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A Double-Blind Comparison of Escitalopram and Paroxetine in the Long-Term Treatment of Generalized Anxiety Disorder

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Background. *This study compared the efficacy and tolerability of escitalopram, a newer SSRI, with paroxetine in the treatment of generalized anxiety disorder (GAD).*
Methods. *Patients with DSM-IV-defined GAD were randomized to receive 24 weeks of double-blind flexible-dose treatment with either escitalopram (10–20 mg/day) or paroxetine (20–50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in Hamilton Anxiety Scale (HAMA) scores was the primary efficacy variable.*
Results. *Mean baseline HAMA scores for the escitalopram (N=60) and paroxetine (N=61) groups were 23.7 and 23.4, respectively. After 24 weeks of treatment, mean changes in HAMA scores were –15.3 and –13.3 for escitalopram and paroxetine, respectively (p=0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6% vs. 22.6%; p=0.02). The frequency of treatment-emergent adverse events was higher with paroxetine vs. escitalopram: overall (88.7% vs. 77.0%), insomnia (25.8% vs. 14.8%), constipation (14.5% vs. 1.6%), ejaculation disorder (30.0% vs. 14.8%), anorgasmia (26.2% vs. 5.9%), and decreased libido (22.6% vs. 4.9%). Conversely, diarrhea and upper respiratory tract infection were reported more with escitalopram than paroxetine (21.3% vs. 8.1%, and 14.8% vs. 4.8%, respectively).*
Conclusions. *These results support the use of escitalopram as a first-line treatment for GAD.*

Keywords Escitalopram, paroxetine, generalized anxiety disorder, clinical trial, treatment, SSRIs

INTRODUCTION

Generalized anxiety disorder (GAD) is a highly prevalent and disabling disorder. Patients with GAD often suffer symptoms such as excessive anxiety and worry throughout adult life. The diagnosis of GAD requires that the anxiety and worry (or concomitant physical symptoms) interfere functionally with the patient's life. Some patients view their predilection for worrying as an aspect of their nature, rather than as symptoms of a treatable disorder (1).

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The selective serotonin reuptake inhibitors (SSRIs), a class that includes escitalopram and paroxetine, are commonly used to treat GAD (1). However, there is a paucity of double-blind, head-to-head comparisons of these compounds to guide selection of a specific agent. Furthermore, to our knowledge, no head-to-head comparison trial of any two antidepressants (of any class) of long-term duration (i.e., at least 24 weeks) in GAD patients has been published. Such data should be relevant for clinicians, since pharmacotherapy for GAD is usually continued beyond acute treatment (1–2).

Escitalopram is the most selective SSRI available (3). Preclinical studies (4–6) have demonstrated that escitalopram has a broad spectrum of anxiolytic activity. Also, three randomized, double-blind, placebo-controlled trials each demonstrated

that escitalopram at doses of 10 to 20 mg/day is effective and well tolerated in the treatment of GAD (7), with mean reductions in Hamilton Anxiety Scale (HAMA) scores of up to 3.9 points greater than placebo treatment (8). An open-label extension study in GAD patients supports the long-term tolerability and effectiveness of escitalopram at these doses (9).

Paroxetine is also well established as an anxiolytic agent, with several positive published trials of paroxetine in the treatment of GAD (10–12). Paroxetine's broad anxiolytic properties have also been demonstrated in animal models (13–15). The dose range of paroxetine 20–50 mg/day was studied in one 8-week flexible dose trial; in this trial, paroxetine decreased mean HAMA scores by approximately 2 points more than placebo treatment (10). One long-term trial in GAD demonstrated that patients treated with paroxetine (20–50 mg/day) were less likely to relapse than placebo-treated patients (12).

The present trial compared 24 weeks of double-blind treatment with escitalopram or paroxetine in moderately to severely ill GAD patients.

METHODS

This randomized, double-blind, flexible dose trial, consisting of a one-week single-blind placebo lead-in period, followed by a 24-week double-blind treatment period, and a 2-week double-blind down-titration period, was conducted at 8 sites in the United States.

