A 24-Week Randomized, Double-Blind, Placebo-Controlled Study of Escitalopram for the Prevention of Generalized Social Anxiety Disorder

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Objective: Escitalopram has proven efficacy in the short-term treatment of generalized social anxiety disorder (SAD). The present relapse prevention study investigated relapse rates during a 24-week, randomized, double-blind, placebo-controlled period in patients with generalized SAD who had responded to 12-week open-label treatment with escitalopram.

Method: A total of 517 patients with a primary diagnosis of generalized SAD (per DSM-IV criteria) and a Liebowitz Social Anxiety Scale (LSAS) total score of ≥ 70 received 12 weeks of open-label treatment with flexible doses (10–20 mg/day) of escitalopram. Of these patients, 371 responded (Clinical Global Impressions-Improvement scale [CGI-I] score of 1 or 2) and were randomly assigned to 24 weeks of double-blind treatment with escitalopram (10 or 20 mg/day) (N = 190) or placebo (N = 181), continuing with the dose level administered at the end of the open-label period. Relapse was defined as either an increase in LSAS total score of ≥ 10 or withdrawal due to lack of efficacy, as judged by the investigator. The study was conducted from January 2001 to June 2002.

Results: Survival analysis of relapse and time to relapse showed a significant advantage for escitalopram compared to placebo (log-rank test: $p < .001$). The risk of relapse was 2.8 times higher for placebo-treated patients than for escitalopram-treated patients ($p < .001$), resulting in significantly fewer escitalopram-treated patients relapsing (22% vs. 50%), at both doses. Escitalopram was well tolerated during double-blind treatment of generalized SAD, and only 2.6% of the escitalopram-treated patients withdrew because of adverse events. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram and 8.3% for patients treated with placebo.

Conclusion: Escitalopram was effective and well tolerated in the long-term treatment of generalized SAD.

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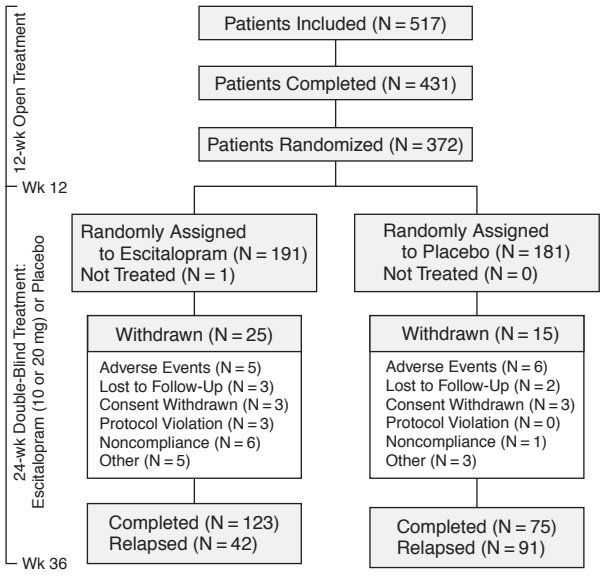
Generalized social anxiety disorder (SAD), also known as generalized social phobia, is a common, chronic disorder characterized by persistent and unreasonable fear of being scrutinized in social situations, such as speaking or eating in public and meeting new people. In order to meet diagnostic criteria for generalized SAD, the feared social situations are avoided or endured with intense anxiety or distress. The avoidance and/or distress interfere significantly with a person's occupational or social functioning. Generalized SAD,[1] involving multiple feared social situations, is the subtype of the disorder with the most impairment.

Generalized SAD is the third most common psychiatric disorder after simple phobia and alcohol dependence, which it often causes,[2] and the lifetime prevalence rates in community studies are reported to be as high as 13% to 16%.[2–4] The age at onset of generalized SAD is generally in the midteens. Unfortunately, the early onset of the disorder means that it starts at the stage of life when the development of social skills is important; it is therefore not surprising that the disorder is associated with impaired social and family life and with reduced educational attainment, resulting in increased levels of unemployment and increased financial dependency.[5]

Generalized SAD is underrecognized and undertreated, despite the morbidity.[6] Because of the nature of the disorder with the characteristic fear of social situations, individuals with generalized SAD are typically slow to seek treatment and often do not reach medical

Figure 1. Disposition of Patients Receiving Escitalopram or Placebo for the Randomized Double-Blind Period of the Study



attention until other conditions such as depression, panic disorder (PD), or alcoholism are present.

