Safety and Efficacy of Escitalopram in the Long-Term Treatment of Generalized Anxiety Disorder

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Introduction: Generalized anxiety disorder (GAD) is a chronic disorder that requires long-term treatment. Escitalopram has previously been shown to be effective and well tolerated in the acute treatment of GAD.

Method: Three 8-week, double-blind, placebo-controlled trials of nearly identical design were conducted of escitalopram in moderate-to-severe GAD (DSM-IV criteria). Patients completing these trials were given the option of entering a 24-week, open-label, flexible-dose trial of escitalopram (10–20 mg/day). Data were collected from September 20, 2000, to August 15, 2002.

Results: Two hundred ninety-nine (56.8%) of 526 patients completed 24 weeks of open-label treatment. The mean Hamilton Rating Scale for Anxiety (HAM-A) score at baseline of open-label treatment was 13.1. Long-term escitalopram treatment led to continuing improvement on all anxiety and quality-of-life (QOL) scores. Of those completing 24 weeks of treatment, 92.0% were responders (Clinical Global Impressions-Improvement scale score ≤ 2), and the mean HAM-A score in the completer analysis was 6.9; using the last observation carried forward (LOCF), 75.9% were responders, and the mean HAM-A score in the LOCF analysis was 9.2 at endpoint. Insufficient therapeutic response and adverse events led to withdrawal of 4.2% and 9.9% of patients, respectively. Mean increase in weight from baseline was 3.0 lb. No clinically notable changes in mean laboratory, vital sign, or electrocardiographic values were observed.

Conclusion: These results support the long-term tolerability and effectiveness of escitalopram in the treatment of GAD.

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Generalized anxiety disorder (GAD) is a persistent disease characterized by excessive, pervasive anxiety or worry that continues over time and is largely uncontrollable.[1] In patients with GAD, the intensity, duration, and frequency of the anxiety and worry are disproportionate to life circumstances. Patients with GAD also experience a number of other psychic and somatic symptoms, including irritability, difficulty concentrating, dry mouth, nausea, and diarrhea.[2] In addition, patients with GAD may also suffer from other comorbid psychiatric or somatic disorders, such as depression or irritable bowel syndrome.[3,4] Individuals with GAD suffer from significant distress or impairment in social, occupational, and other important areas of functioning.[5–8]

Generalized anxiety disorder affects approximately 9 million Americans at some point in their lives.[5] Estimates for adults in community epidemiologic surveys show consistent prevalence rates in the United States. Data from the National Institute of Mental Health Epidemiologic Catchment Area Project showed 1-year prevalence rates of 2% to 3.5% and lifetime prevalence rates of 4.1% to 6.6%.[8] Data from the National Comorbidity Survey show similar findings with a 1-year prevalence rate of 3.1% and a lifetime prevalence rate of 5.1%.[5]

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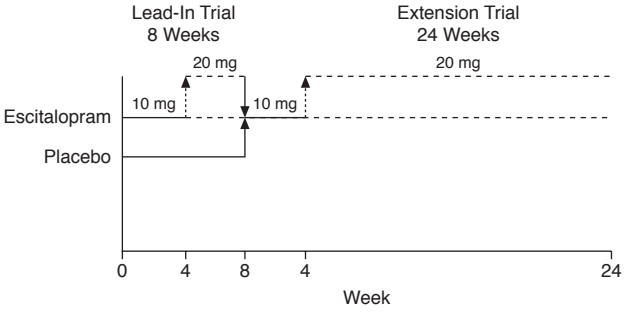
Figure 1. Study Design for a 24-Week, Open-Label Extension Trial of Escitalopram for Outpatients With Generalized Anxiety Disorder[a]



[a]Patients completing an 8-week, double-blind, placebo-controlled lead-in were eligible to enter the 24-week, open-label extension trial.

