

Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis

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Objective: Escitalopram is the most selective of the selective serotonin reuptake inhibitor (SSRI) antidepressants. Previous studies have suggested that escitalopram is superior to citalopram in efficacy. We conducted a meta-analysis of studies in which escitalopram was compared with other antidepressants to assess the relative efficacy of these agents. **Methods:** Data from all randomized, double-blind studies in major depression in which escitalopram was compared with active controls (citalopram, fluoxetine, paroxetine, sertraline and venlafaxine XR [extended release]) were pooled. The 10 studies were conducted in both specialist settings and general practice. Patients met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), for major depressive disorder and were at least 18 years old. In all but 2 studies, patients were required to have a score of 22 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS). The primary outcome measure was the estimated difference in treatment effect in MADRS total score at the end of the study. Secondary outcome measures were the response to treatment (defined as a $\geq 50\%$ reduction in baseline MADRS total score) and remission rate (defined as MADRS total score ≤ 12 at end of study). **Results:** A total of 2687 patients were included in the analyses (escitalopram $n = 1345$, conventional SSRIs $n = 1102$, venlafaxine XR $n = 240$). Escitalopram was superior to all comparators in overall treatment effect, with an estimated difference in treatment effect of 1.07 points (95% confidence interval [CI] 0.42–1.73, $p < 0.01$), and in response (odds ratio [OR] 1.29, 95% CI 1.07–1.56, $p < 0.01$) and remission (OR 1.21, 95% CI 1.01–1.46, $p < 0.05$) rates. In analysis by medication class, escitalopram was significantly superior to the SSRIs and comparable to venlafaxine, although the overall results do not necessarily reflect a significant difference between escitalopram and individual SSRIs. These results were similar in the severely depressed population (patients with baseline MADRS ≥ 30). The withdrawal rate due to adverse events was 6.7% for escitalopram compared with 9.1% for the comparators ($p < 0.05$). **Conclusions:** In this meta-analysis, escitalopram showed significant superiority in efficacy compared with the active controls.

Objectif : L'escitalopram est le plus sélectif des antidépresseurs parmi les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS). Des études antérieures ont indiqué que l'escitalopram est plus efficace que le citalopram. Nous avons procédé à une méta-analyse d'études au cours desquelles on a comparé l'escitalopram à d'autres antidépresseurs afin d'en évaluer l'efficacité relative. **Méthodes :** On a regroupé des données tirées de toutes les études randomisées à double insu sur la dépression majeure au cours desquelles on a comparé l'escitalopram à des témoins actifs (citalopram, fluoxétine, paroxétine, sertraline et venlafaxine XR [à libération prolongée]). Les 10 études ont été réalisées en contexte spécialisé et en médecine générale. Les patients satisfaisaient aux critères du *Diagnostic and Statistical Manual of Mental Disorders*, quatrième édition (DSM-IV), pour le trouble dépressif majeur et avaient au moins 18 ans. Dans toutes les études sauf deux, les patients devaient avoir un score de 22 ou plus sur l'échelle d'évaluation de la dépression de Montgomery-Åsberg (MADRS). La principale mesure de résultat a été la différence estimative au niveau de l'effet du traitement du score total selon

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l'échelle MADRS à la fin de l'étude. Les mesures de résultats secondaires ont été la réponse au traitement (définie comme une réduction de $\geq 50\%$ du score total de référence MADRS) et le taux de rémission (défini comme un score total MADRS de ≤ 12 à la fin de l'étude).

Résultats : Les analyses ont inclus au total 2687 patients (escitalopram, $n = 1345$; ISRS classiques, $n = 1102$; venlafaxine XR, $n = 240$). L'escitalopram a été supérieur à tous les médicaments de comparaison par l'effet total du traitement et la différence estimative au niveau de l'effet du traitement qui a atteint 1,07 point (intervalle de confiance [IC] à 95 %, 0,42–1,73, $p < 0,01$) et par les taux de réponse (coefficient de probabilité [CP] 1,29, IC à 95 %, 1,07–1,56, $p < 0,01$) et de rémission (CP 1,21, IC à 95 %, 1,01–1,46, $p < 0,05$). Une analyse selon la catégorie de médicaments a révélé que l'escitalopram est très supérieur aux ISRS et comparable à la venlafaxine, même si les résultats globaux ne reflètent pas nécessairement une différence importante entre l'escitalopram et des ISRS en particulier. Ces résultats étaient semblables dans la population atteinte de dépression sévère (patients qui ont un score de référence de ≥ 30 selon l'échelle MADRS). Le taux de retrait attribuable à des événements indésirables s'est établi à 6,7 % dans le cas de l'escitalopram comparativement à 9,1 % dans celui des comparateurs ($p < 0,05$). **Conclusions :** Dans cette méta-analyse, l'escitalopram a montré une supériorité importante au niveau de l'efficacité comparativement aux témoins actifs.

Introduction

Depression is a disabling disorder associated with considerable comorbidity, risk of suicide and social consequences that is only surpassed by ischemic heart disease as a major public health issue in industrialized countries.^{1,2} Although antidepressants are among the most prescribed therapeutic agents, recent reviews highlight the significant percentage of depressed patients who fail to achieve a response or remission.