As generalized SAD generally has a chronic and spontaneously unremitting course, pharmacotherapy should be effective over long treatment periods with good tolerability. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line treatment for generalized SAD.[7–9] Several SSRIs have been shown to be effective in placebo-controlled studies in the short-term treatment of generalized SAD, including paroxetine,[10,11] sertraline,[12,13] fluvoxamine,[14] and escitalopram.[15] Escitalopram, the most selective SSRI currently available, has established efficacy in the short-term treatment of generalized SAD,[15] PD,[16] generalized anxiety disorder (GAD),[17] and major depressive disorder (MDD).[18–21]

In a chronic condition, such as generalized SAD, long-term treatment is normally required. This approach is supported by the results of an open-label study[22] and a placebo-controlled relapse prevention study with fluvoxamine.[23] The aim of the present placebo-controlled study was to assess the effect of escitalopram in the treatment of patients with generalized SAD.

METHOD

Study Design

The study was conducted in 76 centers in 11 countries in Europe, Canada, and South Africa from January 2001 to June 2002 (see the acknowledgment section at the end of the article) in accordance with the principles of Good Clinical Practice[24] and the Declaration of Helsinki[25] applicable at the time of the study. The study was approved by the relevant local ethics committees, and patients gave their written informed consent.

This relapse prevention study consisted of a 12-week, open-label period with flexible doses (10–20 mg/day) of escitalopram followed by a 24-week, randomized, double-blind, parallel-group, fixed-dose comparison of escitalopram (10 or 20 mg/day) and placebo (Figure 1).

During the open-label period, patients received 10 mg/day of escitalopram, which could be increased to 20 mg/day at weeks 2, 4, or 8, if clinically indicated. After 12 weeks of treatment with escitalopram, patients who responded (Clinical Global Impressions-Improvement [CGI-I] scale[26] score of 1 or 2) were eligible for entry into the double-blind study. Patients were randomly assigned in a 1:1 ratio using a computer-generated randomization list to 24 weeks of double-blind treatment with escitalopram (continuing with the dose level administered at the end of the open-label period) or an abrupt switch to placebo. No dose changes were permitted during the double-blind period. Response and tolerability were assessed after 1, 2, 4, 8, and 12 weeks of open-label treatment, and 1, 2, 4, 8, 12, 16, 20, and 24 weeks after randomization to double-blind treatment. A safety follow-up was carried out 4 weeks after the last dose of double-blind treatment.

The study medications were tablets for oral administration, of identical appearance, taste, and smell. Patients took the study medication as a single daily dose.

Patients

Patients were mainly recruited via advertisements by psychiatrists in private or hospital outpatient clinics or by specialized clinical research centers. The inclusion criteria were for female and male outpatients between 18 and 80 years of age with a primary diagnosis of generalized SAD according to DSM-IV criteria.[27] At the screening visit, patients were included if they had a total score of ≥ 70 on the Liebowitz Social Anxiety Scale (LSAS),[28,29] in line with previous studies,[30] with exhibited fear or avoidance traits in at least 4 social situations, and had a score of ≥ 5 on 1 or more of the Sheehan Disability Scale (SDS)[31] subscales.

Patients were excluded if they had another Axis I disorder that was considered the predominant diagnosis within the previous 6 months. Patients with a severity of depressive symptoms that may be thought likely to respond to an antidepressant (Montgomery-Asberg Depression Rating scale [MADRS][32] total score of ≥ 18) were excluded in order to test the efficacy of escitalopram on generalized SAD directly. Patients were excluded if they scored ≥ 5 on MADRS item 10 (suicidal thoughts). Other exclusions were DSM-IV diagnosis of alcohol or drug abuse, an eating disorder, MDD, PD, obsessive-compulsive disorder,

body dysmorphic disorder, schizophrenia/other psychotic disorder, mania or hypomania or history thereof, and presence of an Axis II diagnosis. Patients with a known lack of therapeutic response to any SSRI were excluded. Treatment with a psychoactive drug within 2 weeks (5 weeks for fluoxetine) before screening was excluded. Patients who in the prior 2 weeks had received or who planned to initiate formal psychotherapy were not eligible.

Efficacy Assessments

The primary efficacy parameter was the survival analysis estimate of time to relapse in the double-blind period. The relapse criteria were defined as either an increase in LSAS total score of ≥ 10 points over the score at randomization[29] or withdrawal of the patient from the study due to an unsatisfactory treatment response (lack of efficacy), as judged by the investigator.

