therefore, the number of missing data remained unchanged.

**Individual studies results**

*For duloxetine*, 8 publications showing results for 9 trials (each with varying characteristics) were selected, [Figure 1]. [Table 1] matches the publications with the information available from each trial. Mean age varied from 41 to 45 and the percentage of males varied from 25 to 40%. Duration of treatment varied from 8 to 9 weeks and dosages (fixed or variable) were from 40 to 120 mg per day. The effect size comparing duloxetine to placebo was -0.29(0.15). The response and dropouts log odds ratio were 0.58(0.18) and -0.02(0.32) respectively. The funnel plot shape cannot rule out the possibility of a publication
bias; see [Figure 4]. The Funnel plot was not statistically significantly asymmetrical according to the Egger test ($p = 0.9$).

For fluoxetine, 22 papers were selected [Figure 2], presenting a rather heterogeneous picture [Table 2]. Mean age varied from 33 to 47 and the percentage of males varied from 26 to 57%. Duration of treatment varied from 5 to 12 weeks and dosages (fixed or variable) were from 20 to 80 mg per day. It is worth noting that some studies include few patients (from 5 to 169). The effect size comparing fluoxetine to placebo was $-0.46(0.52)$. The response and dropouts log odds ratio were $0.37(0.32)$ and $-0.02(0.23)$, respectively. A positive point worth noting is that publication bias is shown to be minimised (see Figure 4). This figure shows the typical conic shape centred
over the value estimated which indicates little or no bias. The Funnel plot was not statistically significantly asymmetrical according to the Egger test (p = 0.4).

For venlafaxine, 8 papers were selected, see [Figure 3], with the following characteristics [Table 3]. Mean age varied from 40 to 65 and the percentage of males varied from 31 to 60%. Duration of treatment varied from 6 to 12 weeks and the dosages (fixed or variable) were from 75 to 225 mg per day. The effect size comparing venlafaxine to placebo was -0.51 (0.20). The response and dropouts log odds ratio was -0.02 [-0.33;0.29] (Figure 5c) (only 8 fluoxetine studies and 5 duloxetine studies were included because of missing data). None of these results vs. fluoxetine were significant, although a trend can be seen in favor of duloxetine in term of number of responders.

**Log Odds ratios (SD)**

For duloxetine compared with venlafaxine, the estimated effect size was 0.22 [0.06;0.38] for the treatment effect (Figure 5a), demonstrating a significant better efficacy of venlafaxine compared with duloxetine. The estimated response log odds ratio was 0.70 [0.26;1.14] also significantly different in favour of venlafaxine (Figure 5b) (only 6 venlafaxine studies and 6 duloxetine studies were included because of missing data). The estimated dropout log odds ratio was 0.21 [-0.13;0.55] (Figure 5c) (only 7 venlafaxine and 5 duloxetine studies were included because of missing data). Venlafaxine seem more efficacious both in reduction of symptoms and in term of number of responders (the corresponding odds ratio is 2.01) for a similar safety profile.

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### Table 1: Selected studies presentation for duloxetine

