

Escitalopram Versus SNRI Antidepressants in the Acute Treatment of Major Depressive Disorder: Integrative Analysis of Four Double-Blind, Randomized Clinical Trials

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ABSTRACT

Introduction: Recent data suggest that escitalopram may be more effective in severe depression than other selective serotonin reuptake inhibitors.

Methods: Individual patient data from four randomized, double-blind comparative trials of escitalopram versus a serotonin/norepinephrine reuptake inhibitor (SNRI) (two trials with duloxetine and two with venlafaxine extended release) in outpatients (18–85 years of age) with moderate-to-severe major depressive disorder were pooled. The primary efficacy parameter in all four trials was mean change in the Montgomery-Åsberg Depression Rating Scale (MADRS) score.

Results: Significantly fewer escitalopram (82/524) than SNRI (114/527) patients pre-

FOCUS POINTS

- Limited research suggests an efficacy advantage for serotonin/norepinephrine reuptake inhibitors (SNRIs) relative to selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression but trials comparing escitalopram to SNRIs have shown no efficacy advantage.
- Data from four double-blind, randomized trials of escitalopram versus duloxetine or venlafaxine extended release (XR) were pooled for analysis.
- Escitalopram is at least as effective as the SNRIs duloxetine and venlafaxine XR, even in severe depression, and is better tolerated.

turely withdrew from treatment due to all causes (15.6% vs. 21.6%, Fisher Exact: $P=.014$) and adverse events (5.3% vs. 12.0%, Fisher Exact: $P<.0001$). Mean reduction in MADRS score from baseline to Week 8 was significantly greater for the escitalopram group versus the SNRI group

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using the last observation carried forward (LOCF) approach [mean treatment difference at Week 8 of 1.7 points ($P < .01$)]. Similar results were observed in the severely depressed (baseline MADRS score ≥ 30) patient subset (mean treatment difference at Week 8 of 2.9 points [$P < .001$, LOCF]). Observed cases analyses yielded no significant differences in efficacy parameters.

Conclusion: This pooled analysis indicates that escitalopram is at least as effective as the SNRIs (venlafaxine XR and duloxetine), even in severe depression, and escitalopram treatment was better tolerated.

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INTRODUCTION

Major depressive disorder (MDD) is by definition a disabling disorder, and the World Health Organization has identified MDD as one of the leading causes of disability worldwide.¹ When depression is severe, there is significant associated morbidity and a low likelihood of spontaneous remission.² Approximately one-third of depressed patients can be classified as being severely depressed.³

Serotonin reuptake inhibitors (SRIs) are well recognized as first-line pharmacotherapy for MDD; they have supplanted their therapeutic predecessors largely on the basis of improved safety and tolerability.⁴ Two well-established classes of SRIs are those that are selective for serotonin (SSRIs) and those that inhibit the reuptake of both serotonin and norepinephrine (SNRIs). The SSRI class includes fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Venlafaxine, duloxetine, and desvenlafaxine comprise the class of SNRIs currently available in the United States.

Escitalopram is the *S*-enantiomer of the racemate citalopram and there is evidence that it is more effective than citalopram, especially for patients with severe depression^{5,6}; similar results have been reported for escitalopram in comparison with paroxetine.⁷ Moreover, a recent pooled analysis demonstrated superior efficacy of escitalopram versus comparator SSRIs and comparable efficacy to venlafaxine extended release (XR), with a larger effect apparent in severely depressed individuals.⁸

Some researchers have suggested that SNRIs have inherently greater efficacy than SSRIs as a class.⁹⁻¹³ However, a number of trials comparing escitalopram with the SNRIs venlafaxine or duloxetine failed to demonstrate any major difference in efficacy among these agents.¹⁴⁻¹⁸ Indeed, two of these trials demonstrated significant differences in efficacy parameters favoring escitalopram.^{15,18} Thus, although SNRIs are believed to offer superior efficacy to SSRIs as a class, this does not appear to extend to escitalopram.

