Research Article

A PROSPECTIVE STUDY OF ESCITALOPRAM IN THE TREATMENT OF MAJOR DEPRESSIVE EPISODES IN THE PRESENCE OR ABSENCE OF ANXIETY

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This open, multicenter, prospective study in France assessed the efficacy and tolerability of escitalopram in patients with depression, with or without comorbid anxiety. Escitalopram was administered over a 12-week treatment period to 790 depressed patients, including 482 patients with at least one concomitant anxiety disorder. The study was completed by 649 patients. At baseline, the mean Montgomery–Åsberg Depression Rating Scale (MADRS) total score was 31.5 and decreased to 12.4 at end point (last observation carried forward [LOCF]). The MADRS score decreased by 20.5 points in patients with no anxiety disorder and by 18.3 points in patients with at least one concomitant anxiety disorder. The mean Hamilton Anxiety Rating Scale (HAM-A) total score at baseline was 25.6, which decreased to 10.8 at end point (LOCF). The HAM-A score decreased by 13.8 points in patients with no anxiety disorder and by 15.5 points in patients with at least one anxiety disorder. Adverse events were reported by 246 patients (31%). The most frequent adverse events were nausea in 65 patients (8%) and headache in 38 patients (5%); 61 patients (8%) discontinued treatment due to adverse events. Escitalopram was well tolerated and efficacious in reducing symptoms of depression in patients with or without comorbid anxiety over a 12-week treatment period. Depression and Anxiety 24:318–324, 2007.

Key words: *escitalopram; depression; anxiety; efficacy; safety; comorbidity*

INTRODUCTION

The issue of comorbidity in psychiatric disorders has received increasing attention in both clinical research and practice. Comorbidity among the anxiety and depressive disorders is particularly common and has significant implications in terms of clinical presentation, assessment, choice of treatment, and effectiveness, as well as the course of illness, prognosis, and long-term outcome [Belzer and Schneier, 2004].

Estimates of comorbidity among the anxiety and depressive disorders are typically quite high. For example, in the U.S. National Comorbidity Survey Replication (NCS-R), 59.2% of the lifetime cases of DSM-IV major depressive disorder (MDD) were comorbid with anxiety disorders [Kessler et al., 2005]. The results of many large epidemiological surveys conducted in the general population suggest that the extent of comorbidity between these two disorders is considerably higher than would be expected from chance alone [Andrade et al., 1994; Andrews et al., 2001; Bijl et al., 1998; ESEMeD Study Investigators,

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2004a; Kessler et al., 2005]. The most recently published European data indicate a comorbidity rate for MDD varying between 10.2% for social anxiety and 33.7% for generalized anxiety disorder (GAD). In addition, approximately 50–70% of patients diagnosed with depression have moderate anxiety, and 20–25% have severe levels of anxiety [Fawcett and Barkin, 1998].

When these disorders do co-occur, anxiety disorders are more likely to be present first [Bittner et al., 2004]. Comorbid depression and anxiety are associated with more severe symptoms, increased impairment, a more chronic course, poorer outcome, lower quality of life, a higher incidence of suicide, and greater use of health care resources than either syndrome presenting independently [Andrews et al., 2002; Clayton et al., 1991; ESEMeD Study Investigators, 2004b; Fawcett, 1992; Hunt et al., 2004; Keller and Hanks, 1995; Kessler et al., 1999; Roy-Byrne et al., 2000; Wittchen et al., 2000a,b]. It is therefore important to choose a treatment that is effective for both depression and anxiety in such patients.

Several studies have demonstrated escitalopram to be efficacious in the treatment of both MDD [Burke et al., 2002; Gorman et al., 2002] and anxiety symptoms [Bandelow et al., 2006] in patients with major depression. In addition, escitalopram has also been demonstrated to be effective in the treatment of a number of anxiety disorders, including panic disorder [Stahl et al., 2003], social anxiety disorder [SAD; Kasper et al., 2005; Lader et al., 2004; Montgomery et al., 2005] and GAD. [Baldwin et al., 2006; Bielski et al., 2005; Davidson et al., 2004.]