| Study                  | Inclusion criteria | Age | Percent | Duration | Treatment | Dosage (mg/day) | Patients per arm | Effect size (SD) | Response (%) | Dropouts (%) |
|------------------------|-------------------|-----|---------|----------|-----------|-----------------|-----------------|-----------------|--------------|--------------|
| Goldstein et al. [9]   | DSM-IV, Age 18–65 | 42  | 0.34    | 8        | Duloxetine | 40–120          | 70              | -0.3(0.03)      | 0.64         | 0.34         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 70              |                 | 0.48            | 0.24         |              |
| Detke et al. [10]      | DSM-IV, Age ≥ 18  | 42  | 0.33    | 9        | Duloxetine | 60              | 123             | -0.6(0.02)      | 0.62         | 0.29         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 122             |                 | 0.29            | 0.29         |              |
| Detke et al. [12]      | DSM-IV, Age ≥ 18  | 41  | 0.31    | 9        | Duloxetine | 60              | 128             | -0.2(0.02)      | 0.65         | 0.39         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 139             |                 | 0.42            | 0.35         |              |
| Detke et al. [13]      | DSM-IV, Age ≥ 18  | 45  | 0.26    | 8        | Duloxetine | 80              | 95              | -0.3(0.02)      | 0.65         | 0.13         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 93              |                 | 0.71            | 0.10         |              |
| Goldstein et al. [14]  | DSM-IV, Age ≥ 18  | 41  | 0.4     | 8        | Duloxetine | 40              | 86              | -0.4(0.02)      | 0.54         | 0.36         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 80              |                 | 0.56            | 0.42         |              |
| Greist et al. [4]      | DSM-IV, Age ≥ 18  | 41  | 0.4     | 8        | Duloxetine | 120             | 128             | 0.38           | -0.1(0.03)   |              |
| Falissard et al. [3]   | DSM-IV, Age ≥ 18  | 43  | 0.25    | 8        | Duloxetine | 120             | 128             | 0.40           |              |              |
| Greist et al. [4]      | DSM-IV, Age ≥ 18  | 41  | 0.38    | 8        | Duloxetine | 120             | 128             | 0.34           | -0.1(0.03)   |              |
| Falissard et al. [3]   | DSM-IV, Age ≥ 18  | 8   |         |          | Placebo    | 120             | 128             | 0.34           | -0.1(0.03)   |              |
| Brannan et al. [5]     | DSM-IV, Age ≥ 18  | 41  | 0.35    | 9        | Duloxetine | 60              | 141             | 0.39           | -0.2(0.02)   | 0.42         |
| | HAM-D ≥ 15, CGI-S ≥ 4 |     |         |          | Placebo   | 141             |                 | 0.40            | 0.09         |              |

**Log Odds ratios (SD)**

Globally 42 (1) 0.33 8 (0.4) Duloxetine Placebo 20–120 0.29(0.05) 0.58(0.09 - 0.02(0.16)
Sensitivity analyses

For duloxetine compared with fluoxetine, cf. [Table 4] either investigating the primary outcome (efficacy as measured by derived HAMD scale) or the response factor, the results were stable through adjustments, no amelioration in the adjustment was reached (the residual between-study variance estimate remained approximately constant), and confidence intervals remained large and stable. The effect size of the best prediction (smallest residual between-study variance) was 0.12 [-0.14;0.38]. The odds ratio of the response factor varied from 0.81 to 0.95, favouring numerically duloxetine in every analysis and reaching borderline significance when the estimate was close to 0.81. The residual between-study variance was constant. Concerning the dropout factor, the odds ratio varied from 1.21 to 1.40, numerically favouring fluoxetine in every analysis. Adjusting for duration of the study revealed a significant advantage in favour of fluoxetine (corresponding...
Table 2: Selected studies presentation for fluoxetine