Escitalopram, the S-enantiomer of citalopram, is a selective serotonin reuptake inhibitor (SSRI) antidepressant that is the most selective of the SSRIs.³ The efficacy of escitalopram has been demonstrated in major depressive disorder (MDD) in both primary care and specialist settings.^{4–8} Placebo-controlled trials with citalopram as an active comparator have shown superiority for escitalopram, particularly in patients with more severe depression.⁹ Escitalopram has also been compared with venlafaxine XR (extended release) with comparable rates of response and remission.^{4,5} These results are of interest, because it has been suggested that venlafaxine is more effective than SSRIs.^{10,11} The enhanced efficacy of escitalopram is not associated with more side effects, which suggests a more favourable benefit–risk ratio.^{4,6} To investigate whether the superiority of escitalopram is generalizable to other antidepressants, the present analysis examined pooled data from 10 MDD studies in which escitalopram was compared with active controls (citalopram, fluoxetine, paroxetine, sertraline and venlafaxine XR).

Methods

This meta-analysis was performed using original data from patients who participated in all MDD studies sponsored by H. Lundbeck or Forest Laboratories finalized as of July 1, 2004, that directly compared escitalopram with other antidepressants. Details of these studies are given in Table 1.^{4–7,12–16} The studies were comparable randomized, double-blind, active-controlled evaluations of escitalopram (10–20 mg/d) versus citalopram (20–40 mg/d), fluoxetine (20–40 mg/d), paroxetine (20–40 mg/d), sertraline (50–200 mg/d) or venlafaxine XR (75–225 mg/d) and were conducted in the United States, Europe or Canada. Four of the 10 studies also included a placebo arm.^{6,7,12,15} Because similar methodologies

were applied across all trials, it was possible to perform a pooled analysis, whereby raw data from each patient were entered into the analysis.

Results from 5 of these studies have been published to date in their entirety,^{4,7} or in part,¹² whereas results from 4 other studies have been presented as abstracts/posters and are in the publication process in peer-reviewed journals.^{13–16} One study is still to be published. In one study,⁶ 2 fixed doses of escitalopram (10 mg and 20 mg) were compared with citalopram (40 mg). In order to include comparable dosages and to give balanced numbers of patients from each study arm, the escitalopram, 10 mg/d, arm from that study is not included in this analysis. The exclusion of this treatment arm did not affect the results in the total intent-to-treat (ITT) population, but in severely depressed patients (defined as patients with a baseline Montgomery-Åsberg Depression Rating Scale¹⁷ [MADRS] score ≥ 30), it resulted in an increased difference (without affecting the statistical significance) between escitalopram and comparators. It has, however, previously been shown that more severely depressed patients may benefit from the administration of higher doses of escitalopram (i.e., 20 mg/d).¹⁸

Eligible patients met the criteria for MDD of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),¹⁹ and were at least 18 years old. In most studies, patients were required to have an entry score of 22 or more on MADRS; in one study⁵ this criterion was a MADRS score of 18 or more, whereas in another⁴ it was a Hamilton Rating Scale for Depression²⁰ (HAM-D) total score of 20 or more.

Patients with clinically significant renal or hepatic disorders or a recent history of alcohol or drug abuse were excluded from study participation. Clinically significant abnormalities on the baseline physical examination, electrocardiogram or laboratory tests were also criteria for exclusion from study participation. Patients who had a known hypersensitivity to any of the study drugs or those who had been prescribed an investigational or antipsychotic drug or fluoxetine within 30 days, an irreversible monoamine oxidase inhibitor within 14 days, or another antidepressant, anxiolytic or sedative–hypnotic drug within 7 days of the double-blind treatment period were also excluded. Patients were randomly assigned to treatment during the double-blind period at the daily dosages shown in Table 1 after a 1-week lead-in period.

The primary efficacy variable in each of the 10 studies was the MADRS. The primary outcome end point of this meta-analysis was the estimated difference in treatment effect in MADRS total score at the end of double-blind treatment. Secondary outcome measures were the response to treatment (defined as $\geq 50\%$ reduction in baseline MADRS total score) and remission rate (defined as MADRS total score ≤ 12) at the end of treatment.

Statistical analyses

Analyses were performed on pooled data from the ITT population, which included all patients who received at least 1 dose of study medication and had at least 1 valid post-baseline MADRS evaluation. The last-observation-carried-forward (LOCF) approach was used for missing data.

Analysis of variance (ANOVA) was used to assess the comparability of the 3 treatment groups at baseline (escitalopram, conventional SSRIs and venlafaxine XR) in terms of sociodemographic information (age, sex) and baseline severity of depression (MADRS total score).

The meta-analysis on the overall population was performed using an analysis of covariance (ANCOVA) on the MADRS total score, adjusting for baseline value, study centre and treatment. An identical analysis was carried out on the severely depressed population, defined as patients with a baseline MADRS score of 30 or more.

Study-specific treatment effects were analyzed and tested for heterogeneity in order to check whether the fixed-effect models were adequate or whether random-effect models had to be used. The study-specific treatment-effect test was not statistically significant, and the pooled analyses were thus all conducted using fixed-effect models.

For response to treatment and remission rate, treatment effect differences were specified in terms of log-odds ratios, which were estimated using a logistic model with the same structure as the ANCOVA described above. However, for ease of interpretation, the results are presented as odds ratios.

For all efficacy measures, point estimates were expressed with their 95% confidence intervals (95% CI). All statistical tests were 2-sided. The α level was set at 5%.

Sensitivity analyses were performed to examine potential confounding factors in the main pooled analysis. The main analysis was the difference in treatment effect at the end of the study, which was 8 weeks for 8 trials, and 24 and 27 weeks for 2 trials. Sensitivity analyses examined the difference in treatment effect at 8 weeks for all trials, the inclusion of failed trials, the treatment effect in men versus women, the inclusion of a placebo arm, dosage, fixed versus flexible dosing and trial length. Two trials (3 and 8 in Table 1) were technically failed, because they were unable to show efficacy of an established treatment (the active reference) versus placebo.

