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Original article

Remission of major depressive disorder without adverse events: a comparison of escitalopram versus serotonin norepinephrine reuptake inhibitors

James Signorovitch
Karthik Ramakrishnan
Rym Ben-Hamadi
Andrew P. Yu
Eric Q. Wu
Analysis Group, Inc., Boston, MA, USA

Heather Dworak
M. Haim Erder
Forest Research Institute, Inc., Jersey City, NJ, USA

Address for correspondence:
James Signorovitch, PhD, 111 Huntington Avenue, 10th floor, Boston, MA 02199, USA.
Tel.: +1 617 425 8258; Fax: +1 617 425 8001;
jsignorovitch@analysisgroup.com

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Abstract

Objective:
An antidepressant's tolerability, generally captured as the frequency and severity of adverse events (AEs), is often as important as its efficacy in determining treatment success. This study used a composite outcome – remission of major depressive disorder (MDD) without AEs – to compare the benefit–risk profiles of escitalopram versus the norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine extended release (XR).

Methods:
Pooled data from three randomized, double-blind, multicenter trials were analyzed, in which patients with MDD were treated for 8 weeks with either escitalopram ($n = 462$) or an SNRI ($n = 467$).

Clinical trial registration: clinicaltrials.gov identifiers: NCT00108979; NCT00384436.

Main outcome measures:
The composite outcome was defined as remission (Montgomery–Åsberg Depression Rating Scale [MADRS] score ≤ 10) and concurrent absence of an AE. The proportions of remitted patients free of (1) any AEs, (2) moderate-to-severe AEs, and (3) study drug–related AEs were compared between treatment groups at each study visit and longitudinally across study visits common to all trials during the first 8 weeks of treatment.

Results:
At endpoint (week 8), escitalopram-treated patients were more likely than SNRI-treated patients to experience remission free of any AEs (28.4 vs. 21.6%; $p = 0.0179$) and remission free of study drug–related AEs (45.2 vs. 36.8%; $p = 0.0092$). Compared to SNRI-treated patients, escitalopram-treated patients had 38% greater odds of remission free of any AEs, 28% greater odds of remission free of moderate-to-severe AEs, and 34% greater odds of remission free of study drug–related AEs (all $p < 0.05$).

Conclusion:
Treatment of adult MDD patients with escitalopram was significantly more likely to result in remission without concurrent AEs compared to treatment with current SNRIs. Study limitations include focus on only the initial 8 weeks of treatment and exclusion of trials for which individual patient data were not obtained.

Introduction

Major depressive disorder (MDD) affects up to 6.7% of the US population each year[1], resulting in significant physical and social impairment[2], increased morbidity and mortality[3,4], and a substantial economic burden due to lost productivity and increased health care costs[5,6]. Common pharmacotherapies for MDD include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), among others. Though SSRIs and SNRIs can effectively treat depression symptoms, their comparative clinical utility can be limited by side effects such as nausea, nervousness, insomnia, agitation, and sexual dysfunction[7–9].

Among the SSRIs, escitalopram is the most selective serotonin reuptake inhibitor[10], with proven efficacy in treating MDD and onset of antidepressant activity evident within 1–2 weeks of treatment initiation[11–16]. In a recent network meta-analysis, escitalopram had the highest chance among studied SSRIs and SNRIs of being among the best four treatments in terms of efficacy and acceptability. The study looked at the comparative efficacy among 12 antidepressant drugs, directly, and indirectly using fluoxetine as a reference drug[16]. Commonly used SNRIs for MDD, which act by inhibiting both serotonin and norepinephrine reuptake[7], include desvenlafaxine, venlafaxine, venlafaxine extended release (XR) and duloxetine, which have demonstrated efficacy in placebo-controlled[17–19] and active-controlled randomized trials[16,20–25].

At the time this study was initiated, escitalopram, duloxetine and venlafaxine XR were the major remaining branded SSRI/SNRIs. Other SSRIs were available as generics and were likely used as first-line agents. This study can provide useful information to decision makers when it comes to choosing subsequent treatment, in particular whether or not to use a branded SSRI or an SNRI.