| Study               | Inclusion criteria | Age (weeks) | Percent | Duration (weeks) | Treatment | Dosage (mg/day) | Patients per arm | Effect size (SD) | Response (%) | Dropout (%) |
|---------------------|--------------------|-------------|---------|------------------|-----------|-----------------|------------------|------------------|--------------|-------------|
| Fabre et al. [15]   | Age 21–70          | 5           | Male    | Placebo          | Fluoxetine| 40–80           | 22               | -0.8 (0.1)      | 0.50         | 0.44        |
| Stark et al. [16]   | DSM-III, Age 18–70 | 40          | 0.32    | Placebo          | Fluoxetine| 20–80           | 185              | -0.3 (0.01)     | 0.63         | 0.38        |
| Cohn et al. [17]    | DSM-III, Age 20–64 | 41          | 0.40    | Placebo          | Fluoxetine| 20–80           | 54               | -1.3 (0.04)     | 0.72         | 0.30        |
| Fieve et al. [18]   | DSM-III, Age 18–65 | 0.57        | Male    | Placebo          | Fluoxetine| 5               | 14               | -0.5 (0.1)      | 0.72         | 0.30        |
| Rickels et al. [19] | DSM-III, Age 21–70 | 47.2        | 0.21    | Placebo          | Fluoxetine| 20–80           | 18               | -0.7 (0.2)      | 0.90         | 0.39        |
| Goodnick et al. [20]| DSM-III, Age 18–65 | 0.54        | Female  | Placebo          | Fluoxetine| 20–60           | 30               | -1.1 (0.3)      | 0.38         | 0.40        |
| Wernicke et al. [21]| DSM-III, Age 18–65 | 39.8        | 0.43    | Placebo          | Fluoxetine| 20              | 97               | -0.5 (0.03)     | 0.53         | 0.38        |
| Fabre et al. [22]   | DSM-III, Age 18–65 | 38.4        | 0.37    | Placebo          | Fluoxetine| 5              | 94               | -0.5 (0.02)     | 0.54         | 0.33        |
| Wernicke et al. [23]| DSM-III, Age 18–65 | 35.8        | 0.37    | Placebo          | Fluoxetine| 5              | 94               | -0.5 (0.02)     | 0.54         | 0.33        |
| Harto et al. [24]   | DSM-III, Age 18–65 | 38.9        | 0.31    | Placebo          | Fluoxetine| 40–80           | 32               | -1.1 (0.1)      | 0.38         | 0.45        |
| Muijen et al. [26]  | Research Diagnostic Criteria, Age 18–65 | 35.8 | 0.37 | Placebo          | Fluoxetine| 20              | 27               | -1.2 (0.2)      | 0.55         | 0.46        |
Table 2: Selected studies presentation for fluoxetine (Continued)

| Study Authors          | DSM, Age       | HAMD-D17 ≥ 18, RSDM ≥ 8 and RSDM ≥ Covi | Fluoxetine | Placebo | Odds Ratio (SD) | Log Odds Ratios (SD) |
|------------------------|----------------|----------------------------------------|------------|---------|-----------------|----------------------|
| Feighner et al. [27]   | DSM-III, Age 18–70 | HAMD-D21 ≥ 20, RSDM ≥ 8 and RSDM ≥ Covi | 45         | 0.26    | 6               | 150                   | -0.3(0.04)           | 0.51 (0.68)          |
| Dunlop et al. [28]     | DSM-III, Age 18–65 | HAMD-D ≥ 14 and RSDM >Covi             | 39.3       | 6       | Fluoxetine      | 40                    | -0.03(0.03)          | 0.51 (0.41)          |
| Valducci et al. [29]   | DSM-III-R, Age 19–67 | HAMD-D >18                             | 0.43       | 8       | Fluoxetine      | 20                    | -0.9 (0.1)           | 0.70 (0.25)          |
| Heiligenstein et al.   | DSM-III-R, Age 18–65 | HAMD-D17 ≥ 15                          | 44.4       | 8       | Fluoxetine      | 20                    | 0.1 (0.1)            | 0.61 (0.41)          |
| Sramek et al. [32]     | DSM-III-R, Age 18–65 | HAMD-D24 ≥ 21 with item 1 ≥ 2, HAM-A ≤ 18, HAMD-D24 <HAM-A, RSDM ≥ 8 and RSDM >Covi | 33.9       | 0.40    | ABT-200         | 160-320               | -0.3(0.03)           | 0.17 (0.13)          |
| Fava et al. [33]       | DSM-III-R, Age (mean 41.3) HAMD-D17 ≥ 18, Raskin depression score ≥ 8 and superior to Raskin anxiety score | 41.3       | 0.49    | 12      | Paroxetine      | 20-50                 | 0.1 (0.1)            | 0.57 (0.53)          |
| Rudolph et al. [34]    | DSM-IV, Age > 18 | HAMD-D21 ≥ 20                          | 40         | 0.33    | 8               | Venlafaxine XR        | 75-225               | 0.2(0.02)            | 0.50 (0.27)          |
| Coleman et al. [35]    | DSM-IV, Age 18–76 | HAMD-D21 ≥ 20                          | 37.1       | 8       | Bupropion SR    | 150-400               | -0.2(0.01)           | 0.57 (0.37)          |
| Goldstein et al. [9]   | DSM-IV, Age 18–65 | HAMD-D17 ≥ 15 and CGI-S ≥ 4            | 39.7       | 0.35    | 8               | Duloxetine            | 40-120               | -0.2(0.04)           | 0.45 (0.36)          |
| Silverstone et al. [42] | DSM-IV, Age ≥ 18 | HAMD-D21 ≥ 20 (on the first 17 items), Covi ≥ 8 | 43.2       | 0.4     | 12              | Fluoxetine Venlafaxine XR | 20-60               | -0.6(0.02)           | 0.62 (0.26)          |
| Globally               | 40             | 0.39                                    | 7 ± 2      | Fluoxetine | Placebo        | 20-80                 | -0.46(0.11)          | 0.37(0.09) **        | -0.02(0.09) **       |