Results

A total of 2743 patients were recruited in the ITT population of the 10 studies; 2687 (98%) were included in the ITT analysis of the efficacy of escitalopram ($n = 1345$), conventional SSRIs ($n = 1102$) and venlafaxine XR ($n = 240$). The patients' mean age was 47 (standard deviation 16) years, and baseline depression severity scores were not significantly different between groups (Table 2). Within each study, the daily doses of the active drugs were comparable, based on their recommended dosage range (Table 1).

About two-thirds of the patients were women. In one study, a significantly greater proportion of patients randomly

Table 1: Overview of studies included in the meta-analysis

No.	Study	Duration, wk	Design	Treatment (mg/d)	Dose, mg/d, mean/median/mode*	ITT, no. of patients
1	Lepola et al ⁷	8	Flexible	ESC (10–20)	14.0/10.0/10.0	155
				PBO	24.4/20.0/20.0	159
2	Burke et al ⁶	8	Fixed	ESC (20)	—	123
				PBO	—	125
3	Rapaport et al ¹²	8	Flexible	ESC (10–20)	17.6/20.0/20.0	124
				PBO	35.3/40.0/40.0	119
4	Colonna et al ¹³	24	Fixed	ESC (10)	—	165
				CIT (20)	—	174
5	Montgomery et al ⁵	8	Flexible	ESC (10–20)	12.1/10.0/10.0	146
				VLF (75–150)	95.2/75.0/75.0	142
6	Bielski et al ⁴	8	Fixed	ESC (20)	—	97
				VLF (225)	—	98
7	Alexopoulos et al ¹⁴	8	Flexible	ESC (10)	—	104
				SER (50–200)	153.0/200.0/200.0	107
8	Kasper et al ¹⁵	8	Fixed	ESC (10)	—	170
				PBO	—	164
9	Unpublished data	8	Flexible	ESC (10–20)	17.3/20.0/20.0	96
				FLU (20–40)	34.1/40.0/40.0	98
10	Baldwin et al ¹⁶	27	Flexible	ESC (10–20)	13.9/10.0/10.0	165
				PAR (20–40)	25.4/20.0/20.0	156

CIT = citalopram; ESC = escitalopram; FLU = fluoxetine; ITT = intent-to-treat; PAR = paroxetine; PBO = placebo-controlled study; SER = sertraline; VLF = venlafaxine XR (extended release).

*Values at end of study.

allocated to receive escitalopram were female (69%), compared with the proportion of women randomly allocated to receive venlafaxine XR (47%, $p < 0.01$). However, post hoc analyses showed that the higher proportion of women in the escitalopram group relative to the venlafaxine XR group did not bias the efficacy data in favour of escitalopram.⁴

Mean MADRS total score at the end of double-blind treatment

The overall difference in treatment effect was statistically in favour of escitalopram compared with an active comparator, with an estimated difference in treatment effect of 1.07 points on MADRS (95% CI 0.42–1.73, $p < 0.01$) (Fig. 1). Escitalopram was statistically superior to conventional SSRIs, namely, citalopram, fluoxetine, paroxetine or sertraline, with a difference in treatment effect of 1.22 points (95% CI 0.50–1.94, $p < 0.001$) (Fig. 2A). The comparison of escitalopram and venlafaxine XR was not statistically significant, with a treatment difference of 0.38 points (95% CI –1.18–1.94) (Fig. 2A).

Effect of baseline severity of depression on treatment differences

These results were confirmed in the severely depressed population, wherein the estimated differences in treatment effect in MADRS total scores were all greater than those observed in the overall population, leading to a difference in the MADRS total score of 2.34 points (95% CI 1.22–3.47, $p < 0.001$) for escitalopram versus comparators (Fig. 1B). In the severely depressed subgroup, escitalopram was statistically superior to conventional SSRIs, namely, citalopram, fluoxetine, paroxetine or sertraline, with a difference in treatment effect of 2.54 points (95% CI 1.22–2.81, $p < 0.001$) (Fig. 2B). The comparison of escitalopram and venlafaxine XR, although in favour of escitalopram, was not statistically significant, with a treatment difference of 1.57 points (95% CI –0.90 to 4.05) (Fig. 2B).

As can be seen in Figure 3, the more depressed patients were at baseline, the larger the treatment differences between escitalopram and the comparators.

Because failed trials by definition are unable to show efficacy of established comparators versus placebo, they are unlikely to be able to show differences between active treatments. Therefore, it is reasonable to do a sensitivity analysis

excluding such trials. When the 2 failed trials (3 and 8 in Table 1) were excluded, the analysis gave a treatment effect estimate of 0.98 points (95% CI 0.25–1.70, $p < 0.01$) for the total population and an estimate of 1.95 points (95% CI 0.72–3.19, $p < 0.01$) for the severely depressed patients, both in favour of escitalopram. The decrease in estimated difference in treatment effect was the result of the exclusion of trial 8, in which escitalopram was statistically significantly superior to fluoxetine. A sensitivity analysis was also performed on the 8-week data, because 8 of the 10 studies were 8-week trials. For the total population, this analysis gave an estimated difference in treatment effect of 0.78 points (95% CI 0.14–1.42, $p < 0.05$) and for the severely depressed patients an estimate of 1.66 points (95% CI 0.56–2.76, $p < 0.01$), both in favour of escitalopram.