The use of individual randomized controlled trials (RCTs) to evaluate efficacy differences between antidepressants is limited by the practical issue of achieving a sufficient sample size. To achieve the power necessary to detect a treatment difference between two established antidepressants, the sample size would have to be several times greater than that for determining efficacy versus placebo.¹⁹ Therefore, in order to evaluate the efficacy of escitalopram compared to the two SNRIs, venlafaxine and duloxetine, we have undertaken an analysis of pooled data from the four previously published comparative trials for which individual patient data were available. As an additional sensitivity analysis, we also undertook these analyses in the subset of patients from these four trials who were severely depressed at baseline, as the magnitude of antidepressant effect has been shown to increase with baseline severity.²⁰

METHODS

Data from four randomized, double-blind trials of escitalopram compared with either venlafaxine XR or duloxetine were pooled for the present set of analyses (Table 1). Results from each of these individual trials have been previously reported.^{14-16,18} Three of the trials were 8 weeks in duration; Study 4¹⁸ was 24 weeks in duration. All four trials had study visits at baseline and at Weeks 1, 2, 4, and 8 of double-blind treatment. In the 24-week study, Week 8 completers were defined as patients completing at least 56 days of treatment.

Patients

All subjects were adult outpatients with moderate-to-severe MDD, as diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*²¹ criteria (Table 1).

Similar exclusion criteria were applied for each of the four primary studies. In Studies 1-3,

patients with any current primary Axis I disorder other than MDD were excluded. In Study 4, patients with an anxiety disorder (other than obsessive-compulsive disorder, posttraumatic stress disorder, or panic disorder) occurring secondarily to MDD were eligible to participate. Other *DSM-IV-TR* diagnoses including bipolar disorder, schizophrenia, psychotic disorder, and cognitive disorders were also criteria for exclusion. A score of ≥ 5 on item 10 (suicidal thoughts) of the Montgomery-Åsberg Depression Rating Scale (MADRS),²² recent substance abuse or dependence, treatment with antipsychotics, antidepressants, or psychotropics (except for insomnia treatment), and use of other medications thought likely to interfere with the study were additional grounds for exclusion. Patients with medical conditions or medical histories that in the opinion of the investigator may compromise participation in the study were also excluded.

Dosing

Drug dosages and titration schedules were based on the recommendations of the package inserts for each product for the European Union or the US, as appropriate. The escitalopram dose was fixed at 10 mg/day for either the first week (Studies 1 and 2), the first 2 weeks (Study 4), or the first 4 weeks (Study 3), after which the dose was either increased to 20 mg/day (Studies 2 and 4) or flexibly dosed from 10–20 mg/day (Studies 1 and 3). The venlafaxine XR dose was initiated at 75 mg/day and either titrated in two

steps to 225 mg/day in 8 days (Study 2) or fixed at 75 mg/day for the first week and then flexibly dosed from 75–150 mg/day thereafter (Study 1). The duloxetine dose was fixed at 60 mg/day throughout (Studies 3 and 4). In fixed-dose studies, patients unable to tolerate the dose were discontinued from the study. In flexible-dose studies, the dose could be lowered to the minimum allowed in the event of adverse events (AEs); if that dose could not be tolerated, the patient was discontinued from the study.

Statistical Methodology

For all four trials, the protocol-defined primary efficacy parameter was the mean change from baseline to endpoint in MADRS total score, using the last observation carried forward (LOCF) approach; the MADRS was measured at baseline and at every post-baseline study visit. Only data from the first 8 weeks of double-blind treatment from Study 4 were used in the pooling. Severe depression was defined as a baseline MADRS score of 30 or greater.

Patient disposition, demographics, efficacy, and safety analyses were based on the Safety Population, which consisted of all patients who received at least one dose of double-blind study medication in any of the four trials. For sensitivity analyses, additional efficacy analyses were based on the Intent-to-Treat (ITT) population, which consisted of all patients in the Safety Population who received at least one post-baseline MADRS assessment.