** Log Odds ratios (SD)
odds ratio 1.40). This advantage is borderline significant when adjusting for duration (corresponding odds ratio 1.36). The residual between-study variance was constant.

Whatever the parameter of interest or the adjustment factor considered, the fact that variances were imputed did not change the conclusions.

When removing studies one at a time in the analysis set, the conclusions didn't change except when removing [4] or [5] where statistical significance is reached -0.27 [-0.50; -0.01] (Odds ratio 0.76) in favour of duloxetine.

Analyses made on the subgroup of fluoxetine studies (where the number of analysed patients was greater than 20), gave for the efficacy 0.09 [-0.09;0.26] (13 fluoxetine studies) still favouring fluoxetine, for the response factor -0.22 [-0.46;0.02] (10 fluoxetine studies) still favouring duloxetine and for the dropouts factor -0.02 [-0.33;0.28] (7 fluoxetine studies) similar results were found.
For duloxetine compared with venlafaxine, cf. [Table 4] investigating the efficacy score (in the effect size scale) the effect size varied from 0.16 to 0.25 favouring venlafaxine significantly in all analyses except when adjusting for sex repartition where the result is borderline significant 0.16 [-0.01;0.33] though still numerically favouring venlafaxine. The residual between-study variance is small in all analyses, the model which has the best fit (smallest residual between-study variance) gave an estimated effect size of 0.25 [0.11;0.40] significantly in favour of venlafaxine.

Investigating the response factor, the odds ratio varied from 1.75 to 2.46 favouring venlafaxine significantly in all analyses. The residual between-study variance remained stable, the best fit (smallest residual between-study variance) corresponds to an odds ratio of 1.75. Concerning the dropouts the odds ratio varied from 1.14 to 1.30 throughout adjustments favouring numerically venlafaxine in all analyses. The residual between-study variance remained stable and small.