Response rate at the end of double-blind treatment

Figure 4 shows the estimated difference in treatment effect in response ($\geq 50\%$ reduction in baseline MADRS total score). For the full population (Fig. 4A), the overall odds ratio for response to treatment was 1.29 (95% CI 1.07–1.56, $p < 0.01$), showing a statistically significantly higher response rate for patients treated with escitalopram (65.8% v. 61.6% response). The odds ratio of a treatment response in the escitalopram group compared with the other SSRI groups was 1.31 (95% CI 1.06–1.60, $p < 0.05$), whereas the odds ratio of a treatment response for the escitalopram group compared with the venlafaxine XR group was 1.23 (95% CI 0.80–1.89, $p = 0.35$).

The results obtained in the severely depressed population also indicated a statistically significantly higher response rate for patients on escitalopram (67.6% v. 57.8% response), with an odds ratio of 1.93 (95% CI 1.41–2.64, $p < 0.001$) (Fig. 4B). Escitalopram was significantly more efficacious than SSRIs, with an odds ratio of 2.03 (95% CI 1.42–2.92, $p < 0.001$), whereas the odds ratio when comparing escitalopram and venlafaxine XR was 1.61 (95% CI 0.85–3.04, $p = 0.15$).

Remission rate at the end of double-blind treatment

Figure 4 also shows the estimated differences in treatment effect on remission (MADRS total score ≤ 12). For the full population (Fig. 4A), the overall odds ratio for remission rate was 1.21 (95% CI 1.01–1.46, $p < 0.05$), showing a statistically significantly higher remission rate for patients treated with escitalopram (58.1% v. 55.0% of the patients achieved remission). The odds ratio when comparing escitalopram and other SSRIs for remission was 1.20 (95% CI 0.97–1.47, $p = 0.09$), while the odds ratio when comparing escitalopram and venlafaxine XR was 1.29 (95% CI 0.84–1.98, $p = 0.24$).

The results obtained in the severely depressed population also indicated a statistically significantly higher remission rate for patients on escitalopram, with an odds ratio of 1.59 (95% CI 1.16–2.16, $p < 0.01$) (Fig. 4B) (53.8% v. 45.9% remission). Escitalopram was significantly more efficacious than SSRIs, with an odds ratio of 1.56 (95% CI 1.09–2.26, $p < 0.05$), whereas the odds ratio when comparing escitalopram and venlafaxine XR was 1.72 (95% CI 0.91–3.25, $p = 0.10$).

Table 2: Baseline characteristics of the intent-to-treat population in the meta-analysis

Characteristic	Treatment group		
	Escitalopram (n = 1345)	SSRIs (n = 1102)	Venlafaxine XR (n = 240)
Mean age (and SD), yr	47 (17)	47 (17)	43 (14)
Female, %	68.6	68.1	61.2
Mean MADRS total score (and SD)	29.2 (4.4)	29.3 (4.5)	29.4 (5.3)
MADRS score ≥ 30 , %	45.7	45.1	51.7

MADRS = Montgomery–Åsberg Depression Rating Scale; SD = standard deviation; SSRIs = selective serotonin reuptake inhibitors; XR = extended release.

Potential influence of intervening variables

An analysis of potential factors influencing the estimated difference in treatment effect at end of study in MADRS total score showed that sex had no effect on the results, whereas placebo-controlled, fixed-dose or high-dose studies possibly showed greater separation between escitalopram and active comparators than non-placebo-controlled, flexible-dose or low-dose studies (Fig. 2A). Furthermore, studies comparing escitalopram with an SSRI showed a greater difference in

results than the studies of escitalopram versus venlafaxine XR.

The results obtained in the severely depressed population were similar, with the exception of flexible versus fixed-dose treatment, for which the difference was not as great as for the total population (Fig. 2B).

The effect of trial length on the difference in treatment effect at end of study was examined. For the 8-week studies, the estimated difference was 1.03 (95% CI 0.27–1.79) for all patients and 1.19 (95% CI –0.08–2.46) for severely depressed patients. For the 2 longer studies (about 6 months' duration),