The secondary efficacy parameters were based on the LSAS total scores, the LSAS avoidance and fear/anxiety subscale scores, and the SDS scores (work, social life, and family life). The CGI-I scores were recorded only in the open-label period. Only raters who had been trained (using videotapes) were allowed to rate patients. As an aid to investigators who were not comfortable with English, the non-English LSAS versions were translated into the local languages and back-translated to English by a physician. The non-English LSAS versions were then validated by an experienced psychiatrist in each country. Interrater reliability was assessed between the centers, with intraclass correlation coefficients ranging from 0.924 to 0.985.

Safety and Tolerability

Safety and tolerability were evaluated based on spontaneously reported adverse events, electrocardiograms (ECGs), vital signs (systolic and diastolic blood pressure and pulse rate), weight, physical examinations, and clinical safety laboratory tests (hematology and biochemistry). The 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist[33] was used (after the general open questioning used for the recording of adverse events) at the end of the open-label period (at randomization) and 1 and 2 weeks after randomization.

Statistical Analysis

Efficacy analyses were based on the intention-to-treat (ITT) population, which comprised all randomized patients who took at least 1 dose of double-blind study medication and who had at least 1 valid postbaseline assessment of the LSAS total score.

The primary efficacy analysis, comparing relapse in the 2 treatment groups, was based on a log-rank test for survival data, which takes both the number of relapses and the time to relapse into account. This type of analysis utilizes data from all patients in the ITT population by treating data from patients not relapsing as censored data. As a supplement, Kaplan-Meier survival curves were produced, and the Cox proportional hazards model for survival data was used to estimate differences in relapse rates, hazard ratios, and median time to relapse and to evaluate the potential influence of covariates and subgroups. A χ^2 test was used to compare the crude proportions of relapsed patients.

The secondary efficacy parameters were analyzed at week 24 using analysis of covariance, adjusting for center and randomization baseline values.

Safety analyses in the open-label period were based on all patients who took at least 1 dose of escitalopram. The comparison of escitalopram with placebo in long-term treatment was made using the randomized population who had taken at least 1 dose of medication.

RESULTS

Patient Characteristics at Inclusion and at Randomization

Of the 517 patients in the open-label period recruited over a period of 50 weeks, 204 (39%) were recruited from 10 centers with 15 or more patients per center. Twenty-six centers recruited 4 or fewer patients. Four hundred thirty-one patients completed 12 weeks of open-label treatment (Figure 1).

Of the 517 patients, 372 (72%) who had responded (based on the CGI-I score) and consented to continue were randomly assigned to double-blind treatment: 191 to escitalopram and 181 to placebo. Eight eligible patients chose not to continue into the open-label period. One patient in the escitalopram group did not receive treatment—the ITT population thus comprised 371 patients. The randomization code was broken for 1 patient who was hospitalized with major depressive disorder after 82 days of placebo treatment in the double-blind period. The patient was withdrawn from the study, but was included in the ITT efficacy and safety analyses. Of the 517 patients in the study, 308 (60%) were recruited via advertisements. Among the randomized patients, 111 (61%) in the placebo group and 107 (56%) in the escitalopram group were recruited via advertisements.

Patient demography at inclusion and at randomization revealed no significant differences between patients treated with escitalopram or placebo. There were also no significant differences between patients treated with escitalopram or placebo with respect to baseline scores for efficacy parameters (Tables 1 and 2).

Patients entered the open-label period with a mean baseline LSAS total score of 94.8, a mean CGI-Severity of Illness (CGI-S)[26] score of 5.0 (markedly ill), mean SDS subscale (work, family life, and social life) scores between 5.0 and 7.3, and a mean MADRS total score of 7.6 (Table 2). The mean age was 37 years, and the mean age at generalized SAD onset was 17 years. The mean duration of generalized SAD was 20 years.

Table 1. Patient Demography at the Start of Open-Label Treatment With Escitalopram and at Randomization for Relapse Prevention of Generalized Social Anxiety Disorder (GSAD)

	Open-Label Period	Randomization	
Demographic	Escitalopram (N = 517)	Escitalopram (N = 190)	Placebo (N = 181)
Mean age (range), y	37 (18–78)	36 (18–78)	38 (19–68)
Sex (men), %	53	54	51
Race (white), %	95	95	95
Mean body mass index, kg/m^2	24.5	24.2	24.2
Mean age at GSAD onset, y	17	17	17
Mean duration of GSAD, y	20	19	20

A total of 361 (70%) of the patients had their escitalopram dose increased to 20 mg/day during the open-label period, almost all in the first 4 weeks. Among the patients later randomly assigned to double-blind treatment, approximately 75% (placebo: 141 and escitalopram: 139) had had their dose increased during the open-label period.