TABLE 1.
Trials Included in Pooled Analysis

<i>Study</i>	<i>Doses</i>	<i>Minimum Baseline MDD Severity</i>	<i>Allowable Age Range (years)</i>
1 ¹⁶	Escitalopram 10–20 mg/day* Venlafaxine XR 75–150 mg/day*	MADRS ≥ 18	18–85
2 ¹⁴	Escitalopram 20 mg/day Venlafaxine XR 225 mg/day	24-item HAMD ≥ 20	18–65
3 ¹⁵	Escitalopram 10–20 mg/day * Duloxetine 60 mg/day	MADRS ≥ 26 CGI-S ≥ 4	18–80
4 ¹⁸	Escitalopram 20 mg/day Duloxetine 60 mg/day	MADRS ≥ 26 CGI-S ≥ 4	18–65

*These treatment groups were flexibly dosed; all other treatment groups were fixed dose or in the case of venlafaxine in Study 2, a forced titration schedule was followed. For escitalopram 20 mg/day, patients were treated with escitalopram 10 mg/day for the first week (Study 2), or first 2 weeks (Study 4). In Study 3, the escitalopram dose was fixed at 10 mg/day for the first 4 weeks.

MADRS=Montgomery-Åsberg Depression Rating Scale; HAMD=Hamilton Rating Scale of Depression; CGI-S=Clinical Global Impression-Severity.

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Comparisons between groups for changes from baseline for each efficacy parameter were performed using an analysis of covariance (ANCOVA) model, with treatment group and study center as factors and baseline score as covariate, using both the LOCF and the observed cases approaches. For response and remission rates, analyses were based on logistic regression models with treatment group and baseline MADRS total score as explanatory variables.

Safety was evaluated on the basis of reports of treatment-emergent AEs and premature discontinuation of treatment due to AEs. Comparisons between treatment groups of reasons for premature withdrawal were performed using Fisher's Exact test.

RESULTS

Patients

The Safety Population consisted of 524 escitalopram-treated patients and 527 SNRI-treated patients, and the ITT Population consisted of 520 escitalopram-treated patients and 512

SNRI-treated patients (Table 2). Treatment was completed by significantly more escitalopram patients ($n=442$; 84.4%) than SNRI patients ($n=413$; 78.4%; χ^2 : $P=.0128$, Fisher: $P=.014$). Significantly more SNRI-treated patients than escitalopram-treated patients discontinued prematurely due to AEs or withdrawn consent (Table 2). Within the SNRI group, the proportion of patients discontinuing prematurely for these reasons was similar for duloxetine and venlafaxine XR.

The mean \pm SD age of the Safety Population was 43.2 \pm 13.3 years (escitalopram 43.1 \pm 13.7, SNRI 43.4 \pm 12.9; $P=.750$), and 66.7% of the Safety Population were women (escitalopram 69.1%, SNRI 64.3%; $P=.087$).

At baseline, the mean \pm SD baseline MADRS total scores for the escitalopram and SNRI groups were 30.7 \pm 4.7 and 30.8 \pm 4.9, respectively. A total of 300 escitalopram (57.3%) and 322 SNRI (61.1%) patients were severely depressed (MADRS total score of ≥ 30) at baseline, with mean \pm SD baseline MADRS total scores of 33.8 \pm 3.2 for this subset of the escitalopram group and 33.7 \pm 3.3 for the SNRI group.

TABLE 2.
Patient Disposition

	Study 1		Study 2		Study 3		Study 4	
	<i>ESC</i>	<i>VEN XR</i>	<i>ESC</i>	<i>VEN XR</i>	<i>ESC</i>	<i>DUL</i>	<i>ESC</i>	<i>DUL</i>
Randomized, n	148	145	101	101	140	138	144	151
Safety Population, n	146	143	98	100	137	133	143	151
ITT Population, n	146	142	97	98	136	126	141	146
Completed, n (%)	125 (85.6)	124 (86.7)	72 (73.5)	66 (66.0)	119 (86.9)	92 (69.2)	126 (88.1)	131 (86.7)
Pooled Analysis, Safety Population								
					<i>Escitalopram (n=524)</i>		<i>SNRI (n=527)</i>	
					<i>n (%)</i>		<i>n (%)</i>	
Completed					442 (84.4)		413 (78.4)*	
<i>Reasons for Withdrawal</i>								
Adverse Event					28 (5.3)		63 (12.0)*	
Insufficient Therapeutic Response					7 (1.3)		3 (.6)	
Protocol Violation					9 (1.7)		6 (1.1)	
Consent Withdrawn					7 (1.3)		19 (3.6)*	
Lost to Follow-up					28 (5.3)		21 (4.0)	
Other					3 (.6)		2 (.4)	

* $P<.05$ vs. escitalopram

ESC=escitalopram; *VEN XR*=venlafaxine extended release; *DUL*=duloxetine; *ITT*=intent-to-treat; *SNRI*=serotonin/norepinephrine reuptake inhibitor.