When removing studies one at a time from the analysis set, the conclusions didn’t change thus favouring robustness in results.
| Study            | Inclusion criteria | Age | Percent male | duration (weeks) | Treatment       | Dosage (mg/day) | Patients per arm | Effect size (SD) | Response (%) | Dropouts (%) |
|------------------|--------------------|-----|--------------|------------------|-----------------|-----------------|------------------|-----------------|--------------|--------------|
| Khan et al. [36] | DSM-III, HAMD-D ≥ 20 | 41  | 0.44         | 6                | Venlafaxine     | 75              | 23               | -0.8(0.1)       | 0.21         |
|                  |                    | 41  | 0.44         |                  | Venlafaxine     | 75–225          | 22               | -0.6(0.1)       | 0.15         |
|                  |                    | 41  | 0.44         |                  | Venlafaxine     | 150–375         | 22               | -0.7(0.1)       |              |
| Schweizer et al. [37] | DSM-III-R, Age 24–63, HAMD-D ≥ 20 | 46  | 0.60         | 6                | Venlafaxine     | 75              | 15               | -0.6(0.1)       | 0.43         |
|                  |                    | 46  | 0.60         |                  | Venlafaxine     | 225             | 15               | -1.2(0.2)       | 0.57         |
|                  |                    | 46  | 0.60         |                  | Venlafaxine     | 375             | 14               | -1.1(0.2)       |              |
| Cunningham et al. [38] | DSM-III-R, Age ≥ 18, HAMD-D ≥ 20 | 41  | 0.33         | 6                | Venlafaxine     | 25–200          | 72               | -0.4(0.03)      | 0.29         |
|                  |                    |     |              |                  | Trazodone       | 50–400          | 77               | 0.72            | 0.55         |
|                  |                    |     |              |                  | Placebo         |                 | 76               | 0.55            | 0.36         |
| Schweizer et al. [39] | DSM-III-R, Age ≥ 18, HAMD-D21 ≥ 20 | 41  | 0.31         | 6                | Imipramine      | 75–225          | 73               | -0.6(0.03)      | 0.36         |
|                  |                    |     |              |                  | Venlafaxine     | 75–225          | 73               | 0.77            | 0.47         |
|                  |                    |     |              |                  | Placebo         |                 | 78               | 0.47            | 0.27         |
| Cunningham et al. [40] | DSM-III-R, Age ≥ 18, HAMD-D ≥ 20 | 40  | 0.38         | 12               | Venlafaxine XR  | 75–150          | 97               | -0.5(0.02)      | 0.29         |
|                  |                    | 43  | 0.39         |                  | Venlafaxine IR  | 75–150          | 96               | 0.68            | 0.40         |
|                  |                    |     |              |                  | Placebo         |                 | 100              | 0.52            | 0.40         |
| Thase et al. [41] | DSM-IV, Age ≥ 18, HAMD-D21 ≥ 20 | 40  | 0.39         | 8                | Venlafaxine XR  | 75–225          | 91               | -0.6(0.02)      | 0.27         |
|                  |                    |     |              |                  | Placebo         |                 | 100              | 0.58            | 0.29         |
| Rudolph et al. [34] | DSM-IV, Age ≥ 18, HAMD-D21 ≥ 20 | 40  | 0.32         | 8                | Fluoxetine      | 20–60           | 103              | -0.1(0.02)      | 0.19         |
|                  |                    |     |              |                  | Venlafaxine XR  | 75–225          | 100              | 0.57            | 0.42         |
|                  |                    |     |              |                  | Placebo         |                 | 98               | 0.42            | 0.21         |
| Silverstone et al. [42] | DSM-IV, Age ≥ 18, HAMD-D21 ≥ 20 (on the first 17 items), Covi ≥ 8 | 41  | 0.39         | 12               | Fluoxetine      | 20–60           | 121              | -0.4(0.02)      | 0.29         |
|                  |                    |     |              |                  | Venlafaxine XR  | 75–225          | 128              | 0.67            | 0.43         |
|                  |                    |     |              |                  | Placebo         |                 | 119              | 0.43            | 0.40         |
| Globally         | NA                 | 42±2| 0.43         | 8±3              |Venlafaxine      | 75–225          | 768              | -0.51(0.07)     | 1.28(0.26)*** |
|                  |                    |     |              |                  | Placebo         |                 | 613              | -0.25(0.12)*** |              |

** Log Odds ratios (SD)
Discussion

The use of the meta-regression method to indirectly compare duloxetine with each active comparator revealed that there was no significant difference with fluoxetine either in efficacy or in safety. Findings only suggest that more patients might respond to duloxetine. Results suggest that duloxetine might be significantly less effective compared with venlafaxine, (in terms of treatment effects and number of response) with similar dropouts rates. Results given by sensitivity analyses showed relatively good consistency, as no analysis changed the conclusions. The results became nonsignificant in one analysis comparing venlafaxine with duloxetine, but the estimated value seldom moved. When removing [4] or [5] from the analysis set, duloxetine treated patients had statistically more chance to respond than when treated with fluoxetine. These findings were obtained by removing the less favourable studies for duloxetine, and we found no differences in the design or patients’ characteristics that may explain why. These tests showing significance (when comparing fluoxetine to duloxetine) or non-significance (when comparing venlafaxine to duloxetine), as in every study where multiple testing is performed, may be due to a drop in statistical power, which can bias the conclusions. As some robust trends have been found between the different drugs, the findings are considered robust to the confounding factors that have been investigated.