Open-Label Period

Response to the 12-week open-label treatment was reflected in a substantial reduction from baseline in the LSAS total and subscale scores (avoidance and fear/anxiety) and CGI and SDS scores (work, social life, and family life).

Efficacy in Relapse Prevention

Of the 371 patients in the ITT population continuing into the double-blind period of the study, 198 (123 escitalopram-treated [65%] and 75 placebo-treated [41%] patients) completed the 24-week double-blind study. In the escitalopram group there were 42 relapses (22%), and there were 91 (50%) in the placebo group. In the primary efficacy analysis, there was a significant advantage in the survival analysis for escitalopram compared to placebo (log-rank test, $p < .001$) (Figure 2). The estimated median time to relapse for patients treated with escitalopram was 407 days versus 144 for patients treated with placebo.

In the secondary analysis of relapse rates, based on the Cox proportional hazards model, the risk of relapse was 2.8 times higher with placebo than with escitalopram (χ^2 test, $p < .001$; hazard ratio = 2.83; CI = 1.95 to 4.11).

Analyses with covariates (sex, age, weight or body mass index [BMI], country, LSAS score at randomization, duration of generalized SAD, age at generalized SAD onset, or method of recruitment) revealed no interactions with treatment or any noteworthy change in the estimated relapse risk. There was a significant advantage for both escitalopram 10 mg and 20 mg compared to their own placebo groups in the survival analysis ($p < .001$). No comparison was made between the 2 doses, as they were different populations with more early nonresponders by definition in the 20-mg group.

Escitalopram was effective in preventing relapse in men (23 [22%] of 103 escitalopram patients relapsed vs. 51 [55%] of 93 placebo patients) and in women (19 [22%] of 87 escitalopram patients relapsed vs. 40 [45%] of 88 placebo patients) (χ^2 test, $p < .001$). Similarly, escitalopram was effective in preventing relapse in patients with generalized SAD for the median of 18 years' duration or less (23 [22%] of 104 escitalopram patients relapsed vs. 41 [47%] of 88 placebo patients) and in patients with SAD for more than the median duration of 18 years (19 [23%] of 84 escitalopram patients relapsed vs. 50 [54%] of 93 placebo patients) (χ^2 test, $p < .001$) (Table 3).

Of the patients who relapsed, 122 (91.7%) of 133 met the criterion for relapse of an increase of 10 points on the LSAS. Thirty-seven (19%) of 190 patients in the escitalopram group and 85 (47%) of 181 patients in the placebo group relapsed and met the LSAS relapse criterion (χ^2 test, $p < .001$). Eleven patients (8.3%) relapsed as judged by the investigator, but did not meet the LSAS criterion (5 in the escitalopram group and 6 in the placebo group).

Further improvement was seen on the LSAS in the escitalopram group (8.3 points) and deterioration in the placebo group (4.5 points) during the 24-week study (Table 2). Adjusted mean change in LSAS total scores (ITT, last observation carried forward) is shown by visit for both treatment groups in Figure 3. There was a significant advantage for escitalopram compared to placebo on all of the secondary measures (LSAS total and subscales, CGI-S, SDS, MADRS) (Table 2).

Seventeen patients who (5 [6%] in the escitalopram group and 12 [29%] in the placebo group) relapsed within the first 7 days and 50 patients (14 [7%] in the escitalopram group and 36 [20%] in the placebo group) within the first 14 days. An exploratory analysis was conducted, excluding relapses that occurred within 14 days after randomization in order to avoid possible confounding effects with potential discontinuation symptoms upon the abrupt switch from treatment with escitalopram to placebo. In this analysis, escitalopram (28 relapses [15%] of 190 patients) was also significantly superior to placebo (55 relapses [30%] of 181 patients) with respect to the survival analysis of time to relapse of generalized SAD [$p < .001$]) (Figure 4).