Although these studies provide evidence for the efficacy of escitalopram in patients with pure depressive states or pure anxious states, little information is available on the activity of the drug in patients with comorbid depression and anxiety. This is because patients with comorbidities are generally excluded from randomized clinical trials in an attempt to ensure maximal homogeneity of the study sample, thus minimizing treatment-unrelated variance in outcome.

However, studies without strict exclusion criteria provide an opportunity to assess treatment effects in patients, as they would present to their physician in the community, often with comorbid MDD and anxiety disorder. Such an opportunity has been provided by the NAVIGADE (a NAturalistic inVestIGAtion in DEpression) program. This international, open-label, multicenter, prospective, observational study program assessed the effectiveness, tolerability, and safety of escitalopram in patients requiring pharmacological treatment for MDD managed in a naturalistic treatment setting. Our study is part of this program, and was performed in France with psychiatrists as investigators.

The primary objective was to assess the efficacy of escitalopram in the treatment of patients with MDD, as they would present to their physician. Secondary objectives were as follows:

1. To assess any association between changes in the scores of depression rating scales over the study period and the scores of anxiety rating scales at baseline.
2. To evaluate the safety and tolerability of escitalopram in this patient population.
3. To assess correlations between physician and patient measures of efficacy.

METHODS

PATIENTS

The study, conducted in 217 centers in France, included male or female patients over 18 years of age with a diagnosis of MDD according to the DSM-IV-TR diagnostic criteria for Axis I psychiatric disorders [American Psychiatric Association, 2000]. Patients were required to comply with the recommended indications and contraindications for escitalopram provided in the Summary of Product Characteristics (SPC). Individuals meeting these criteria were provided written information on the study and were required to sign an informed consent form.

Exclusion criteria included a serious risk of suicide (as judged by the investigator), pregnancy or lactation, and any contraindication to escitalopram. Furthermore, patients who had previously been unresponsive to three consecutive antidepressant treatment trials, or who were known by the investigator not to tolerate or respond to citalopram were excluded. Concomitant medications were allowed if not contraindicated with escitalopram in the SPC, as were short-acting hypnotics/anxiolytics (half-life <5 hours), if used for insomnia.

TREATMENT AND FOLLOW-UP

Treatment with escitalopram was initiated at the baseline visit. The initial dose of 10 mg/day followed the recommendation of the SPC. The dose could then be adjusted at the investigator's discretion up to 20 mg/day as a function of patient response. All patients were to be followed up for 12 weeks after inclusion. Four formal study visits were programmed at baseline and at weeks 2, 6, and 12. At the baseline visit, demographic data and medical history were recorded. Assessments included the Montgomery–Åsberg Depression Rating Scale [MADRS; Montgomery and Åsberg, 1979], the Hamilton Anxiety Scale [HAM-A; Hamilton, 1959], and the Clinical Global Impression—Severity scale [CGI-S; Guy, 1976]. At each visit the improvement was evaluated by the physician using the Clinical Global Impression—Improvement scale [CGI-I; Guy, 1976] and by the patient by using the Patient Global Evaluation [PGE; Guy, 1976], an identical question-

naire to the CGI-I, but completed by the patient. All investigators participated in rating training sessions for the MADRS and the HAM-A prior to study initiation.

OUTCOME MEASURES

The prespecified primary efficacy outcome measure was the change from baseline on the MADRS total score. Secondary efficacy outcome measures included the change from baseline on the HAM-A, the CGI-S, and global improvement at study end measured with the CGI-I and PGE. Tolerability was evaluated by incidence of treatment-emergent adverse events (AEs), withdrawals due to AEs, and serious adverse events.