Randomized trials of escitalopram versus SNRIs in MDD have shown escitalopram to be at least as effective as venlafaxine XR or duloxetine with a better safety and tolerability profile, and with significantly lower rates of discontinuation due to adverse events (AEs) ($p < 0.05$)[12–15,26]. Additionally, escitalopram demonstrated faster onset of sustained response by 4.6 days and longer sustained remission by 6.6 days compared to venlafaxine XR[14]. A trial of escitalopram versus duloxetine concluded that escitalopram was better tolerated than duloxetine, and that duloxetine was non-inferior to escitalopram in terms of response by week 2 or week 8.

Safety and efficacy have been reported as separate outcomes for these trials. However, in clinical practice individual patients may experience clinical remission (benefits) with or without concurrent AEs (risks). Hence, a combined measure of benefits and risks may provide a more comprehensive and clinically relevant comparison of treatment options. Montgomery and Andersen[27] provide a combined benefit–risk comparison pooling data from two head-to-head trials of escitalopram and venlafaxine XR[12,14], comparing patients in terms of an 8-level benefit–risk scale. In this analysis, escitalopram was associated with a 46% relative benefit over venlafaxine XR[27].

This paper provides clinicians with a comparison of escitalopram and SNRIs based on a straightforward combined measure of benefits and risks and examines the rate at which patients achieve clinical remission for MDD without concurrent AEs, using data pooled from randomized trials of escitalopram versus duloxetine and escitalopram versus venlafaxine XR.

Patients and methods

Data sources

Data were pooled from three phase III, multicenter, randomized, double-blind, parallel-group clinical studies comparing the efficacy and safety of escitalopram versus SNRIs (duloxetine or venlafaxine XR) among patients with moderate-to-severe MDD[12,13,28]. Two of these trials have the following clinicaltrials.gov identifiers: NCT00108979[13]; NCT00384436[28]. The third one[12] was completed prior to the mandatory posting date of 9/27/2007 for clinicaltrials.gov or the 7/1/2005 date imposed by ICMJE for listing in a WHO primary registry.

Randomized patients included male and female outpatients aged 18–80 years who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR)[29] criteria for a current episode of MDD with a minimum score of 26 on the Montgomery–Åsberg Depression Rating Scale (MADRS)[30] or a minimum score of 20 on the 24-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{24}$)[31] at both the screening and baseline visits. The trials excluded patients with evidence of active suicidal ideation, a recent suicide attempt, or any DSM-IV Axis I disorder other than MDD. Two of the included studies compared fixed doses (after an initial dose escalation schedule) in which patients were randomly assigned to receive 8 weeks of double-blind treatment with either escitalopram or the active comparator: venlafaxine XR[12] or duloxetine[28]. In the variable-dosing trial comparing escitalopram to duloxetine[13], patients received a fixed dose of escitalopram 10 mg/day for the first 4 weeks of the study, after which the dose could be increased to 20 mg/day if, in the investigator's judgment, clinical response was insufficient. Patients randomized to the duloxetine treatment group received a fixed dose of 60 mg/day throughout the treatment period. Patients enrolled in the trial conducted by Asnis *et al.*[28] were initially treated with single-blind escitalopram 10 mg/day for

Table 1. Baseline characteristics by trial.

Baseline characteristics	Bielski *et al.*[12]		Khan *et al.*[13]		Asnis *et al.*[28]	
	Escitalopram ($n=97$)	Venlafaxine XR ($n=98$)	Escitalopram ($n=136$)	Duloxetine ($n=126$)	Escitalopram ($n=229$)	Duloxetine ($n=243$)
Age (mean, SD)	37.5 (12.2)	37.4 (11.5)	43.4 (13.3)	41.9 (12.6)	43.1 (12.0)	41.6 (12.1)
Male *n* (%)	30 (30.9)	52 (53.1)	56 (41.2)	44 (34.9)	91 (39.7)	102 (42.0)
Race *n* (%)						
White	75 (77.3)	71 (72.5)	107 (78.7)	103 (81.8)	175 (76.4)	193 (79.4)
Black	12 (12.4)	14 (14.3)	19 (14.0)	19 (15.1)	34 (14.9)	32 (13.2)
Other	10 (0.1)	13 (0.1)	10 (0.1)	4 (0.0)	20 (0.1)	18 (0.1)
Number of past episodes of MDD (mean, SD)	4.9 (12.4)	6.9 (17.9)	4.3 (9.6)	5.7 (13.2)	3.8 (5.4)	3.2 (3.9)
Time since onset of MDD, years (mean, SD)	8.5 (10.2)	9.6 (10.3)	10.8 (11.2)	12.2 (12.2)	11.7 (10.4)	11.5 (11.1)
Montgomery–Åsberg Depression Rating Scale (MADRS) total score (mean, SD)	30.7 (4.6)	29.9 (5.0)	31.6 (3.8)	30.9 (3.7)	29.3 (6.1)	28.3 (5.7)