Subjects

Male or female outpatients (18–65 years) who met DSM-IV criteria for GAD (as determined at screening by the Mini-International Neuropsychiatric Interview) were eligible for participation in this trial if at both screening and baseline their HAMA (16) score was 18 or higher, their Hamilton Depression Rating Scale (HAMD) (17) score was 17 or lower, and their Covi Anxiety Scale (18–19) score was greater than their Raskin Depression Scale (20) score.

Patients were excluded if they met the essential DSM-IV criteria for any Axis I disorder other than GAD, or had a history of any DSM-IV-defined psychotic disorders. Patients with any psychotic features, personality disorders, substance abuse or dependency (defined by DSM-IV criteria), or who posed a suicide risk, were also excluded. Women of child-bearing potential were allowed to participate if practicing a reliable method of contraception, and women were excluded if pregnant or breast feeding.

The study protocol was approved by the institutional review boards for all participating study centers, and all subjects provided written informed consent.

Study Flow

Patients who met eligibility criteria at both the screening and baseline visits were randomly assigned to 24 weeks of double-blind treatment with escitalopram or paroxetine. Patients randomly assigned to escitalopram received 10 mg/day for the first 4 weeks of double-blind treatment, after which the dose could be increased to 20 mg/day. Patients randomly assigned to paroxetine received 20 mg/day for the first 2 weeks of double-blind treatment; subsequently the dose could be increased every 14 days by 10 mg/day, until a maximum allowed dose of 50 mg/day by Week 8. Throughout the 24-week double-blind period, dosage could be decreased at any time to improve tolerability (or due to adverse events). The minimum allowed doses were escitalopram 10 mg/day and paroxetine 20 mg/day.

At the end of 24 weeks, patients began a 2-week double-blind down-titration period, during which the doses of escitalopram and paroxetine were decreased in 10 mg/day decrements until a final dose of 10 mg/day was reached. For example, patients receiving escitalopram 20 mg/day at the end of week 24 were down titrated to receive 10 mg/day for the 2-week down-titration period; patients receiving escitalopram 10 mg/day at the end of 24 weeks were maintained at that dose. Similarly, patients receiving paroxetine 20 mg/day at the end of 24 weeks had their dose reduced to 10 mg/day for the 2-week down-titration period. Patients receiving doses of paroxetine higher than 20 mg/day had their doses stepped-down in 10 mg/day decrements at regular intervals until the final dose of 10 mg/day was reached. For example, patients receiving paroxetine 50 mg/day at the end of the 24-week study received 40 mg/day on days 1–3, 30 mg/day on days 4–6, 20 mg/day on days 7–10, and finally, 10 mg/day on days 11–14 of the down-titration period. Patients discontinuing prematurely also could be down-titrated, if judged to be appropriate by the investigator.

The active treatments were provided as identically appearing tablets, and matching placebo tablets were used in the escitalopram arm to maintain blinding both during the 24 weeks of treatment and the 2-week down-titration period.

Study visits were conducted at screening and baseline, and after 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks of double-blind treatment. The baseline visit occurred at the end of the placebo lead-in. All Week 24 evaluations were performed upon early termination. Safety assessments were conducted at all visits, and included monitoring of vital signs and recording of adverse events. Patients were not queried about specific adverse events. Additionally, safety assessments were conducted at Week 26, following the 2-week down-titration period. Complete efficacy evaluations were performed at baseline and after 8 and 24 weeks of double-blind treatment: HAMA, Clinical Global Impressions (21) of Improvement and Severity Scales (CGI-I and CGI-S; CGI-I was not conducted at baseline), and the short form of the Quality of Life (QOL) scale (22). Additionally, the HAMA was conducted at every study visit through Week 24.

Statistical Analysis

The primary efficacy endpoint was change from baseline to Week 24 in HAMA total score for the intent-to-treat (ITT) population using the last-observation-carried-forward (LOCF) analysis. Comparisons between escitalopram and paroxetine were performed using an analysis of covariance (ANCOVA) model with treatment group and center as factors and baseline score as covariate. For CGI-I scores, an analysis of variance (ANOVA) model was used, with treatment and center as factors. Response rates were analyzed using logistic regression with treatment group and baseline scores as explanatory values.