Our findings should, however, be interpreted with caution. Findings of superior efficacy by indirect comparisons are observational and therefore vulnerable to bias. Yet, several articles have recently shown that indirect comparisons adjusted at the aggregate level usually agree with direct comparisons. An indirect meta-analysis of studies comparing olanzapine with haloperidol and risperidone with haloperidol yielded conclusions similar to those found in a direct comparative randomized clinical trial of olanzapine and risperidone [43]. Song et al. [44] demonstrated that the results of adjusted indirect comparisons were usually similar to those of direct comparisons. In their study, there were a few significant discrepancies between the direct and the indirect estimates, although the direction of discrepancy was unpredictable. The authors concluded that empirical evidence presented in their study clearly indicates that in most cases, results of adjusted indirect comparisons are not significantly different from those of direct comparisons.

While we recognize that none of the trials involving duloxetine used venlafaxine as an active comparator, our results are in accordance with a recent meta-analysis comparing duloxetine and venlafaxine in the treatment of MDD [45] and a review comparing second-generation antidepressants [46].

Vis et al. used results of 6 trials with duloxetine and 4 with venlafaxine to report the efficacy and safety of either venlafaxine or duloxetine compared with placebo. They found that venlafaxine rates for remission and response were respectively 17.8% (CI_{95%} 9.0–26.5) and 24.4% (CI_{95%} 15.0–37.7) greater than placebo, compared with

Table 4: Sensitivity analyses: adjustment for confounding factors

| EFFECT | RESPONSE | DROPOUTS |
|--------|----------|----------|
|        | mean     | Confidence interval | Est. bet. | st. variance | mean     | Confidence interval | Est. bet. | st. variance | value     | Confidence interval | Est. bet. | st. variance |
| AGE    |          |            |          |            |          |            |          |            |          |            |          |            |
| venlafaxine | 0.25 | 0.11 | 0.40 | 0.002 | 0.90 | 0.49 | 1.31 | 0.049 | 0.26 | -0.09 | 0.61 | 0.000 |
| Fluoxetine | 0.13 | -0.14 | 0.39 | 0.097 | -0.10 | -0.37 | 0.17 | 0.000 | 0.23 | -0.14 | 0.60 | 0.000 |
| MALE PERCENT |          |            |          |            |          |            |          |            |          |            |          |            |
| venlafaxine | 0.16 | -0.01 | 0.33 | 0.008 | 0.66 | 0.21 | 1.12 | 0.096 | 0.23 | -0.13 | 0.59 | 0.001 |
| Fluoxetine | 0.12 | -0.14 | 0.38 | 0.010 | -0.17 | -0.43 | 0.08 | 0.000 | 0.31 | -0.26 | 0.64 | 0.000 |
| DURATION |          |            |          |            |          |            |          |            |          |            |          |            |
| venlafaxine | 0.23 | 0.07 | 0.39 | 0.009 | 0.56 | 0.18 | 0.95 | 0.047 | 0.13 | -0.23 | 0.48 | 0.000 |
| Fluoxetine | 0.10 | -0.16 | 0.36 | 0.100 | -0.21 | -0.45 | 0.03 | 0.000 | 0.34 | 0.02 | 0.67 | 0.000 |
| DOSAGE   |          |            |          |            |          |            |          |            |          |            |          |            |
| venlafaxine | 0.22 | 0.06 | 0.37 | 0.008 | 0.70 | 0.26 | 1.15 | 0.096 | 0.22 | -0.12 | 0.56 | 0.000 |
| Fluoxetine | 0.19 | -0.10 | 0.48 | 0.094 | -0.05 | -0.38 | 0.27 | 0.000 | 0.19 | -0.19 | 0.57 | 0.000 |
| IMPUTATION |          |            |          |            |          |            |          |            |          |            |          |            |
| venlafaxine | 0.22 | 0.06 | 0.37 | 0.008 | 0.74 | 0.29 | 1.18 | 0.093 | 0.18 | -0.18 | 0.54 | 0.000 |
| Fluoxetine | 0.11 | -0.14 | 0.36 | 0.096 | -0.20 | -0.44 | 0.04 | 0.000 | 0.27 | -0.06 | 0.60 | 0.000 |