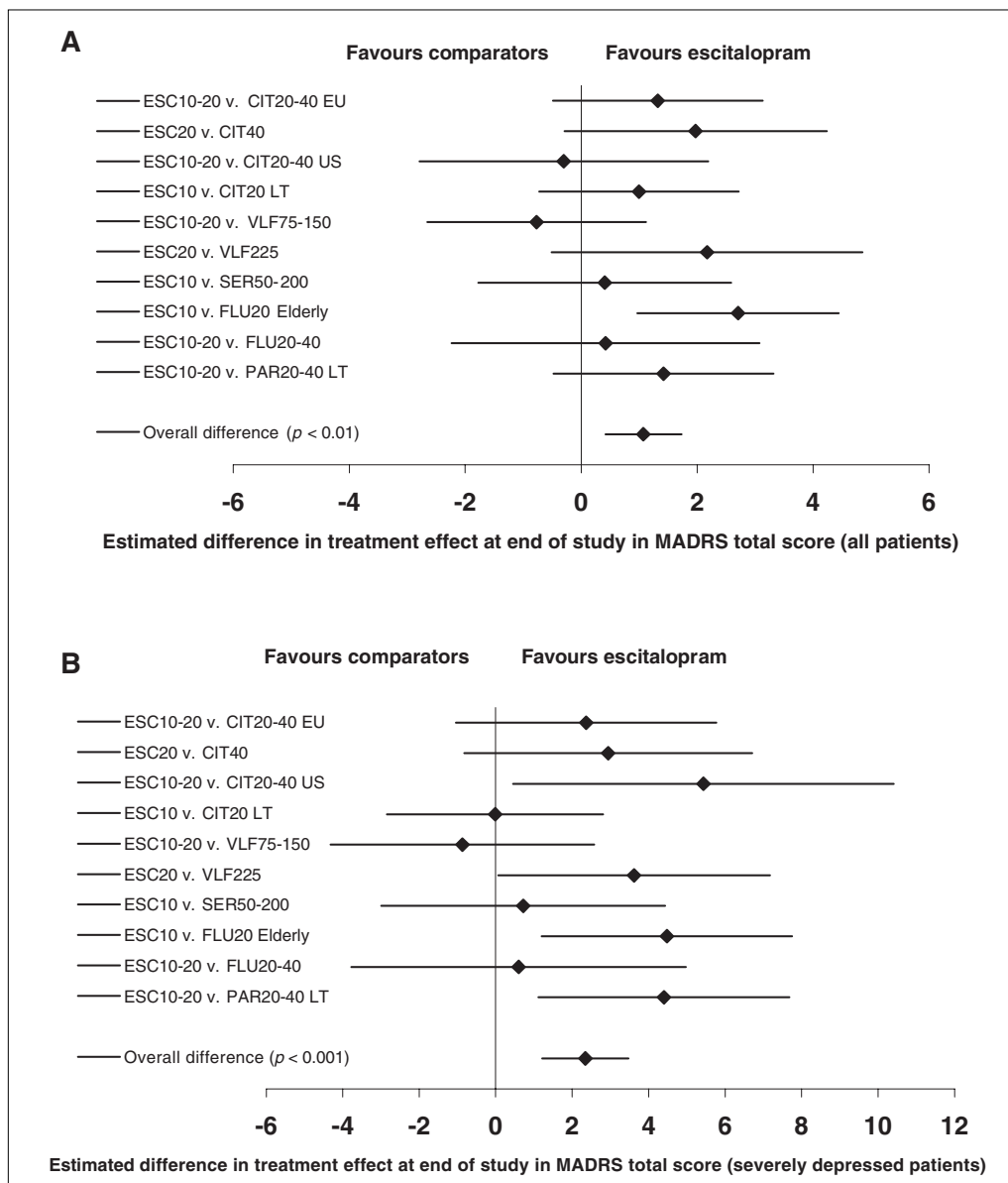


Fig. 1: Estimated difference in treatment effect in MADRS total score at end of study shown with 95% confidence intervals (A) for all patients and (B) for severely depressed patients (baseline MADRS ≥ 30). Positive values are in favour of escitalopram, whereas negative values are in favour of comparators. CIT = citalopram, ESC = escitalopram, EU = European study, FLU = fluoxetine, LT = long-term study, MADRS = Montgomery-Åsberg Depression Rating Scale, PAR = paroxetine, SER = sertraline, US = US study, VLF = venlafaxine XR.

the estimated difference was 2.41 (95% CI 1.09–3.73) for all patients and 2.08 (95% CI –0.08–4.24) for severely depressed patients (Fig. 2).

Withdrawal rates

The total withdrawal rate for all patients was 17.8% for escitalopram compared with 20.6% for the comparators ($p < 0.05$). The withdrawal rate due to adverse events was 6.7% for escitalopram compared with 9.1% for the comparators ($p < 0.05$). The difference between escitalopram (6.9%) and

the SSRIs (9.4%) was not significant, but it was statistically significant when citalopram was excluded (6.8% v. 10.7%, $p < 0.01$), as was the case for escitalopram compared with venlafaxine XR (6.8% v. 13.5%, $p < 0.05$).

Discussion

To date, there are no large published randomized clinical trials involving direct comparisons of several antidepressants from the same or different classes with large enough numbers of patients in each arm to detect small but clinically