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Efficacy

Escitalopram treatment led to significantly greater improvement in MADRS total scores relative to SNRI treatment at Weeks 1, 2, 4, and 8 (LOCF) for the total dataset (Safety Population) (Figure 1). The mean treatment difference at Week 8 was 1.7 points in favor of escitalopram ($P<.01$). Similar results were seen for patients with a baseline MADRS total score ≥ 30 (Figure 2), with a mean treatment difference at Week 8 of 2.9 points ($P<.001$). Using the observed cases approach, the mean treatment difference at Week 8 was 0.9 points in favor of escitalopram ($P=0.0896$), and 1.3 points for patients with a baseline MADRS total score ≥ 30 ($P=.1053$).

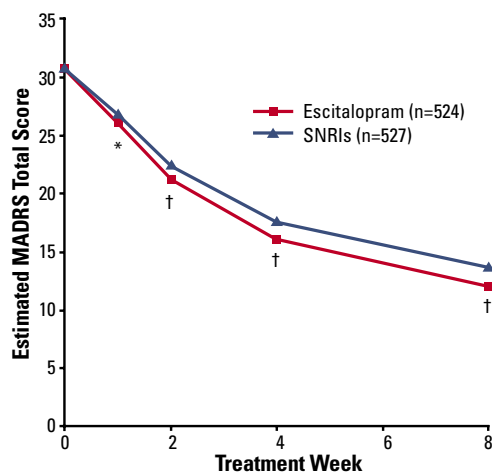
The mean difference between treatment groups in change from baseline to Week 8 (LOCF) was analyzed for MADRS single items. Escitalopram was significantly superior to SNRIs on 6 of 10 items: items 1 (apparent sadness), 3 (inner tension), 4 (reduced sleep), 6 (concentration difficulties), 7 (lassitude), and 10 (suicidal thoughts). For patients with a baseline MADRS total score ≥ 30 , escitalopram was statistically significantly superior to SNRIs on 9 items: items 1, 2 (reported sadness), 3, 4, 5 (reduced appetite), 7, 8 (inability to

feel), 9 (pessimistic thoughts), and 10. The SNRIs did not achieve superiority versus escitalopram on any of the MADRS single items.

Efficacy was also assessed by remission (MADRS total score ≤ 12 or ≤ 10) and responder rates ($\geq 50\%$ decrease from baseline in MADRS total score). Response to treatment at Week 8 was statistically significantly greater for patients treated with escitalopram, as was remission when defined as MADRS ≤ 12 . For severely depressed patients (baseline MADRS total score ≥ 30), there were statistically significantly greater response and remission rates, whether defined as MADRS ≤ 12 or ≤ 10 , for patients treated with escitalopram (Table 3). The number needed to treat (NNT) based on response rates for escitalopram versus the SNRIs was 11 for all patients and 7 for severely depressed patients. For each definition of remission, the NNTs for escitalopram versus venlafaxine for all patients was 14 (MADRS ≤ 12) and 12 (MADRS ≤ 10); for severely depressed patients, NNTs for remission were 10 and 13, respectively, in favor of escitalopram.

Efficacy analyses of the ITT Population using the LOCF approach yielded qualitatively similar results, except that no significant treatment dif-

FIGURE 1.
MADRS total score by visit for all patients



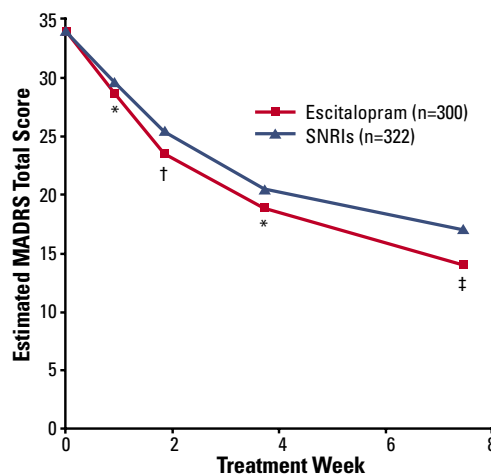
Safety Population, LOCF, ANCOVA.

* $P<.05$, † $P<.01$, in favor of escitalopram.