Tolerability

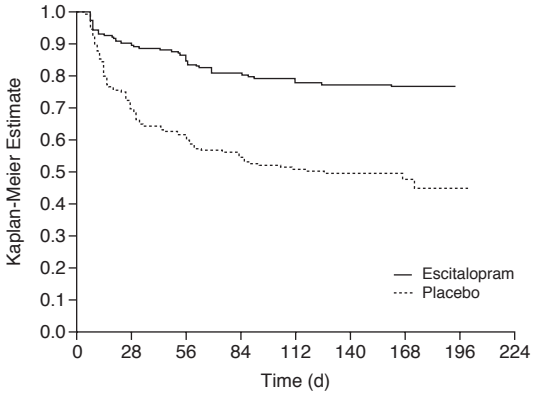
Open-label period. During the open-label period, 6 treatment-emergent adverse events (TEAEs) occurred at an incidence of ≥ 10% (headache, nausea, fatigue, dizziness, increased sweating, and insomnia) with a pattern similar to that seen in open-label studies in other disorders, such as depression,[34] GAD,[17] and PD.[16] A total of 86 patients (17%) withdrew during the 12-week open-label period; 48 (9%) withdrew because of adverse events (the most common being nausea [10 patients], fatigue [7 pa-

Table 2. Secondary Efficacy Measures: Change From Randomization to Week 24 of the Double-Blind Period in Patients Treated With Escitalopram or Placebo for Generalized Social Anxiety Disorder[a]

Efficacy Parameter	Mean ± SD Inclusion Score (N = 517)	Mean ± SD Score at Randomization		Point Change After 24 Weeks of Double-Blind Treatment		Mean ± SE Treatment Difference (95% CI)
		Escitalopram (N = 190)	Placebo (N = 181)	Escitalopram	Placebo	
LSAS score						
Total	94.8 ± 15.3	44.3 ± 20.8	43.2 ± 19.9	–8.3	+4.5	12.8 ± 2.1 (8.7 to 16.9)*
Avoidance	46.1 ± 8.7	19.8 ± 10.7	19.5 ± 10.2	–4.2	+2.3	6.5 ± 1.1 (4.3 to 8.6)*
Fear/anxiety	48.8 ± 7.7	24.4 ± 11.1	23.6 ± 10.7	–4.2	+2.3	6.6 ± 1.1 (4.5 to 8.7)*
CGI-S score	5.0 ± 0.8	2.7 ± 1.0	2.6 ± 1.0	–0.3	+0.3	0.7 ± 0.1 (0.4 to 0.9)*
SDS score						
Work	6.8 ± 2.1	3.0 ± 1.9	2.8 ± 2.1	–0.6	+0.7	1.3 ± 0.2 (0.8 to 1.7)*
Social life	7.3 ± 1.6	2.8 ± 1.9	2.9 ± 2.0	–0.4	+0.6	1.0 ± 0.2 (0.5 to 1.4)*
Family life	5.0 ± 2.5	2.0 ± 1.9	2.0 ± 1.9	–0.1	+0.7	0.8 ± 0.2 (0.5 to 1.2)*
MADRS total score	7.6 ± 4.5	3.2 ± 3.1	3.3 ± 3.5	+0.8	+2.6	1.8 ± 0.5 (0.9 to 2.7)*

[a]Intention-to-treat, last observation carried forward.
*Significantly different from placebo: $p < .001$ (analysis of covariance, last observation carried forward).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, CI = confidence interval, LSAS = Liebowitz Social Anxiety Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale.

Figure 2. Kaplan-Meier Survival Analysis of Relapse in Patients Receiving Escitalopram or Placebo[a]



[a]Time to relapse showed a significant advantage for patients treated with escitalopram compared to patients treated with placebo (log-rank test; $p < .001$).

Table 3. Median Time to Relapse in Days for Patients With Generalized Social Anxiety Disorder (GSAD) Randomly Assigned to Placebo or Escitalopram

Population	Placebo, Days (N)	Escitalopram, Days (N)[a]	Hazard Ratio	χ^2
Intention-to-treat	144 (181)	407 (190)	2.829	30.9*
Men	81 (93)	245 (103)	3.019	19.2*
Women	172 (88)	453 (87)	2.634	12.0*
GSAD duration ≤ 18 y	198 (88)	503 (104)	2.542	12.8*
GSAD duration > 18 y	96 (93)	288 (84)	3.003	16.6*

[a]Estimated median time to relapse (escitalopram) = median time to relapse (placebo) × hazard ratio.
*$p < .001$ vs. placebo.

tients], headache [6 patients], dizziness [5 patients], and anxiety [5 patients]).