* estimated between study variance
fluoxetine. The relative benefit: 1.12 (CI

Concerning available comparisons with fluoxetine, of the

A review of second-generation antidepressants’ efficacy in

Our study had some limitations. First, the time frame dif-

Superiority of one antidepressant medication relative to

14.2% (CI_{95\%} 8.9–26.5) and 18.6% (CI_{95\%} 13.0–24.2) for
duloxetine. Reported adverse events were comparable between
active drugs. The authors concluded that venlafaxine showed a favorable trend in remission and
response rates compared with duloxetine, but that no
significant between-drug differences were observed for drop-
out rates and adverse events. Due to the nature of the
methodology used, no objective evidence concerning how
venlafaxine performs when compared with duloxetine can be
drawn. Nonetheless, the numerical trend seen in
this paper is in accordance with the ones found here.

The primary goal was comparison of duloxetine

Concerning available comparisons with fluoxetine, of the

Superiority of one antidepressant medication relative to

Another needs to be established by means of prospectively
designed, adequately powered, head-to-head clinical tri-

As the results of placebo-controlled trials are often suf-
ficient to acquire the regulatory approval of new drugs,
pharmaceutical companies may not be motivated to sup-
port trials that compare new drugs with existing active
treatments. Lack of evidence from direct comparison
between active interventions makes it difficult for cli-
nicians to choose the most effective treatment for patients
[49]. Because of the lack of direct evidence, indirect com-
parisons have been recommended [50]. Adjusted indirect
comparison is a way to compare two compounds through
their relative effect vs. a common comparator (placebo in
our study). The indirect approach to meta-analysis
requires certain conditions to yield optimal results. Differ-
ences in study designs, inclusion/exclusion criteria,
patients characteristics at baseline as well as difference in
drug dosage [48] and publication bias are limitations that
may lead to unbalanced conclusions [43] and merit dis-
cussion.

Secondly, sample sizes seem to be smaller for the
fluoxetine studies and include patients with lower HAM-
D score (14 to 19). Thirdly the patients characteristics,
even if they vary only slightly can act as confounding fac-
tors and bias the results. Fourthly, dosages varied between
studies and between drugs. Lastly, the missing data might
not be balanced between treatments. All these sources of
heterogeneity could lead to bias. Considering that the
computation of an effect size included adjustment for
baseline severity differences and that influence of patient
characteristics and study designs were assessed through
sensitivity analyses, some confidence can be put on the
results if they show stability over the different analyses.
Also, the random effect nature of the model used here
should be able to deal with the remaining amount of bias
that couldn't be measured or properly modelled. Finally,
the other major issue in any meta-analysis is the potential
publication bias. Publication bias is a major source of sys-
tematic bias in overviews, where trials with positive results
are more likely to be published than those with neutral or
negative results, especially if the trials are small. We there-
fore tested for publication bias using the Egger test for fun-
nel plot asymmetry [51]. Ruling out completely
publication bias is nearly impossible. Even so, any bias
would most likely be in favour of the newer drug and its
existence would not undermine the results presented here
[52].
Conclusion
In the absence of a well-powered randomised placebo controlled direct comparison trial, meta-regression analysis offers the most rigorous evidence science can buy. Even if it's true that the level of evidence provided by indirect comparisons is lower than the level provided by direct comparisons; in some cases [43] indirect comparisons have actually been able to predict the results of head-to-head-clinical trials. The capacity of prediction is nonetheless indirectly linked to the quality of the methodology used and the information available. Both have been discussed in the core of this paper, and in this context the results seem stable enough to be confident that the bias are controlled and that the results provide valuable additional information to health care professionals, health economists and the pharmaceutical industry. These results suggest evidence of venlafaxine superiority compared with duloxetine and absence of a difference between fluoxetine and duloxetine. In any case, investigating the relative efficacy of duloxetine compared directly with other existing antidepressants – particularly venlafaxine – in a well-designed trial would be welcomed to challenge or reinforce our findings.

Authors’ contributions
Each author has made substantial contributions at every phase in the planning and writing of the manuscript. Each have each equally contributed to the drafting and critical revision of this work.

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