MADRS=Montgomery-Åsberg Depression Rating Scale; SNRIs=serotonin/norepinephrine reuptake inhibitors; LOCF=last observation carried forward; ANCOVA=analysis of covariance.

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FIGURE 2.
MADRS total score by visit for patients with a baseline MADRS ≥ 30



Safety Population, LOCF, ANCOVA.

* $P<.05$, † $P<.01$, ‡ $P<.001$ in favor of escitalopram.

MADRS=Montgomery-Åsberg Depression Rating Scale; SNRIs=serotonin/norepinephrine reuptake inhibitors; LOCF=last observation carried forward; ANCOVA=analysis of covariance.

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ferences were observed in remission rates at Week 8. Observed cases analyses yielded no significant differences in any of the efficacy parameters presented above (Table 3).

Safety

A total of 376 (71.8%) escitalopram-treated patients and 403 (76.5%) SNRI-treated patients reported at least one treatment-emergent AE (Table 4). The most common treatment-emergent AEs in both treatment groups were: nausea, headache, ejaculation disorder, insomnia, and dry mouth. Significantly more SNRI than escitalopram patients discontinued treatment prematurely due to AEs [28 (5.3%) escitalopram versus 63 (12.0%) SNRI; $P<.001$]. Based on AE withdrawal rates, the number needed to harm was 15; that is, for every 15 patients treated, 1 additional patient treated with an SNRI versus escitalopram would withdraw due to an AE.

DISCUSSION

In this analysis, we pooled data from four comparative trials in an attempt to generate sufficient statistical power to discern efficacy differences between escitalopram (the most selective SSRI for the serotonin transporter)²³ and comparator SNRIs. Detection of treatment differences in efficacy depended on the statistical approach used to analyze the data. The LOCF approach consistently yielded significant differences in efficacy results favoring escitalopram over SNRIs, whereas observed cases analyses did not yield any sig-

nificant differences in mean rating scale improvements between treatments at Week 8.

Similarly, when the ITT population was used for analyses of efficacy, remission rates were not significantly different between groups. It is probable that differences in tolerability influenced these outcomes, in that there were more discontinuations due to AEs for the SNRI group, particularly between baseline and Week 1. Nevertheless, regardless of the statistical approach used, the pooled SNRI data set never yielded greater improvement in rating scale scores than escitalopram in any efficacy outcome. Thus, these analyses provide no evidence that dual-action SNRIs offer any efficacy advantage over escitalopram.¹²

It is notable that qualitatively similar results were obtained when the comparison of escitalopram with SNRIs was conducted in severely depressed patients and in the whole study population. These results are consistent with a meta-analysis showing an increasing difference in treatment effect for escitalopram versus comparators as a function of increasing baseline severity.⁸ A meta-analysis comparing duloxetine with two SSRIs (ie, paroxetine and fluoxetine) found comparable efficacy among the drugs in the overall study population but significantly higher remission rates in favor of duloxetine in patients with more severe depression (17-item Hamilton Depression Rating Score ≥ 19).²⁴ In these studies, paroxetine and fluoxetine doses were fixed at 20 mg/day (recommended ranges: 20–50 mg/day and 20–80 mg/day, respectively)^{25,26} and duloxetine fixed doses ranged

TABLE 3.
Response and Remission Rates at Week 8 (Safety Population)

Efficacy Parameter		All patients		Severely depressed patients*	
		Escitalopram (n=524)	SNRIs (n=527)	Escitalopram (n=300)	SNRIs (n=322)
Responders [†]	LOCF	68.3% [§]	59.0%	68.7%	54.3%
	OC	75.6% [‡]	68.4%	74.4% [‡]	65.1%
Remitters					
MADRS ≤ 12	LOCF	57.8% [‡]	50.5%	53.0%	40.4%
	OC	64.4%	58.1%	57.8%	48.6%
MADRS ≤ 10	LOCF	48.7%	44.0%	44.0% [‡]	36.3%
	OC	54.7%	50.7%	48.4%	43.5%

*Baseline MADRS total score ≥ 30 , [†] $\geq 50\%$ reduction in MADRS total score, [‡] $P<.05$, [§] $P<.01$, ^{||} $P<.001$ versus SNRIs

SNRIs=serotonin/norepinephrine reuptake inhibitors; LOCF=last observation carried forward; OC=observed cases; MADRS=Montgomery-Åsberg Depression Rating Scale.