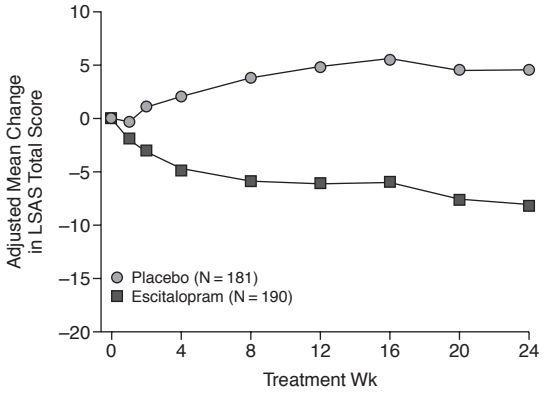
Double-blind, placebo-controlled relapse prevention period. The overall discontinuation rate, excluding relapses, was 13.2% for patients treated with escitalopram (25 patients), and 8.3% for patients treated with placebo (15 patients). Reasons for withdrawal other than relapse are shown in Figure 1. During the double-blind period, 3.3% of the patients in the placebo group and 2.6% of the patients in the escitalopram group withdrew because of adverse events.

Nine TEAEs occurred at an incidence of ≥ 5% in either group (Table 4). In both groups, the majority of the TEAEs were mild to moderate. The incidence of TEAEs was lower in the escitalopram group (62.6%) than in the placebo group (71.8%). Three TEAEs were significantly higher in the placebo group than in the escitalopram group in the first 2 weeks following discontinuation of escitalopram: dizziness, increased sweating, and nervousness ($p < .05$). When the TEAEs in the first 2 weeks following randomization were excluded from the analyses, the adverse events were similar in the placebo and escitalopram groups.

The mean total score on the DESS was similar in both groups at randomization (escitalopram 1.0 and placebo 0.9). After 1 week and 2 weeks of double-blind treatment, the mean total DESS score was significantly lower in the escitalopram group than in the placebo group (week 1: escitalopram = 1.17 and placebo = 2.61; week 2: escitalopram = 1.02 and placebo = 1.78) ($p < .01$). One week after randomization, 9% of the patients in the escitalopram group had a total DESS score of ≥ 4, compared to 27% of the patients in the placebo group ($p < .001$). Two weeks after randomization, these percentages had decreased to 8% and 16%, respectively ($p < .05$).

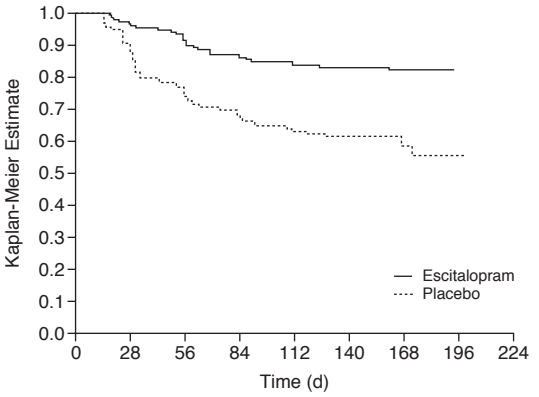
Analysis of clinical safety laboratory tests, vital signs, body weight, and ECG parameters revealed no clinically

Figure 3. Adjusted Mean Change in LSAS Total Scores From Randomization to 24 Weeks in Patients Receiving Escitalopram or Placebo[a,b]



[a]Intention-to-treat, last observation carried forward.
[b]Escitalopram is significantly better than placebo ($p < .001$).
Abbreviation: LSAS = Liebowitz Social Anxiety Scale.

Figure 4. Kaplan-Meier Survival Analysis of Relapse in Patients Receiving Escitalopram or Placebo When the First 2 Weeks of Randomization Are not Included[a]



[a]Time to relapse shows significant advantage for escitalopram (log-rank test; $p < .001$).

relevant mean changes from baseline either within the 2 treatment groups or between groups.

DISCUSSION

This study demonstrated a significant reduction in relapses during 24 weeks of treatment with escitalopram compared to placebo in generalized SAD patients responding to acute treatment. The advantage for escitalopram over placebo was shown on the primary survival analysis of time to relapse as well as on all of the secondary measures. The risk of relapse on the Cox proportional hazards model was 2.8 times higher in patients treated with placebo than in patients treated with escitalopram, demonstrating the clear-cut advantage of long-term treatment of generalized SAD.

It is difficult to compare relapse rates on drug and placebo from studies that used different durations of open treatment, different criteria for response for randomization, and different criteria for relapse. The ratio of relapse on drug to placebo in this study is broadly in line with the results from the other large study carried out with paroxetine despite the difference in design.[35] The small study of sertraline[36] had a much longer duration of acute treatment (24 weeks), and this may have increased the number of stable responders on the SSRI.