Generalized anxiety disorder follows a fluctuating, waxing and waning course over several years or decades.[9] While DSM-IV criteria require that the symptoms characterizing GAD be present most days for a minimum of 6 months,[2] the average duration of current episode in recent clinical trials is 10 years.[10] Generalized anxiety disorder has a poor long-term outcome, with the probability of remission at 52 weeks reaching only 11%.[11] Prospectively obtained data from a naturalistic short-interval follow-up study have indicated that the remission rate is low, with a probability of 0.38 at 5 years.[12] Moreover, relapses are common at 3 years (probability = 0.27) and more likely for patients attaining only partial remission from symptoms.[12] Given the chronic nature of GAD, long-term treatment may be necessary for successful management.[9] Effective treatment should ultimately aim at the elimination of anxiety symptoms and the complete restoration of normal functioning.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant that has a broad spectrum of anxiolytic activity.[13–15] Three 8-week double-blind, placebo-controlled, registration studies have demonstrated the efficacy and safety of escitalopram in the treatment of GAD and formed the basis of the approval for escitalopram for this indication.[16] The present study was designed as a 24-week, open-label extension of these 3 studies to evaluate the long-term safety and efficacy of escitalopram in patients diagnosed with GAD.

METHOD

Study Design

This 24-week, flexible-dose, open-label extension study was conducted at 63 centers in the United States from September 20, 2000, to August 15, 2002. The objective of this study was to evaluate the safety and efficacy of long-term escitalopram treatment in adult outpatients with GAD who had previously completed 8 weeks of acute treatment with escitalopram or placebo. The protocol was approved by the institutional review boards at all study centers.

Study visits were conducted at baseline and at the end of 1, 2, 4, 8, 12, 16, 20, and 24 weeks of open-label escitalopram treatment (Figure 1). Patients who met all of the eligibility criteria at baseline received escitalopram, 10 mg/day, for weeks 1 through 4. Medication was to be taken at the same time of day as in the last week of the lead-in study, but could be switched to the morning or evening if preferred. Beginning at the end of week 4, patients who had not exhibited a satisfactory therapeutic response in the opinion of the investigator were allowed a dose increase to 20 mg/day. The dose of medication could have been decreased to 10 mg/day at any time due to adverse events.

Patient Selection

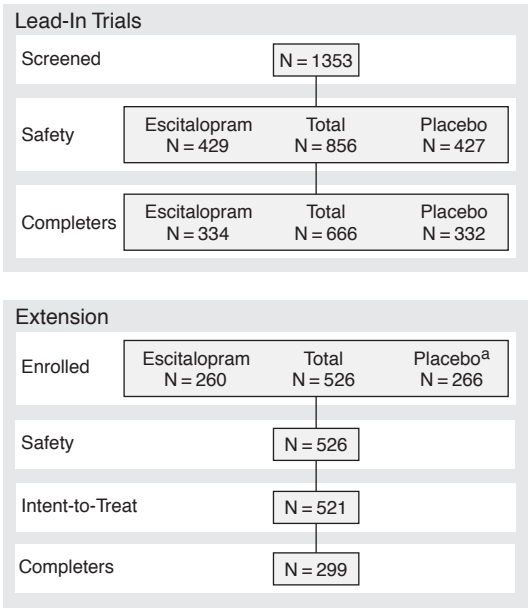
Male or female outpatients, aged 18 to 81 years, were eligible if they had completed one of the three 8-week lead-in GAD trials within 72 hours prior to study entry. Patients entering the lead-in trials were required to have a current diagnosis of GAD (DSM-IV criteria).[16] Patients were excluded if they had a principal diagnosis meeting DSM-IV criteria for any Axis I disorder other than GAD, as were patients who met DSM-IV criteria for bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, mental retardation, any pervasive developmental disorder, or cognitive disorder. Also excluded were those with a recent history or current diagnosis of drug or alcohol dependence, current suicidal ideation and/or history of suicide attempt, history of any DSM-IV psychotic disorder or psychotic features, or any personality disorder of sufficient severity to interfere with participation in the study.

Other exclusion criteria included a history or presence of a medical disease that might compromise the study or be detrimental to the patient (e.g., malignancy, renal or hepatic disease) and the use of any neuroleptic, anxiolytic, or any psychotropic drug (except zolpidem for sleep). Women who were pregnant or breastfeeding and women of childbearing potential who were not practicing a reliable method of birth control were also excluded from the study. Signed informed consent was obtained from each patient before lead-in study enrollment and prior to beginning the open-label phase of the study.