STATISTICAL ANALYSIS

After the study, all patients were classified into three subgroups according to baseline HAM-A total anxiety score (cutoffs: ≤ 20, 21–28; ≥ 29). The cutoff values were chosen to correspond to a mild, moderate, or severe level of anxiety symptoms. Two patient populations were analyzed: The all-patients-treated set (APTS), which consisted of all patients who took at least one dose of escitalopram (used for safety analyses) and the "intent-to-treat" (ITT) population, which included all patients in the APTS with at least one valid postbaseline outcome measure (used for efficacy analyses). In the ITT population, missing data were assigned using the principle of last observation carried forward (LOCF). The results are reported with two-sided *P*-values (with $P<.05$ being considered significant) throughout.

We evaluated the change in the various scores on the rating scales using analysis of variance (ANOVA). Subgroups based on HAM-A baseline scores were compared using Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Spearman's rank-order correlation coefficient and its associated probability were calculated for possible correlation between the changes from baseline in CGI-I and PGE, and for improvement in both anxiety symptoms (HAM-A) and depressive symptoms (MADRS) during the 12-week treatment. We analyzed all data centrally using the SAS software package (Version 8.2; Cary, NC).

RESULTS

STUDY POPULATION

Of the 797 patients enrolled in the study, 649 (81%) completed the 12-week study period. Reasons for withdrawal are shown in Table 1. The safety population consisted of 790 patients, because seven patients received no escitalopram. Sixteen patients did not have an efficacy assessment before withdrawal, so the ITT population comprised 774 patients.

Baseline patient characteristics are presented in Table 2. The median age of patients was 45 years, and over two-thirds were women. The mean MADRS score at inclusion was 31.5, the mean HAM-A score at inclusion was 25.6, and the mean CGI severity grade was 5 (*markedly ill*).

To be eligible for this trial, patients had to have a diagnosis of MDD. However, a large proportion (61%) of patients had a comorbid anxiety disorder: GAD (27%), SAD (11%), panic disorder with or without agoraphobia (10%), obsessive–compulsive disorder (6%), agoraphobia (4%), and posttraumatic stress disorder (3%). Of the 790 patients, 308 patients had no anxiety disorder, 349 patients had one anxiety disorder, and 129 patients had two or more anxiety disorders, with incomplete information for 4 patients.

TABLE 1. Patient disposition

Total number of patients	*n* (%)
Enrolled	797 (100%)
Safety population	790
ITT	774
Completed	649 (81%)
Withdrawn	145 (18%)
Missing	3 (<1%)
Reasons for withdrawal	
AEs	61 (7.7%)
Lost to follow-up	36 (4.5%)
Lack of efficacy	14 (1.8%)
Other	12 (1.5%)
Withdrawal of consent	9 (1.1%)
Protocol violation	8 (1.0%)
Lack of compliance	3 (0.4%)
Pregnancy	2 (1%)

TABLE 2. Clinical and demographic features of patients stratified according to baseline HAM-A anxiety scores

Demographic characteristics	HAM-A total score ≤ 20 ($n=210$)	HAM-A total score 21–28 ($n=286$)	HAM-A total score ≥ 29 ($n=293$)	Total ($n=790$)[a]
Female *n* (%)	134 (64%)	207 (72%)	216 (74%)	557 (70%)
Age, years ($M \pm SD$)	44.2 ± 12.2	44.1 ± 12.8	45.2 ± 12.4	44.5 ± 12.5
Range	18 to 82	18 to 85	18 to 81	18 to 85
MADRS ($M \pm SD$)	28.4 ± 5.8	30.6 ± 4.5	34.6 ± 5.4	31.5 ± 5.8
HAM-A ($M \pm SD$)	16.1 ± 3.6	24.5 ± 2.2	33.7 ± 4.2	25.6 ± 7.8

[a]One patient had no baseline HAM-A total score.

Of the 774 patients in the efficacy analysis, 209 had mild or no symptoms of anxiety (HAM-A $\leq$20), 278 had moderate symptoms (HAM-A = 21–28), and 287 severe symptoms (HAM-A $>$29) of anxiety.