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from 40 mg/day (recommended range: 40–60 mg/day)²⁷ up to 120 mg/day. Thus, one might have expected a potentially greater response in the severely depressed patients to SNRIs.

The four trials in the present analysis—two comparing escitalopram and venlafaxine XR and two comparing escitalopram and duloxetine—have been analyzed previously as separate pools.^{28,29} In the pooled analysis of trials comparing escitalopram with venlafaxine XR, there was no treatment difference with respect to the primary efficacy measure (MADRS total score mean change from baseline to Week 8) for the total population. However, the pooled data from the studies that compared escitalopram and duloxetine demonstrated a significantly superior treatment effect in favor of escitalopram, with a mean treatment difference of 3.7 points ($P<.01$). These results suggest that the results of the present analysis may have been more heavily influenced by the comparison between escitalopram and duloxetine than between escitalopram and venlafaxine XR.

It is not clear mechanistically why escitalopram would perform better when compared to duloxetine than to venlafaxine. A global benefit-risk assessment of venlafaxine and duloxetine derived from pooled data from two randomized, double-blind studies found no significant differences between these drugs.³⁰ It is possible that a higher dose of duloxetine may have performed better; however, no efficacy advantage has been demonstrated with doses higher than 60 mg in dose-finding meta-analyses.^{31,32} Similarly, the results of a recent study did not demonstrate a difference in remission rates when patients who did not experience sufficient symptom improvement following treatment with 60 mg of duloxetine were randomized to continue treatment with 60 mg or 120 mg.³³ An 8-month comparison of duloxetine and escitalopram that permitted dose increases to 120 mg and 20 mg, respectively, after an initial 8 weeks fixed at 60 mg and 10 mg, respectively, found similar rates of remission for both treatments.³⁴

It has been suggested that antidepressants that inhibit reuptake of both serotonin and norepinephrine may offer efficacy advantages relative to the SSRIs.¹² The controversy persists, in part, because methodological problems limit the sensitivity of RCTs to detect differences between active antidepressant treatments. Meta-analyses of data pooled from RCTs comparing the SSRIs with venlafaxine or duloxetine have demonstrated potentially greater efficacy for these two SNRIs except in relation to escitalopram.¹² Results from our analysis of pooled data from four previously published comparative trials of venlafaxine or duloxetine versus escitalopram, support the position that escitalopram is at least as effective as the SNRI comparators.

A number of factors limit the interpretability of the efficacy findings from these analyses. One is that not all published comparator trials were included in this analysis, and only studies sponsored by the manufacturers of escitalopram have been included. However, the only other acute treatment study completed to date of which the authors are aware failed to show an efficacy advantage for duloxetine over escitalopram.¹⁷ Second, no corrections were made for multiplicity of comparisons. Third, dosing was conducted per product labeling, but this may not reflect dosing used in clinical practice. Nevertheless, the rapid titration of the SNRI in several of these protocols did not lead to an enhanced effect in those patients who were severely depressed at baseline.

TABLE 4.
Adverse Events (Safety Population)*

	Escitalopram (n=524) n (%)	SNRI (n=527) n (%)
Patients with at least 1 AE	376 (71.8)	403 (76.5)
Nausea	84 (16.0)	141 (26.8)
Headache	81 (15.5)	73 (13.9)
Ejaculation disorder†	12 (7.4)	25 (13.3)
Insomnia	40 (7.6)	68 (12.9)
Dry mouth	43 (8.2)	60 (11.4)
Dizziness	24 (4.6)	46 (8.7)
Fatigue	29 (5.5)	41 (7.8)
Somnolence	43 (8.2)	37 (7.0)
Diarrhea	39 (7.4)	36 (6.8)
Constipation	21 (4.0)	36 (6.8)
Increased sweating	18 (3.4)	30 (5.7)
Anxiety	22 (4.2)	29 (5.5)
Anorexia	13 (2.5)	27 (5.1)
Pharyngitis	41 (7.8)	26 (4.9)

* Events with an incidence of at least 5% in either treatment group.

† Based on the number of male patients, escitalopram n=162, SNRI n=188.