Measurements

The final visit for the lead-in study corresponded with the baseline assessment for the long-term, open-label phase of the study. At that time, patients received a physical examination, laboratory tests including determinations for pregnancy and for drugs of abuse, 12-lead electrocardiogram, and assessment with the Hamilton Rating

Figure 2. Patient Disposition for the Placebo-Controlled Trials and Open-Label Extension Trial of Escitalopram



[a]These patients received placebo during the lead-in trials only.

Table 1. Demographics of the Safety Population of Outpatients Treated With Escitalopram (N = 526)[a]

Demographic Parameter	Value
Age, mean ± SD, y	39.8 ± 12.8
Women, N (%)	282 (53.6)
Weight, mean ± SD, lb	173.7 ± 43.2
Race, N (%)	
White	409 (77.8)
Black	40 (7.6)
Asian	20 (3.8)
Other	57 (10.8)
Duration of current episode, mean, y	10.5
Duration of current episode > 5.0 y, N (%)	282 (53.6)

[a]All patients who received at least 1 dose of open-label escitalopram.

Table 2. Reasons for Premature Discontinuation Among Escitalopram-Treated Patients Included in the Safety Population (N = 526)

	Value	
Variable	N	%
Completed study	299	56.8
Withdrew from study	227	43.2
Reasons for withdrawal		
Adverse event	52	9.9
Insufficient therapeutic response	22	4.2
Protocol violation	32	6.1
Withdrawal of consent	40	7.6
Lost to follow-up	65	12.4
Other reason	16	3.0

Scale for Anxiety (HAM-A),[17] the Clinical Global Impressions scale (CGI),[18] the Hospital Anxiety and Depression scale (HAD),[19] the Quality of Life Scale (QOL—a modified version of the Quality of Life Enjoyment and Satisfaction Questionnaire short form),[20] and the Hamilton Rating Scale for Depression (HAM-D).[21]

Data Analysis

The safety population included all patients who received at least 1 dose of escitalopram in the extension study; i.e., all treated patients were included in the safety analyses. Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all patients in the safety population who had at least 1 HAM-A assessment in the extension study.

Baseline for all analyses was defined as the last visit of the lead-in trial. Both the last-observation-carried-forward (LOCF) and the observed-cases approaches were used. This being an open-label extension study, no hypothesis tests were performed at baseline or postbaseline comparing patients who received escitalopram in the lead-in trials ("escitalopram-escitalopram") versus patients who received placebo in the lead-in trials ("placebo-escitalopram"). In addition, no within-group test for change from baseline over the extension period was carried out. Only descriptive statistics were calculated by lead-in study treatment group ("escitalopram-escitalopram" or "placebo-escitalopram") and overall. The primary efficacy instrument was the HAM-A. For post hoc analyses, response was defined as a CGI-Improvement scale (CGI-I) score ≤ 2, and remission as a HAM-A score ≤ 7.

Safety was evaluated on the basis of reports of treatment-emergent adverse events, treatment discontinuation due to adverse events, and the results of assessments of vital signs, laboratory determinations, and electrocardiography (ECG). Adverse events were identified from spontaneous patient reports as well as from nonspecific questioning by study site personnel.

RESULTS

Demographics

A total of 1353 patients were screened for enrollment in the lead-in trials (Figure 2). Double-blind treatment was completed by 666 (77.8%) of 856 patients.[16] Of these, 526 patients were enrolled in this extension study and received at least 1 dose of escitalopram, including 266 who received placebo in the lead-in study and 260 who received escitalopram. A total of 521 treated patients also had at least 1 postbaseline HAM-A assessment and were included in the ITT population.

Overall, approximately half of the subjects (53.6%) were female, and the majority (77.7%) were white. The mean age for all patients was 40 years (Table 1). A total of 299 patients (56.8%) completed the study (Table 2). The

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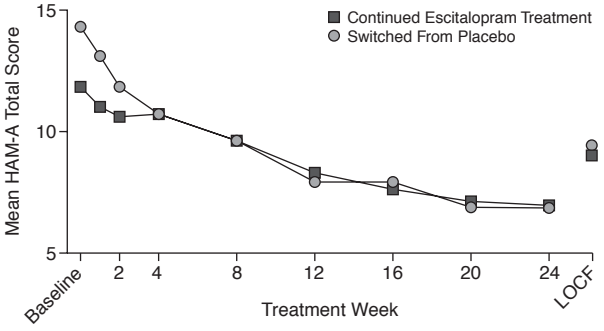
Figure 3. Mean Change From Baseline in HAM-A Total Score by Visit (ITT, OC by visit; LOCF, endpoint) in Patients Who Had Been Treated With Escitalopram (i.e., who then continued on escitalopram treatment) or Placebo (i.e., who then were switched from placebo to escitalopram treatment) in the Lead-in Study



Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent-to-treat, LOCF = last observation carried forward, OC = observed cases.