This study shows that patients with generalized SAD who have responded to escitalopram treatment at 12 weeks show further therapeutic gains during escitalopram treatment over the subsequent 24 weeks in contrast to a deterioration seen in patients switched to placebo. These results, which are similar to reports from other relapse prevention studies, indicate that while response during open treatment was substantial, the period of 12 weeks was insufficient to achieve optimum response. A much longer period of treatment may be more appropriate. This study was not designed to determine the optimal length of treatment, but it does show that the response at 9 months is better than at 3 months and a longer period might have achieved even greater gains. An open-label study[23] reported that further therapeutic gains were seen up to 2 years with fluvoxamine.

The concept that no further treatment is needed once a patient with generalized SAD responds is not supported by the present study, in which patients in the placebo group suffered a deterioration. Generalized SAD is a chronic disorder in which further benefit can be expected during long-term treatment, which needs to be continued to prevent deterioration. In this respect, generalized SAD is closer to other chronic disorders such as rheumatoid arthritis and hypertension, for which the benefits of treat-

Table 4. Treatment-Emergent Adverse Events (TEAEs) With an Incidence ≥ 5% in Either Group (placebo or escitalopram) During the 24-Week Double-Blind Treatment Period (intention-to-treat), %

	Placebo (N = 181)		Escitalopram (N = 190)	
Adverse Event	0–2 Wk	0–24 Wk	0–2 Wk	0–24 Wk
Patients with TEAEs	56	72	29	63
Dizziness	18*	18	2	5
Increased sweating	12*	12	4	5
Headache	10	14	8	16
Nervousness	7*	7	2	2
Fatigue	7	8	4	7
Insomnia	6	8	2	4
Nausea	5	7	2	3
Rhinitis	3	6	2	5
Influenza-like symptoms	< 1	7	1	8

*$p < .05$ vs. escitalopram.

ment may only be expected while treatment is continued. Similar results are seen in other studies with continued improvement reported on paroxetine and deterioration on placebo[35] and continued further improvement seen between 12 and 24 weeks in the placebo-controlled study of escitalopram.[15]

A change of at least 10 points on the LSAS has been indicated as clinically relevant.[29] This criterion, which is used here in a relapse prevention study, is apparently effective in capturing almost all (91.7%) of the relapses registered. A further 8.3% of patients were judged to have relapsed, according to clinical judgment, but did not meet the LSAS relapse criterion. The clinical relevance is also supported by the finding of significantly lower disability scores for patients treated with escitalopram compared with placebo in all the domains of the GSDS (work, social life, and family life), as well as significant differences in the global assessment of the clinician on the CGI-S.[26]

This is the first relapse prevention study in generalized SAD to analyze separately the efficacy of treatment at different doses. Both doses of escitalopram chosen on the basis of clinical judgment in open treatment showed a significantly lower relapse rate than placebo in responders to that dose. In other words, the dose that achieved response at 12 weeks was shown to reduce the risk of relapse in long-term treatment.

Duration of illness is characteristically very long in generalized SAD patients, and the patients included in our study had a mean prior duration of 19 to 20 years. In an analysis of response according to prior duration, we were able to show that even patients with a very long prior duration of generalized SAD (> 18 years) showed a good response to open-label treatment with escitalopram (responder rate = 72%). The analysis of the relapse prevention data showed that escitalopram is effective compared to placebo in long-term treatment independent of prior duration. The result emphasizes the need for persuading generalized SAD sufferers to come forward and enter treatment, regardless of the prior duration of the disorder.

One of the problems associated with a study design that uses discontinuation on to placebo is the risk that possible discontinuation effects and relapses might be confused. Our principal definition of relapse was an increase of 10 points on the LSAS, a scale chosen because it measures fear and anxiety or avoidance in specific social situations and is therefore unlikely to be contaminated by possible discontinuation symptoms. As an additional precaution against confusing discontinuation symptoms with relapse, we carried out a secondary analysis of relapses excluding the first 2 weeks since the discontinuation symptoms, which appear to be relatively minor with escitalopram, have been shown to peak in the first week and to have largely resolved by the second week. In this analysis, excluding the first 2 weeks made no difference to the significant reduction in relapses seen with escitalopram compared to placebo in the remaining 22 weeks.

The patients in this study were representative of a population with moderate to severe generalized SAD, as reflected by the high mean LSAS and CGI-S scores at baseline. The symptoms were similar in severity to those seen in another relapse prevention study[35] and in the placebo-controlled short-term efficacy studies.[13,15] The patients were suffering from substantial disability with a mean SDS score of 7.3 for social life, 6.8 for work, and 5.0 for family life (total 19.1). The SDS is a self-rated instrument, and it is clear that the population in the study rated themselves as severely impaired. The levels of disability reflected in these scores are in line with those of patients included in other studies[9] and reinforce the perception of generalized SAD as a disorder associated with substantial impairment in social, occupational, and family life.