2 weeks. Patients who did not respond (MADRS reduction <50%) were then randomized to 8 weeks of double-blind treatment with escitalopram 20 mg/day or duloxetine 60 mg/day. The present study only included outcomes (AEs and MADRS scores) occurring during the double-blind treatment period for randomized non-responders. Baseline characteristics are comparable across the three trials (Table 1). Further details of study inclusion/exclusion criteria and study design have been reported previously[12,13,28]. A search of clinicaltrials.gov identified two additional phase III or later trials comparing escitalopram with duloxetine for the treatment of MDD, but individual patient data were not readily available from these trials[15,26]. The top-line results of these two trials are considered in the Discussion section.

Study outcomes

Treatment efficacy for MDD was measured by the MADRS index score[32] with assessments at screening, baseline, and each follow-up visit (weeks 1, 2, 4, 6, and 8) common to all pooled trials. Safety assessments and monitoring for AEs were conducted throughout the 8-week study period. AEs were reported with a starting date and ending date and were further classified by investigators based on their severity (mild, moderate, or severe) and relationship to the study drug (not related, possibly related or related to study drug).

The primary outcome for the present study was AE-free remission. At each day of follow-up, patients were considered to have AE-free remission if they had a MADRS score ≤10 and did not report an AE on the day in question. Missing MADRS scores were imputed by carrying the last MADRS assessment score forward. The time covered by an active AE was identified from the start and stop dates recorded on the AE report form. AEs with missing end dates were assumed to continue to week 8. AE-free remission in treatment groups was measured at each post-baseline study visit (weeks 1, 2, 4, 6, and 8) and longitudinally across these post-baseline study visits.

Separate analyses were conducted for remission free of all AEs, remission free of moderate-to-severe AEs, and remission free of study drug–related AEs. Remission free of moderate-to-severe AEs is of particular interest because, by definition, these AEs have a high potential to impact patients' health-related quality of life. Per study protocol, moderate AEs were defined as those causing discomfort and interrupting usual activities. Severe AEs were defined as those causing considerable interference with the subject's usual activities and those that may be incapacitating or life-threatening. These are standard AE definitions based on FDA requirements. Remission free of drug-related AEs was included because these events may be more likely to reflect clinically relevant differences in safety profiles between drug treatments.

Statistical analysis

Analyses were conducted for patients who were randomized and had at least one post-baseline assessment during the 8-week trial period. Baseline demographic characteristics (age, gender, race) and indicators of disease severity (time since MDD onset, number of past episodes of MDD, mean MADRS score at baseline) were compared between treatment arms using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. To assess the pooled effect of escitalopram versus SNRIs on the odds of achieving AE-free remission longitudinally across all study visits, a longitudinal logistic regression model was used, adjusting for treatment group and time. Robust *p*-values and 95% confidence intervals were obtained using generalized estimating equations (GEEs) with an unstructured working correlation to account for correlation across multiple assessments of the same patient. Proportions of patients with AE-free remission at individual study visits and proportions of

Table 2. Comparison of baseline characteristics in pooled study population: escitalopram versus duloxetine or venlafaxine XR.