Table 3. Change From Baseline to Endpoint in Efficacy Parameters for the Intent-to-Treat Population of Outpatients Treated With Escitalopram (N = 521)[a]

		Change at Endpoint	
Measure	Baseline	OC	LOCF
HAM-A			
Total scale	13.06 ± 0.29	–5.31 ± 0.37	–3.87 ± 0.28
Psychic anxiety subscale	7.82 ± 0.18	–3.28 ± 0.24	–2.35 ± 0.18
Somatic anxiety subscale	5.24 ± 0.14	–2.04 ± 0.19	–1.53 ± 0.14
CGI-S	3.03 ± 0.05	–1.10 ± 0.06	–0.78 ± 0.05
QOL	55.90 ± 0.43	4.63 ± 0.52	2.97 ± 0.42

[a]All values shown as mean ± SEM.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, OC = observed cases, QOL = Quality of Life Scale.

most frequent reason for premature discontinuation from the study was loss to follow-up (N = 65; 12.4%). The second most frequent reason for premature study discontinuation was occurrence of an adverse event with a total of 52 patients (9.9%) discontinuing for this reason. The mean daily dose of escitalopram was 13.4 mg/day. The percentage of patients receiving a dose of 20 mg/day was 47.7% at week 8 and 56.1% at week 24.

Efficacy

At baseline of this extension study, mean scores on efficacy measures were consistent with greater improvement for patients who had received escitalopram in the lead-in trials relative to patients who had received placebo in the lead-in trials. These 2 groups of patients achieved parity by week 4 of open-label treatment based on HAM-A total score and subsequently maintained a similar pattern of improvement throughout to the end of the study (Figure 3). Treatment with open-label escitalopram led to continued overall improvement, observed consistently across all efficacy measures (Table 3).

A total of 49% of patients entering the extension trial were responders (CGI-I score ≤ 2). Of those completing the extension trial, 92% were responders; based on the LOCF analysis, 76% were responders. The mean HAM-A score at week 24 was 6.9 in the completer analysis (9.2 in the LOCF analysis). For the HAM-A tension and anxiety items, 84% and 86% of completers, respectively, had scores of 0 ("not present") or 1 ("mild"). Of note, 60% of patients completing the total 32 weeks of treatment with escitalopram were remitters (HAM-A score ≤ 7); using LOCF, 49% were remitters.

Table 4. Most Frequent (in ≥ 10% of all patients) Treatment-Emergent Adverse Events for the Safety Population of Outpatients Treated With Escitalopram (N = 526)

Variable	N	%
At least 1 treatment-emergent adverse event	470	89.4
Headache	134	25.5
Ejaculation disorder	39	16.0[a]
Upper respiratory tract infection	81	15.4
Nausea	80	15.2
Insomnia	78	14.8
Dry mouth	59	11.2
Diarrhea	58	11.0
Somnolence	56	10.6
Rhinitis	55	10.5
Decreased libido	53	10.1

[a]Percentage is relative to the number of male patients in the safety population (N = 244).

Safety

Escitalopram was well tolerated in the extension trial. Adverse events led to study withdrawal in 9.9% of patients. The most frequent adverse events leading to study withdrawal were ejaculation disorder (1.6%), insomnia (1.3%), and nausea (1%). Serious adverse events were reported by 11 (2.1%) of 526 patients, including 1 completed suicide. The completed suicide occurred in a patient treated with placebo in the lead-in trial and with escitalopram for 111 days in the extension trial; the suicide occurred 15 days following treatment cessation. The most common (≥ 10%) adverse events experienced during the study are listed in Table 4. The most frequent adverse events were headache, ejaculation disorder, upper respiratory tract infection, nausea, insomnia, dry mouth, diarrhea, somnolence, rhinitis, and decreased libido. The majority of adverse events were mild to moderate in severity. For both systolic and diastolic blood pressure, mean change from baseline to endpoint was +0.7 mm Hg, and mean change from baseline to endpoint in pulse rate was –0.8 b.p.m. Mean change from baseline to endpoint in weight was an increase of 3.0 lb. Mean changes in laboratory test results and ECG assessments were small in magnitude and not clinically significant.