TREATMENT

This was a flexible-dose study, and psychiatrists were allowed to increase the daily dose depending on the individual patient's response to early treatment. The overall mean dose of escitalopram (across the entire study period) was 12.1 $\pm$ 4.2 mg/day, and the median dosage was 10 mg/day.

In each of the three subgroups defined by HAM-A total scores at baseline, the percentage of patients treated with a daily dose of 20 mg/day increased with severity of anxiety (29%, 32%, and 41% in patients with HAM-A $\leq$20, HAM-A = 21–28, and HAM-A $\geq$29, respectively.

Patients were permitted to take benzodiazepine-like anxiolytics concomitantly with escitalopram: 165 of the 774 patients (21.3%) in the efficacy population (ITT) took benzodiazepine-like anxiolytics.

EFFICACY OUTCOMES

Primary outcome: Montgomery–Åsberg Depression Rating Scale. MADRS scores decreased from 31.5 at inclusion to 12.4 at 12 weeks (Fig. 1). At the end of the study, 558 patients (72.1% [95% CI: 68.8–75.2%]) were responders (defined as a decrease $\geq$50% from baseline MADRS score). The number of remitters (defined as a MADRS total score $\leq$12) was 448 (57.8% [95% CI: 54.3–61.4%]).

The MADRS score decreased by 20.5 in patients with no anxiety disorder and by 18.3 points in patients with at least one anxiety disorder, a statistically significantly estimated treatment difference of 2.2 points (LOCF; $P<.0024$). The improvement in MADRS scores from baseline to study end, analyzed by analysis of covariance (ANCOVA) with HAM-A subgroup as covariate (LOCF), was slightly lower in the subgroup with the highest anxiety level (HAM-A $\geq$29).

There were no significant differences in the mean change from baseline in MADRS total score between men and women, or elderly patients (over 65 years old) compared to younger patients (from 18 to 65 years old). The mean change in MADRS total score from baseline did not differ significantly between patients who had received at least one dose of a concomitant anxiolytic medication and patients who received no anxiolytic treatment [MADRS change of -17.9 ± 10.9 and -19.4 ± 9.7, respectively (LOCF)].

SECONDARY OUTCOMES

Hamilton Anxiety Scale. HAM-A anxiety scores decreased over the course of the study from 25.6 at inclusion to 10.8 after 12 weeks (Fig. 2), corresponding to a mean change of -14.9 ± 9.1. At the end of the study, 534 patients (69.0% [95% CI: 65.6–72.2%]) were responders (defined as a decrease $\geq$50% in the baseline HAM-A score), and 295 patients (38.1% [95% CI: 34.7–41.6%]) were remitters (defined as a HAM-A anxiety score $<$7 at the end of the study). The HAM-A score decreased by 13.8 points in patients with no anxiety disorder and by 15.5 points in patients with at least one anxiety disorder, a statistically significantly estimated treatment difference of 1.79 points (LOCF; $P = .0078$). Nevertheless, the extent of improvement in anxiety symptoms measured with the HAM-A over the 12-week study period remained closely correlated with the extent of improvement in depressive symptoms measured with the MADRS (Spearman's rank-order

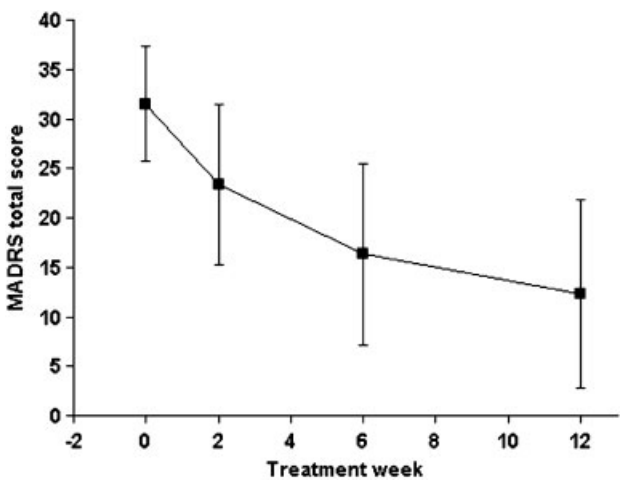

Figure 1. MADRS total scores for the ITT population (n = 774). Data are presented as mean values with standard deviations (LOCF).