Baseline characteristics	Escitalopram [A]	Duloxetine or venlafaxine XR [B]	Difference* [A]–[B] or [A]/[B]	*p*-value† [A] vs. [B]
Study sample	462	467		
Age (years), mean (SD)	40.8 (12.4)	42.0 (12.5)	–1.1	0.1792
Male, %	38.3	42.4	0.9	0.2040
Race, *n* (%)				0.8010
White	77.3	78.6	1	
Black	14.1	13.9	1	
Other	8.7	7.5	1.2	
Time since onset of MDD (years), mean (SD)	11.1 (11.3)	11.0 (10.6)	0.1	0.6300
Number of past episodes of MDD, mean (SD)	4.3 (9.6)	4.6 (10.4)	–0.3	0.2550
MADRS total score, mean (SD)	29.6 (5.1)	30.1 (5.4)	–0.5	0.1068

*The relative risk is calculated for proportions; the difference is calculated for continuous variables.
†The Wilcoxon rank sum test is used for comparing continuous variables; the chi-square test is used for comparing categorical variables.

Table 3. Proportion of patients with MADRS remission or adverse events at week 8: escitalopram versus duloxetine or venlafaxine XR.

	Escitalopram ($n=462$)	Duloxetine or venlafaxine XR ($n=467$)	Odds ratio*	*p*-value*
MADRS remission†	48.3	39.8	1.41	0.0096‡
Adverse events				
Any AE (%)	41.6	48.0	0.77	0.0496‡
Moderate-to-severe AEs (%)	22.1	25.7	0.83	0.1964
AE related to study drug (%)	4.6	6.9	0.65	0.1322

*Computed using a logistic regression for the effect of treatment group.
†MADRS score ≤10, obtained using last observation carried forward (LOCF) in the case of missing week 8 values.
‡Indicates significance at 5% level.
MADRS indicates Montgomery–Åsberg Depression Rating Scale; AE, adverse event.

patients with ≥5 or ≥10 AE-free remission days were compared between treatment arms using chi-square tests. *P*-values less than 0.05 were considered statistically significant.

Results

The three randomized trials included 929 patients. The pooled escitalopram ($n=462$) and SNRIs ($n=467$) treatment groups were well balanced with no significant differences in demographic or clinical characteristics (Table 2). The mean duration of MDD was 11 years in both treatment groups ($p=0.6300$). Mean MADRS scores at baseline were 29.6 and 30.1 for the escitalopram and SNRI groups, respectively ($p=0.1068$), and baseline MADRS scores in both groups were within the cutoff score commonly used as a threshold to delineate moderate depression on the MADRS scale (Table 2).

Escitalopram treatment was associated with 41% higher odds of MDD remission at week 8 compared to SNRI treatment ($p=0.0096$). In addition, 41.6% of escitalopram-treated patients versus 48.0% of SNRI-treated patients experienced AEs during the study period ($p=0.0496$). No statistically significant differences were observed in rates of moderate-to-severe AEs and drug-related AEs for escitalopram versus SNRI treatment (Table 3).

Over the 8 weeks of follow-up, escitalopram-treated patients had 41% higher odds of experiencing ≥5 days of AE-free remission compared to SNRI-treated patients ($p=0.0207$) and 33% higher odds for moderate-to-severe AEs and for AEs related to the study drug ($p=0.0404$ and $p=0.0369$, respectively) (Table 4). There were trends toward higher odds of ≥10 AE-free remission days for escitalopram versus SNRIs, but the difference was only statistically significant for any AEs (odds ratio = 1.42; $p=0.0247$) (Table 4). Escitalopram-treated patients experienced a mean of 6.7 AE-free remission days (free of any AEs) during the 8-week study period compared to a mean of 5.2 AE-free remission days for SNRI-treated patients ($p=0.0116$).

In analyses of AE-free remission by study visit, escitalopram-treated patients were more likely to experience AE-free remission at week 8 than SNRI-treated patients, with significant differences for remission free of any AE (28.4 vs. 21.6%; $p=0.0179$) and remission free of AEs related to study drug (45.2 vs. 36.8%; $p=0.0092$) (Figures 1A and B). When outcomes across study visits (weeks 1, 2, 4, 6 and 8) were pooled, escitalopram treatment compared with SNRI treatment was associated with

Table 4. Patients with AE-free remission days stratified by type of AE.