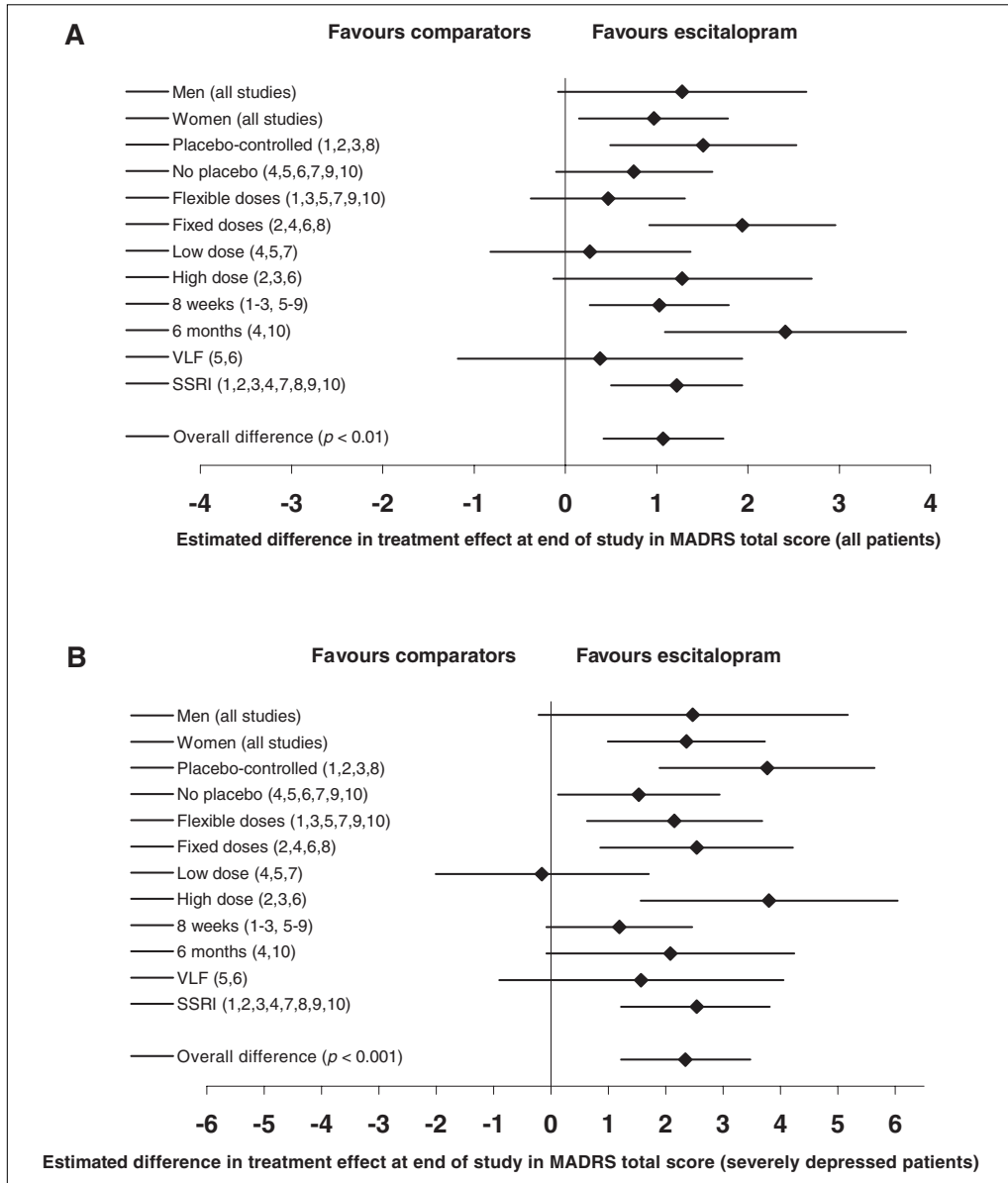


Fig. 2: Explorative analysis of potentially influential factors (A) for all patients and (B) for severely depressed patients (baseline MADRS ≥ 30). Numbers in parentheses refer to study number (see Table 1). Positive values are in favour of escitalopram, whereas negative values are in favour of comparators. MADRS = Montgomery–Åsberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitors, VLF = venlafaxine XR.

meaningful differences. In the absence of such trials, several meta-analytic techniques have been employed to detect differences between classes of antidepressant drugs (e.g., see Anderson²¹).

This meta-analysis involved a cross-section of depressed patients from Europe and North America who took part in 10 double-blind randomized clinical trials involving escitalopram. About two-thirds of the population were women, and almost half had depression categorized as "severe," defined by a baseline MADRS score of 30 or more. These trials reflect a balance between primary care and specialist settings (4 primary care, 4 specialist and 2 mixed), as well as a wide range of active comparator antidepressants (4 citalopram, 2 fluoxetine, 1 paroxetine, 1 sertraline and 2 venlafaxine XR). The sample was large enough to allow separate analyses of the severely depressed group on each of the contrasts defined a priori, as well as exploratory analyses of potentially influential variables such as fixed or flexible dosing schedule and the presence or absence of placebo control.

The principal finding in this meta-analysis is that escitalopram consistently demonstrated greater efficacy, as assessed by MADRS, on a series of end-point comparisons involving change in scores from baseline and in response and remission rates. The improvement in MADRS with escitalopram was 1.22 points greater than with conventional SSRIs. This magnitude of difference is comparable to the effect size of 1.2 points on the HAM-D scale found in meta-analyses of venlafaxine compared with conventional SSRIs.¹¹ Based on the published results of 3 individual pivotal trials and preliminary data from a fourth,¹³ the superiority of escitalopram versus other SSRIs, particularly citalopram, has been questioned.²² A

pooled analysis from 4 trials showed a significant superiority of escitalopram versus citalopram,⁹ and this has been confirmed in a direct comparison of escitalopram and citalopram in severely depressed patients.²³

In the present meta-analysis, the estimated difference in treatment effect between escitalopram and other agents also increased with severity of depression at baseline. For example, in patients with a baseline severity score above 30 on the MADRS, the separation between escitalopram and comparators was 2.34 points in favour of escitalopram. This was also true for rates of response and remission, where the difference between escitalopram and comparators was significantly greater in the severely depressed population compared with the total population. This was a secondary analysis, so these results must be interpreted with caution, although previous studies conducted among patients with severe MDD have demonstrated that antidepressant effects and response rates are lower than those observed in less severely depressed patients.²⁴ Placebo response rates are also lower in patients with severe MDD,²⁵ so that randomized clinical trials conducted in this population are more sensitive in demonstrating the efficacy of an antidepressant. In these circumstances, the impact of potential confounding factors may be less important and, consequently, the observed effects may reflect more precisely the true antidepressant effect. The greater efficacy of escitalopram in the severely depressed population found in this comprehensive pooled analysis, using a consensus definition of severe depression,²⁶ extends previous findings where escitalopram was shown to be more efficacious than citalopram.²⁵ These results suggest that some heterogeneity exists within the class of SSRIs in terms of magnitude of antidepressant effect.²⁷