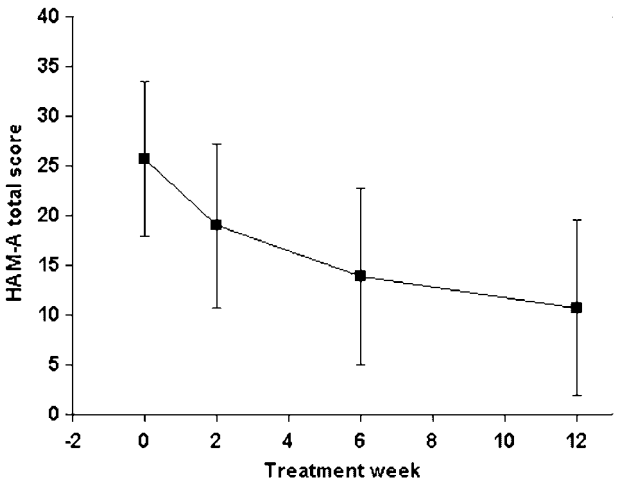

Figure 2. HAM-A total scores for the ITT population (n = 774). Data are presented as mean values with standard deviations (LOCF).

TABLE 3. Change in HAM-A from baseline (LOCF) in patients with or without concomitant anxiolytic medication

	No. of patients	HAM-A
No anxiolytic	609	−15.0±8.9
At least one anxiolytic	165	−14.2±9.9
Total	774	−14.9±9.1

correlation coefficient ρ = .727; $P<.001$; LOCF). This correlation was observed at all study visits.

The change in HAM-A total score from baseline did not significantly differ in the subgroup of patients who had received at least one dose of anxiolytic and the other patients who had no anxiolytic treatment (Table 3).

Global assessments (physician and patient). Based on the CGI-I scale, 548 patients (70.8% [95% CI: 67.5–74.0%]) were rated *very much improved* (1) or *much improved* (2) at study end and were thus considered to be responders.

Using the PGE improvement, 512 patients (68.0%) considered themselves very much or much improved at study end. There was a statistically significant correlation between improvement assessed by the physician using the CGI-I and that assessed by the patient using the PGE (Spearman's rank-order correlation coefficient ρ = .809; $P<.001$).

TOLERABILITY

Two hundred forty-six patients (31%) reported at least one AE. When assessed by visit (i.e., by duration of exposure to escitalopram), more patients reported AEs between the baseline and week 2 visits than between later visits. The withdrawal rate for AEs was 8% (61 patients), mainly due to nausea (11 patients) and headache (8 patients). AEs with an incidence ≥1% are presented in Table 4. Eighteen patients reported 19 serious AEs, principally aggravation of psychiatric symptoms requiring hospitalization (6 patients for depression, 3 for anxiety disorders, and 1 for suicide attempt).

TABLE 4. AEs with an incidence ≥1%

	n (%)
Safety population	790
Patients with at least one AE	246 (31%)
Nausea	65 (8.2%)
Headache	38 (4.8%)
Insomnia	30 (3.8%)
Anxiety	30 (3.8%)
Diarrhoea	21 (2.7%)
Aggravated depression	11 (1.4%)
Somnolence	12 (1.5%)
Dyspepsia	11 (1.4%)
Increased sweating	9 (1.1%)
Vertigo	9 (1.1%)
Migraine	8 (1.0%)

DISCUSSION

The results of this trial indicate that escitalopram is a valid treatment choice for MDD as it presents in this community sample (i.e., with considerable comorbidity with various anxiety disorders). Despite the well-validated finding that the presence of comorbidity requires more intensive interventions, including higher doses, this was not found in this trial, because the median dose of escitalopram was 10 mg/day and most patients refrained from using anxiolytics.