AE-free remission categories*	Escitalopram ($n=462$)	Duloxetine or venlafaxine XR ($n=467$)	Odds ratio†	p-value
Free of any AE (%)				
≥5 days	30.5	23.8	1.41	0.0207‡
≥10 days	27.1	20.8	1.42	0.0247‡
Free of moderate-to-severe AEs (%)				
≥5 days	37.9	31.5	1.33	0.0404‡
≥10 days	34.2	29.8	1.23	0.1473
Free of AE related to study drug (%)				
≥5 days	41.6	34.9	1.33	0.0369‡
≥10 days	39.4	33.8	1.27	0.0785

*Remission (MADRS ≤10) was imputed between study visits using the LOCF method.
†Based on a logistic regression model for the effect of treatment.
‡Indicates significance at 5% level.
AE, adverse event; LOCF, last observation carried forward.

increased odds for remission free of any AE (odds ratio: 1.38; $p=0.0163$) (Figure 1A), free of AEs related to the study drug (odds ratio: 1.34; $p=0.0157$) (Figure 1B) and free of moderate-to-severe AEs (odds ratio: 1.28; $p=0.0447$) (Figure 1C). When rates of remission and all AEs were studied separately by study visits (Figure 2), escitalopram compared to SNRIs was found to have statistically higher remission rates and lower rates of AEs at weeks 2 and 8 ($p<0.05$).

Discussion

In this pooled analysis of randomized trials, MDD treatment with escitalopram compared with SNRIs was associated with higher rates of remission free of concurrent adverse events during the first 8 weeks of treatment. When benefits and risks were measured separately, escitalopram was associated with a higher remission rate and a lower total rate of AEs compared to SNRIs in the pooled trial data across all study visits, with statistically significant differences at weeks 2 and 8. These findings are consistent with a recent network meta-analysis, combining clinical trials for all second-generation antidepressants, which found that escitalopram had superior efficacy and acceptability compared with duloxetine and better acceptability compared with venlafaxine[16].

The clinical implication of this study is that patients are more likely to achieve acute-phase remission free of AEs with escitalopram than with duloxetine or venlafaxine XR. Selecting an antidepressant with the best benefit–risk profile is important because side effects and lack of response are common causes of antidepressant therapy discontinuation[33,34], which in turn is associated with relapse, recurrence, and poor long-term outcomes[35,36]. In this context, AE-free remission is the long-term goal of depression treatment and also may be an important short-term factor influencing initial adherence to antidepressant therapy.

Traditionally, clinical studies and meta-analyses comparing antidepressant therapies have analyzed efficacy and safety outcomes separately[16]. In clinical practice, however, the occurrence of AEs may not be independent of a patient's clinical response to therapy, and treatments may differ in terms of how much of the AE burden falls on patients who respond versus those who do not respond to therapy[37]. Patients treated at higher doses may experience higher rates of clinical remission and higher rates of AEs than patients treated at lower doses. Venlafaxine, for example, has been associated with dose-dependent risk of cardiovascular events[7]. Separate comparisons of average risks and benefits may therefore not accurately represent the benefit–risk tradeoffs for individual patients with depression[38,39]. A single composite metric that combines both safety and efficacy data may better inform clinical decision making[37], though it should be noted that benefits and risks of treatment can vary among individual patients due to differences in comorbidity profile, drug–drug interactions or other factors.

Prior studies in depression have used a global benefit–risk (GBR) assessment to study patient-level risk and benefits[38–40]. This method involves classifying patients into ordered categories according to their experience of risks and benefits ranging from the most desirable outcome (patient receives benefits with no AEs) to the least desirable outcome (patient does not benefit from treatment and experiences AEs). GBR scores are then obtained by weighting these benefit–risk categories. While this approach provides a comprehensive summary of the benefits and risks of treatment, the choices of benefit–risk categories needed to implement this method and the weighting scheme are subjective. Other frequently used measures are the number needed to treat (NNT) and the number needed to harm (NNH), which are computed by