The presence of comorbid disorders typically found in patients with generalized SAD was low, as required by the protocol. In order to establish efficacy in generalized SAD for a medication that is already licensed as an antidepressant, it is necessary to exclude comorbidity to avoid confounding effects of any secondary activity on the comorbid depression. In common with all pivotal efficacy studies for registration, our study excluded all significant comorbidity including major depressive disorder. The patients were not depressed and had a mean baseline MADRS total score of 7.6, which is below the usual remission criterion for patients with MDD. The efficacy results therefore appear to reflect a specific effect of escitalopram on generalized SAD and are not secondary to an effect on depression.

The low level of depressive symptoms in the patients entering the study should probably be regarded as the "depressive" symptoms that are part of generalized social phobia. During the 12-week open-label period, the MADRS scores dropped to 3.8. During the relapse prevention period, there was a slight worsening of depressive symptoms with escitalopram (0.8 points) compared with a deterioration of 2.6 points with placebo, following a similar pattern to the other secondary efficacy scales. This result tends to suggest that these symptoms are part of generalized SAD.

Comorbidity with MDD is common in generalized SAD, and a limitation of our study was the exclusion of these patients. However, the efficacy of escitalopram compared to placebo in relapse prevention in MDD has already been demonstrated,[34] and it has been shown to be independently effective both in generalized SAD and in major depressive disorder. SSRIs are recommended as first-line medication for generalized SAD patients with or without comorbid depression.[8,37]

A further possible limitation is that our study was a multicenter investigation carried out in several countries.

In order to reduce variability among centers, training sessions were conducted on the LSAS using the English version. In addition, as an aid to the investigator, the LSAS was provided in a translation into the local language that was checked for accuracy by back-translation. The study was not powered to allow an analysis of the results by individual country, but it appears that, despite the small numbers, a significant difference between escitalopram and placebo was observed independently in 6 countries: Canada, Finland, Italy, Norway, South Africa, and the United Kingdom. Caution is needed in interpreting this post hoc analysis, but interestingly it indicates low variability between centers and that the use of the LSAS in this study appeared to be robust.

Previous studies have examined predictors for successful SSRI treatment effect in patients with generalized SAD and have reported a better effect for patients with later generalized SAD onset[38] and more clear-cut results in severely ill patients,[30] although nonresponders (to treatment with an SSRI or monoamine oxidase inhibitor) were more severely ill at baseline in another study.[39] In the present study, tests for predictors of treatment response found no evidence of an effect of sex, age, weight or BMI, dose, baseline LSAS total score, duration of generalized SAD, age at generalized SAD onset, country, or method of recruitment (advertisement vs. patient known in clinic or first visit).

In this study the incidence of adverse events was lower in long-term treatment than short-term treatment. After excluding the first 2 weeks, when discontinuation symptoms appear to have increased the TEAEs on placebo, the adverse event profiles of escitalopram and placebo were similar. This finding is consistent with the results of previous studies in relapse prevention.

It appears that dizziness, increased sweating, insomnia, nausea, and increased nervousness seen on placebo in the overall 0- to 24-week period might be accounted for by the appearance of discontinuation symptoms in the first 2 weeks following abrupt discontinuation of escitalopram.

The total scores of the DESS checklist were low and similar at randomization in the 2 treatment groups. At 1 week, the discontinuation symptoms on the DESS appeared to have peaked with a small (less than 2 points in a 43-item scale) but significant increase in the placebo group compared to escitalopram. At 2 weeks, the discontinuation symptoms had diminished.

The discontinuation symptoms observed in this study are modest, transient, and self-limiting. Discontinuation symptoms with escitalopram have been found in other studies to be significantly lower than with paroxetine (mean increase in DESS value after 1 week taking escitalopram [1.17] or paroxetine [3.97]) in generalized SAD[40] or venlafaxine (mean increase in DESS value after 1 week taking escitalopram [2.4] or venlafaxine [5.0]) in MDD.[41]

In conclusion, escitalopram in daily doses of 10 and 20 mg reduces the risk of relapses in patients with generalized SAD. Treatment with escitalopram in the long term produces significant therapeutic gains in the symptoms and function in contrast to the deterioration observed when treatment is discontinued.

Drug names: escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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