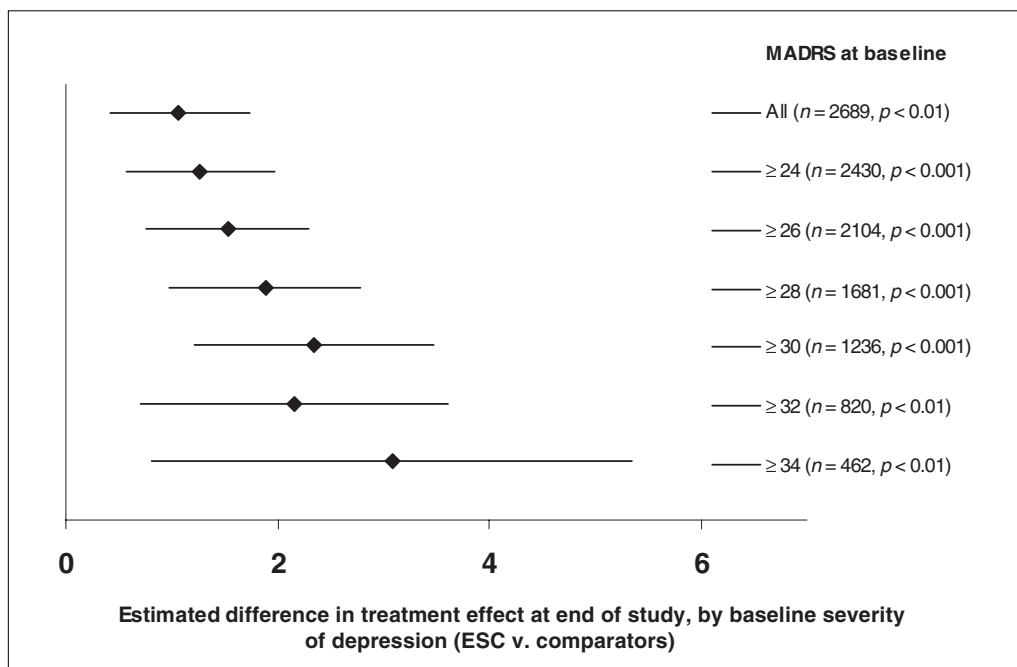


Fig. 3: Estimated difference in treatment effect (shown with 95% confidence intervals) between escitalopram and comparator MADRS total score at end of study, by baseline severity of depression. ESC = escitalopram, MADRS = Montgomery-Åsberg Depression Rating Scale.

What are the potential explanations for the apparently superior efficacy of escitalopram versus conventional SSRIs, particularly in the treatment of more severe depression? One explanation that has recently been proposed relates to an allosteric modulation of the serotonin transporter following administration of escitalopram compared with citalopram.²⁸ In addition to a primary, high-affinity binding site that mediates the inhibition of serotonin reuptake, there is a

low-affinity allosteric site that modulates the affinity of ligands at the primary site.²⁹ Recent work has shown that escitalopram, when bound to the allosteric site, appears to potentiate its own binding to the primary binding site. R-citalopram, however, also potentiates the binding of escitalopram to the primary binding site, but to a lesser extent than escitalopram.²⁸