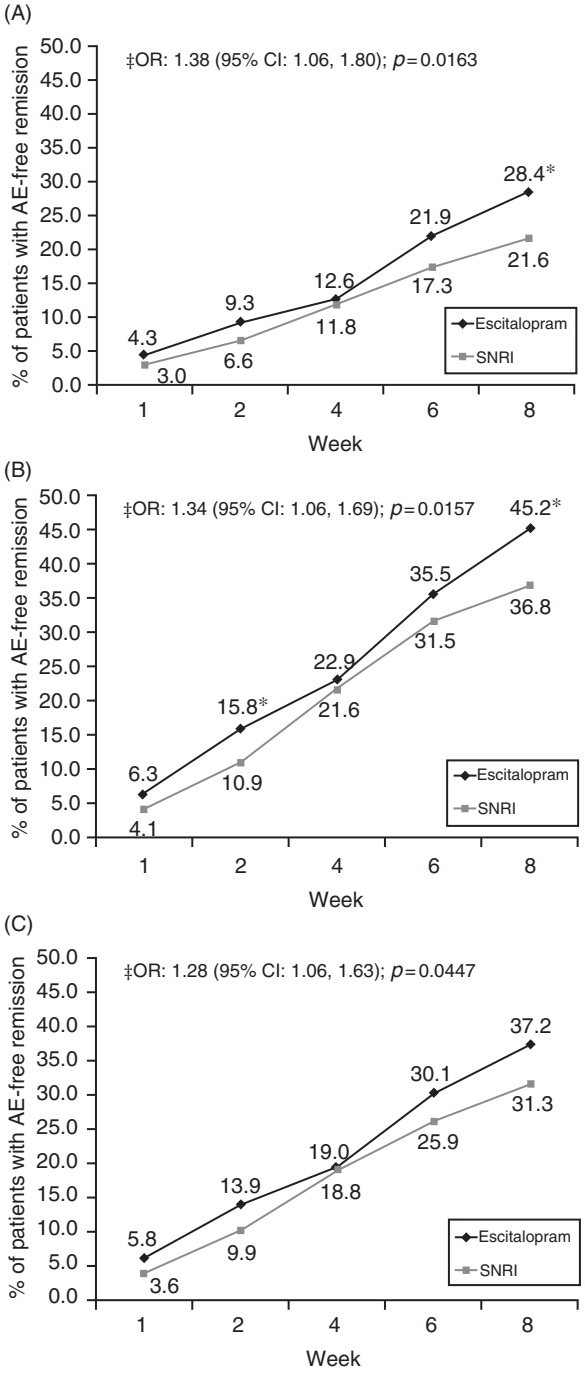

Figure 1. (A) Remission free of any adverse event. (B) Remission free of adverse events related to study drug. (C) Remission free of moderate-to-severe adverse events. *Visit-specific difference, $p \leq 0.05$. ‡The effect of escitalopram vs. SNRIs on the odds of AE-free remission across study visits estimated from a longitudinal model. Remission (MADRS ≤10) was imputed for missing study visits using the last observation carried forward method.

taking the reciprocal of the absolute risk difference between the experimental treatment group and placebo or another comparator treatment. The results are expressed as the average number of treated patients needed to expect one occurrence of treatment benefit (NNT) or treatment harm (NNH)[37,41]. However NNT and NNH measure benefits and risks separately. If benefits and risks are not independent, which can occur, for example, when efficacy and risk are dose related[37,41], then separate comparisons of NNT and NNH across therapies may not adequately reflect the experiences of individual patients.

The findings of the present analysis complement the benefit–risk analyses of Montgomery and Andersen, where escitalopram was found to have a superior benefit–risk profile compared to venlafaxine XR[27]. The present study found that escitalopram was associated with a superior benefit–risk profile compared with duloxetine and venlafaxine XR. The AE-free remission outcome studied in the present paper also combines benefits and risks at the patient level as in Montgomery and Andersen, but avoids assigning weights to multiple risk–benefit categories as in the GBR approach[27]. By focusing on AE-free remission, the ideal patient-level benefit–risk outcome, the present study provides a transparent comparison of risks and benefits that may be more interpretable for physicians and patients. Use of a dichotomous outcome also facilitates comparison of the number of days of AE-free remission and remission free of particular types of AEs.