DISCUSSION

Generalized anxiety disorder is a chronic disorder, and this characteristic is reflected in the DSM-IV diagnostic criteria,[2] which require a minimum episode duration of 6 months. In practice, the duration of the disorder is generally very much longer. For example, the patient sample that entered the present trial had a mean prior duration of GAD that exceeded 10 years. Generalized anxiety disorder is also frequently a relapsing condition,[22] and appropriate treatment should also be aimed beyond acute treatment.

Previous-generation antidepressant therapies used for treating anxiety, such as some of the tricyclic antidepressants (TCAs), were complicated by an undesirable side effect profile and toxicity or lethality in overdose.[23] The benzodiazepines have been shown to have a rapid onset of anxiolytic action in patients with GAD and to positively impact the somatic manifestations of anxiety. However, they are less effective in alleviating the psychic symptoms of anxiety, particularly worry.[24–26] With the introduction of the SSRI antidepressants, effective therapies for depression and anxiety disorders without the toxic side effects associated with TCAs or the abuse liability associated with benzodiazepines were available. The SSRIs escitalopram and paroxetine, and the nonselective agent venlafaxine, have received approval in the United States for the treatment of GAD.

Patients began the lead-in trials with mean rating scale scores indicating moderate-to-severe illness.[16] At the start of this extension trial, patients who had been treated with escitalopram had somewhat lower mean HAM-A scores than those who had been treated with placebo. The anxiolytic response to escitalopram continued throughout the additional 24 weeks of treatment. Those patients originally receiving placebo for the 8 weeks of the lead-in trial quickly improved when switched to escitalopram, and the improvement observed in this group mirrored the improvement during the remaining 5 months of the study of those who had received escitalopram in the lead-in trial. Additionally, escitalopram appeared to be effective in alleviating both the psychic and somatic symptoms of anxiety. Remission rates (defined as a HAM-A score of 7 or less) for patients who received 32 weeks of escitalopram treatment reached 60%. Overall, these results demonstrate the potential for maintained pharmacotherapy to impact the course of GAD. The authors are aware of at least 5 completed randomized, placebo-controlled, acute treatment trials of escitalopram in the treatment of GAD, 4 of which were positive from the standpoint of separation from placebo on the protocol-specified primary efficacy measure. These include the 3 trials that served as lead-in treatment for the present study[16] (the other 2 trials were Baldwin et al.[27] and data on file; Forest Laboratories, Inc.; 2005). Thus, the present results are consistent with the known anxiolytic efficacy of escitalopram.

An important consideration for any long-term pharmacotherapy is tolerability, which can directly impact patient compliance.[28] Escitalopram was found to be well tolerated in long-term chronic dosing. Most of the adverse events were either mild or moderate in severity, and adverse events led to the discontinuation of approximately 10% of patients over 6 months of study. Long-term escitalopram treatment had no clinically significant effect on vital signs. Escitalopram also had minimal effect on weight, as shown by a mean weight gain of 3 lb at endpoint. Weight changes were similarly low for escitalopram-treated patients in a recent 24-week, double-blind, paroxetine-controlled trial in patients with GAD. In that trial, escitalopram was at least as effective as paroxetine and was better tolerated.[29]

The present efficacy and tolerability results should be interpreted within the inherent limitations of an open-label trial. While open-label, flexible-dose treatment mimics typical clinical practice, there is the potential for confounds due to rater biases and placebo response. Although the magnitude of placebo effect cannot be determined, the sustained improvement seen in this study is more consistent with a treatment effect. A further limitation is the exclusion of patients with a second primary Axis I psychiatric diagnosis. Generalized anxiety disorder is frequently comorbid with other disorders such as major depressive disorder.[30] The enrolled patient population, which may be somewhat comparable to those studied in many drug trials in GAD, may nevertheless not reflect patients seen in routine practice.

These results support the use of escitalopram in the treatment of GAD and illustrate the importance of long-term therapy to treat this chronic condition.

Drug names: escitalopram (Lexapro), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor), zolpidem (Ambien).

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