These results provide an alternative explanation to the

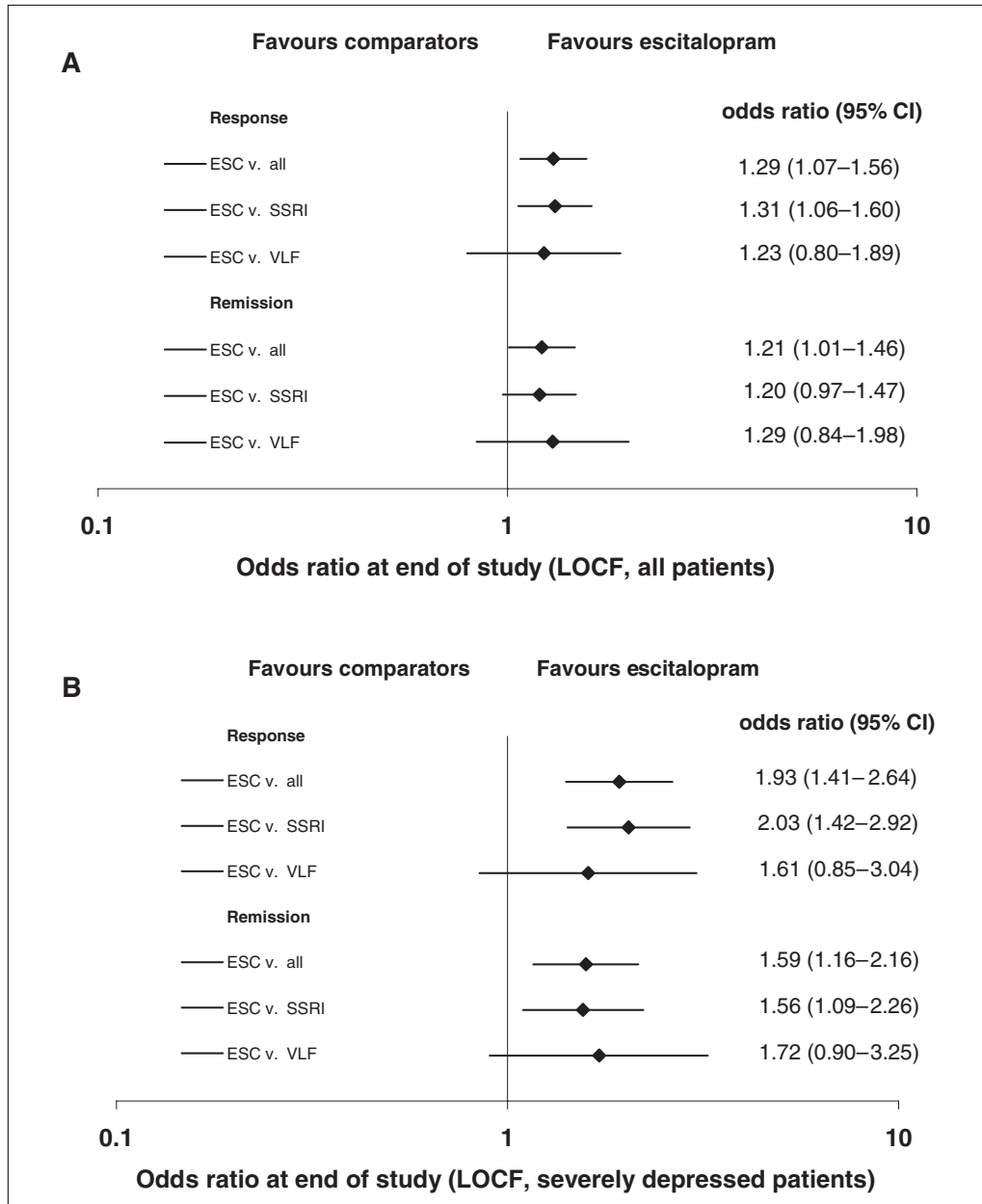


Fig. 4: Response (defined as a $\geq 50\%$ reduction in baseline MADRS total score; LOCF) and remission (defined as MADRS total score ≤ 12 ; LOCF) rates following treatment at end of study (A) for all patients and (B) for severely depressed patients (baseline MADRS ≥ 30). Positive values are in favour of escitalopram, whereas negative values are in favour of comparators. Data are odds ratios with 95% confidence intervals. ESC = escitalopram, LOCF = last observation carried forward, MADRS = Montgomery–Åsberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitors, VLF = venlafaxine XR.

hypothesis that dual reuptake inhibition of serotonin and norepinephrine is necessarily associated with superior antidepressant efficacy of venlafaxine compared with SSRIs. Escitalopram decreases its own dissociation rate from the serotonin transporter, possibly via the allosteric site,²⁸ leading to more prolonged inhibition of the transporter and higher extracellular serotonin levels. A persistent increase in serotonin levels may be essential for the antidepressant effect. Thus, although venlafaxine may be more efficacious than most SSRIs, the proposed mechanism of action of escitalopram may explain why it is as efficacious as venlafaxine, with the superior tolerability of an SSRI.^{4,5}

A potential limitation of the present meta-analysis relates to an inconsistency in duration of treatment. Although most of the data come from week 8 (8/10 studies), in the 2 long-term trials week 24 and week 27 end-point data were used. Although these long-term end points were slightly better, the sensitivity analysis performed on week 8 data from all 10 studies showed that the results still hold. The same is true if the 2 long-term trials are excluded from the meta-analysis.

When evaluating the ad hoc analyses, we must consider whether receiving placebo or not could affect treatment outcome due to patient selection bias and patient expectations.³⁰ Thus, whereas the analyses show that escitalopram is superior to active comparators in placebo-controlled studies, as well as in fixed-dose and high-dose studies, statistical comparisons between these factors have not been performed and can only be considered as explorative in nature. These factors are relevant for randomized clinical trials and may not be generalizable to treatment in primary care.

As in other published meta-analyses,^{10,11} there is a disproportionate weighting toward 1 or 2 comparators. In this case, citalopram ($n = 577$) accounted for the majority of patients who received an active SSRI comparator as compared with fluoxetine ($n = 262$), paroxetine ($n = 156$) and sertraline ($n = 107$), and the overall results do not necessarily reflect a significant difference between escitalopram and each SSRI. However, the potential for a disproportionate influence of one or more studies is limited, because the number of patients in each study was roughly similar, varying from 194 (study 9) to 339 (study 4). Finally, although 1 late-life depression study was included in the present meta-analysis and some patients over 65 years of age participated in the other studies, there are insufficient data to apply these results to the elderly population.

What is the clinical relevance of these results? A treatment difference between drug and placebo of at least 2 points on the MADRS is usually considered clinically significant. In this pooled analysis, the estimated mean treatment difference of 1.07 points on the MADRS is small, but statistically significant. For patients with a more severe baseline depression (MADRS ≥ 30), who accounted for almost half of the patients, the estimated mean treatment difference is 2.34 points. In the 5 placebo-controlled escitalopram trials in MDD,^{6-8,12,31} the adjusted mean treatment difference on the MADRS is 3.0 points, and the LOCF response rates after 8 weeks are 37.3% for placebo ($n = 738$) and 52.9% for escitalopram ($n = 851$).

For severely depressed patients, the corresponding adjusted mean treatment difference on the MADRS is 3.3 points, with response rates of 34.5% for placebo ($n = 333$) and 50.8% for escitalopram ($n = 384$). This corresponds to a difference in response rates of over 15%, which is considered to be a clinically meaningful difference.³² In a trial with severely depressed patients, an adjusted mean treatment difference on the MADRS of 2.1 points corresponds to a difference of 14.6% in response rates (76.1% for escitalopram and 61.5% for citalopram).²³ It has been noted that even a modest difference between treatments in the proportion of patients achieving remission is likely to be associated with advantages in important "real-world" domains.³⁰

In conclusion, in this meta-analysis, escitalopram had greater efficacy compared with the comparators (citalopram, fluoxetine, paroxetine, sertraline and venlafaxine XR), as assessed by MADRS on a series of end-point comparisons involving change in efficacy scores from baseline and in response and remission rates. The proposed mechanism of action of escitalopram may explain its enhanced efficacy compared with conventional SSRIs. Given its favourable tolerability profile based on withdrawals due to adverse events, these results suggest that escitalopram may have an improved benefit-risk ratio compared with other antidepressant medications.

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