At the end of the 12-week treatment period, 57.9% of the patients had achieved remission, based on their MADRS scores, and 71.0% were much or very much improved, based on the CGI-I. These treatment responses are of similar amplitude to what was observed in two other open-label studies conducted in a community environment with escitalopram in France [Lançon et al., 2004] and in the United States [Rush and Bose, 2005].

A large proportion (61%) of the patients were found to have a comorbid anxiety disorder. This figure is somewhat higher than that observed for comorbidity of major depression with anxiety disorders in recent surveys, whether in the United States [Kessler et al., 2005] or in Europe [ESEMeD Study Investigators, 2004a]. This difference may be due to the fact that patients included in this study were severely depressed (mean MADRS score at inclusion was 31), and that severity of illness is known to be strongly related to meeting criteria for more than one disorder. Nonetheless, the types of comorbid anxiety disorders and their relative frequency were similar to those observed in the ESEMeD study, with the exception of SAD, which had a higher incidence in our study.

The extent of comorbid depression and anxiety needs to be taken into account in the treatment of such individuals, with the aim of resolution of both types of disorders. The ability of escitalopram to treat isolated depressive episodes and anxiety disorders independently was indicative of its potential effect in treating patients with comorbid depression and anxiety, and this was illustrated in our study. Choice of a single drug active on both symptom classes may be a more rational and cost-effective way to manage comorbidity than the use of separate drugs for anxiety and depression.

The results of our study show that anxiety symptoms, as measured with the HAM-A, improved in parallel to the improvement in depressive symptoms following initiation of treatment with escitalopram, and the two

measures were highly correlated. Patients with at least one anxiety disorder had a greater improvement in HAM-A score than those without comorbid anxiety, but there was no statistically significant difference in the improvement in HAM-A scores as a function of baseline severity of depression, indicating that comorbid depression did not affect response to treatment of anxiety. The remission rate for anxiety symptoms (38.1%) is very close to the 36% reported in a randomized, double-blind clinical trial of escitalopram in patients with pure GAD [Davidson et al., 2004]. Patients with a comorbid anxiety disorder responded well to treatment, particularly those with GAD, SAD, or obsessive–compulsive disorder.

Our study also assessed the relationship between improvement assessed by the physician and by patient self-reporting. The two measures were highly correlated at all time points and a majority of patients were rated as *much improved* or *very much improved* by both the physician and the patients themselves. This finding suggests that the impact of escitalopram on psychiatric symptoms as measured by self-rating scales is of real relevance to those being treated.

Escitalopram was found to be safe and well tolerated in this study, and the rate of discontinuation for AEs was low (≈8%). Most adverse events were transient, and there was no evidence for a different tolerability profile in patients with or without concomitant anxiety, or according to the baseline severity of anxiety. The AE profile observed in this study is consistent with the known tolerability profile of escitalopram and with the underlying indication. The most common events reported (nausea and headache) are identical to those observed in randomized, double-blind clinical trials of citalopram in pure depression [Gorman et al., 2002] or anxiety disorders [Davidson et al., 2004], although the overall incidence of events is somewhat lower, as may be expected from the naturalistic setting of the study.

Our study has, however, a number of limitations. The open-label design and lack of a control group is a limitation in estimating the size of the treatment effect. Another limitation relates to the allowance, although restricted, of the use of concomitant benzodiazepine-like anxiolytic medication. An exploratory analysis of the response of patients having received such concomitant medication versus those who did not was nevertheless unable to detect any significant difference in treatment responses, either for depression or anxiety. In addition, severity of anxiety was measured using the HAM-A scale, and not a disorder-specific instrument.

In conclusion, escitalopram was effective in the treatment of MDD with or without comorbid anxiety disorders, in this naturalistic treatment setting. Improvements in depressive and anxious symptoms were well correlated. The study demonstrates that escitalopram can be used to treat patients with comorbid depression and anxiety, with satisfactory control of both types of symptoms.

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