This study has several limitations. First, patients selected into clinical trials may not experience the full spectrum of AEs seen in clinical practice[42]. The present study also considered only benefits and risks during the initial 8 weeks of treatment. Longer-term studies of AE-free remission would be needed to describe the benefits and risks of maintenance antidepressant treatment. Second, the last assessment carried forward method of imputing clinical remission between scheduled visits in the assessment of AE-free remission days assumes that average MADRS scores remain constant between visits. Though the validity of this assumption was not assessed, its application to both treatment arms should preclude systematic bias. Third, the composition of AE types may have varied between the escitalopram and SNRI treatment groups due to different mechanisms of action. While efforts were made in this study to analyze comparable subtypes of AEs by severity and relatedness to study drug, the AEs in each group could still have differing impacts on the patient's quality of life, and clinical and economic outcomes. Future analysis to better differentiate AEs and more accurately assess overall patient experience may allow for more informative comparisons. Fourth, in this study, treatment effects were described in terms of depression symptoms and adverse events. However, it is important to also consider treatment effects on health-related quality of life when comparing treatments. Finally, due to unavailability of individual patient data, it was not possible to include two clinical trials of escitalopram versus duloxetine or venlafaxine XR in the present study. The trial of escitalopram (20 mg daily) versus duloxetine

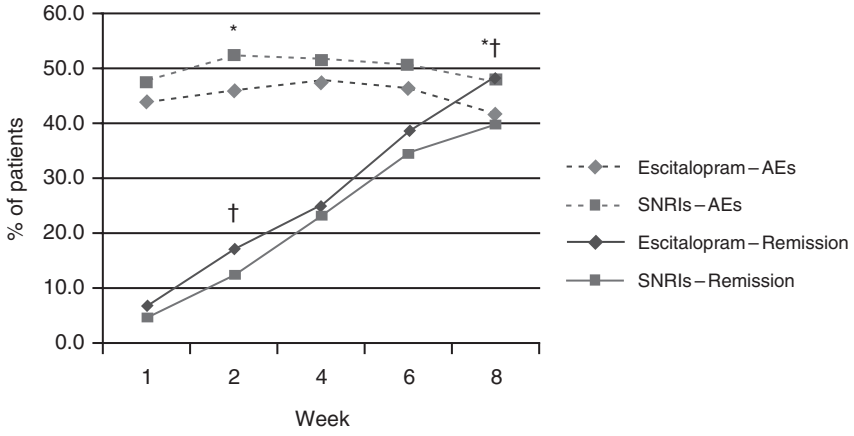

Figure 2. Rates of remission and adverse events by study visit. *Visit-specific difference in AE-rates $p < 0.05$; †visit-specific difference in remission rates $p < 0.05$. AEs, adverse events; SNRIs, serotonin norepinephrine reuptake inhibitors (in this study, duloxetine and venlafaxine XR).

(60 mg daily) reported by Wade *et al.* (2007)[15] found that escitalopram was associated with significantly greater improvements in MADRS at weeks 1, 2, 4, 8, 12, and 16, and significantly lower rates of withdrawal due to adverse events, compared to duloxetine. The trial of escitalopram (10 mg daily) versus duloxetine (60 mg daily) reported by Nierenberg *et al.* (2007)[26] found that duloxetine was associated with significantly greater reductions in the 17-item Hamilton Rating Scale for Depression at weeks 3 and 6, but not at other weeks, and also concluded that escitalopram was better tolerated at the 10 mg starting dose than duloxetine at the 60 mg starting dose. Though individual patient data were not available from these studies, their aggregate tolerability outcomes are consistent with the current study findings in detecting better tolerability with escitalopram versus the SNRI duloxetine.

Conclusion

This study used a composite outcome – remission of major depressive disorder (MDD) without AEs – to compare the benefit–risk profiles of escitalopram versus duloxetine and venlafaxine XR among adult patients with MDD. Patients treated with escitalopram were substantially more likely to experience remission of depression symptoms without concurrent AEs compared to those treated with duloxetine and venlafaxine XR.

Transparency

Declaration of funding

This study was funded by Forest Research Institute, Inc., Jersey City, NJ, USA.

Declaration of financial/other relationships

J.S., K.R., R.B-H., A.P.Y., and E.Q.W. have disclosed that they are employees of Analysis Group, a company that received funding from Forest Research Institute, Inc. to conduct this study. H.D. and M.H.E. have disclosed that they were employees of Forest Research Institute, Inc. at the time the study was conducted. *CMRO* peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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