SNRI=serotonin/norepinephrine reuptake inhibitors; AE=adverse events.

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CONCLUSION

In conclusion, this pooled analysis indicates that escitalopram is at least as effective as the SNRIs (venlafaxine XR and duloxetine), even in severe depression, and escitalopram is better tolerated.

REFERENCES

- Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370:851-858.
- Thase ME. Treatment of severe depression. *J Clin Psychiatry*. 2000;61(Suppl 1):17-25.
- Thase ME. Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr*. 2004;9:808-816, 818-821.
- Papakostas GI, Fava M. Monoaminergic-based pharmacotherapy for depression. In: Licinio J, Wong ML, eds. *Biology of Depression: From Novel Insights to Therapeutic Strategies*. 1st ed. Weinheim, Germany: Wiley-VCH; 2005:87-140.
- Lam RW, Andersen HF. The influence of baseline severity on efficacy of escitalopram and citalopram in the treatment of major depressive disorder: an extended analysis. *Pharmacopsychiatry*. 2006;39:180-184.
- Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol*. 2005;20:131-137.
- Boulenger JP, Huusom AK, Florea I, Baekdal T, Sarchiapone M. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. *Curr Med Res Opin*. 2006;22:1331-1341.
- Kennedy SH, Andersen HF, Lam RW. Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J Psychiatry Neurosci*. 2006;31:122-131.
- Nemeroff CB, Entsuah R, Benattia I, Demitrack M, Sloan DM, Thase ME. Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. *Biol Psychiatry*. 2008;63:424-434.
- Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008;63:699-704.
- Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biol Psychiatry*. 2007;62:1217-1227.
- Thase ME. Are SNRIs More Effective than SSRIs? A Review of the Current State of the Controversy. *Psychopharmacol Bull*. 2008;41:58-85.
- Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.
- Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. *J Clin Psychiatry*. 2004;65:1190-1196.
- Khan A, Bose A, Alexopoulos GS, Gommoll C, Li D, Gandhi C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. *Clin Drug Investig*. 2007;27:481-492.
- Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology*. 2004;50:57-64.
- Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin*. 2007;23:401-416.
- Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. *Curr Med Res Opin*. 2007;23:1605-1614.
- Lieberman JA, Greenhouse J, Hamer RM, et al. Comparing the effects of antidepressants: consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. *Neuropsychopharmacology*. 2005;30:445-460.
- Khan A, Brodhead AE, Kolts RL, Brown WA. Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. *J Psychiatr Res*. 2005;39:145-150.
- Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
- Montgomery SA, Å M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.
- Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol Psychiatry*. 2001;50:345-350.
- Thase ME, Pritchett YL, Ossanna MJ, Swindle RW, Xu J, Detke MJ. Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. *J Clin Psychopharmacol*. 2007;27:672-676.
- Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
- Prozac [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
- Cymbalta [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.
- Lam RW, Andersen HF, Wade AG. Escitalopram and duloxetine in the treatment of major depressive disorder: a pooled analysis of two trials. *Int Clin Psychopharmacol*. 2008;23:181-187.
- Montgomery SA, Andersen HF. Escitalopram versus venlafaxine XR in the treatment of depression. *Int Clin Psychopharmacol*. 2006;21:297-309.
- Perahia DG, Pritchett YL, Kajdasz DK, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. *J Psychiatr Res*. 2008;42:22-34.
- Bech P, Kajdasz DK, Porsdal V. Dose-response relationship of duloxetine in placebo-controlled clinical trials in patients with major depressive disorder. *Psychopharmacology (Berl)*. 2006;188:273-280.
- Pritchett YL, Marciniak MD, Corey-Lisle PK, Berzon RA, Desai D, Detke MJ. Use of effect size to determine optimal dose of duloxetine in major depressive disorder. *J Psychiatr Res*. 2007;41:311-318.
- Kornstein SG, Dunner DL, Meyers AL, et al. A randomized, double-blind study of increasing or maintaining duloxetine dose in patients without remission of major depressive disorder after initial duloxetine therapy. *J Clin Psychiatry*. 2008;69:1383-1392.
- Pigott TA, Prakash A, Arnold LM, Aaronson ST, Mallinckrodt CH, Wohlreich MM. Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder. *Curr Med Res Opin*. 2007;23:1303-1318.