All statistical tests were two-sided with a 5% significance level. All efficacy analyses were based on the ITT population (those who had received at least one dose of double-blind study medication and had at least one post-baseline HAMA assessment). All patients who received at least one dose of double-blind study medication were included in the safety analyses. All efficacy results presented are based on the LOCF analysis.

RESULTS

One hundred and twenty-three patients received at least one dose of double-blind treatment, 61 with escitalopram, and 62 with paroxetine. Of these, 60 escitalopram- and 61 paroxetine-treated patients also had at least one post-baseline HAMA assessment, and comprised the ITT population. There were no statistically or clinically significant differences in baseline demographic characteristics (Table 1). The average age at baseline was approximately 37, and the majority of patients were Caucasian and female. Baseline efficacy values indicate a patient population suffering from moderate to severe GAD, with patients reporting low quality of life. Mean duration of GAD was 11 and 10 years for the escitalopram and paroxetine groups, respectively.

Table 1 Demographic Profile for Safety Population

	Escitalopram (N = 61)	*Paroxetine (N = 62)*
Age (years)		
Mean ± SD	36.8 ± 10.9	37.4 ± 9.6
Gender —n (%)		
Female	34 (55.7%)	42 (67.7%)
Race —n (%)		
Caucasian	44 (72.1%)	49 (79.0%)

A total of 64% of escitalopram-treated patients and 53% of paroxetine-treated patients completed all 24 weeks of double-blind treatment. With the exception of adverse events (see below), there were no statistically significant differences in reasons for premature discontinuation between the two treatment groups. The most common reasons for withdrawal overall were adverse events (15%), lost to follow-up (11%), and withdrawal of consent (7%). The mean daily doses were escitalopram 14.4 mg/day and paroxetine 29.9 mg/day.

Both drugs led to improvements over time in all efficacy measures. Week 8 and Week 24 analyses of efficacy data indicated no statistically significant differences between treatment groups (Table 2). For the escitalopram and paroxetine treatment groups, the proportion of patients who met the response criterion (defined as CGI-I of 1 or 2) at Week 8 was 65.0% and 55.7%, respectively, and 78.3% and 62.3%, respectively, at Week 24 (Table 2); these differences also were not statistically significant.

Statistically significantly more patients withdrew prematurely due to adverse events from the paroxetine group than the escitalopram group (22.6% vs. 6.6%; p=0.02, Fisher exact test). No adverse event was reported as a reason for discontinuation from escitalopram treatment by more than one patient; for paroxetine, headache, insomnia, and nausea each led to the discontinuation of two or more patients. The incidence of treatment emergent adverse events overall was 88.7% for paroxetine and 77.0% for escitalopram. Of note, sexual adverse events (ejaculation disorder, anorgasmia, and decreased libido), constipation, and insomnia were more frequent in paroxetine-treated patients than in escitalopram-treated patients. Conversely, diarrhea and upper respiratory tract infection were more likely to be reported by escitalopram- than paroxetine-treated patients (Table 3).

Mean weight at baseline was 168.7 ± 37.1 lbs for the escitalopram group and 167.9 ± 39.5 lbs for the paroxetine group. For patients completing 24 weeks of double-blind treatment,

Table 2 Efficacy Results at Weeks 8 and 24

	Baseline		Week 8		Week 24	
HAMA	Escitalopram (N=60)	Paroxetine (N=61)	Escitalopram (N=60)	Paroxetine (N=61)	Escitalopram (N=60)	Paroxetine (N=61)
Total score	23.7 ± 0.5	23.4 ± 0.4	–13.0 ± 0.7	–11.7 ± 0.9	–15.3 ± 0.8	–13.3 ± 1.0
Psychic anxiety subscale	13.5 ± 0.3	13.0 ± 0.3	–7.6 ± 0.5	–6.3 ± 0.5	–9.0 ± 0.5	–7.3 ± 0.6
Somatic anxiety subscale	10.2 ± 0.3	10.4 ± 0.3	–5.5 ± 0.4	–5.4 ± 0.5	–6.4 ± 0.4	–6.0 ± 0.5
CGI-I	–	–	2.2 ± 0.1	2.4 ± 0.1	1.8 ± 0.1	2.1 ± 0.2
CGI-S	4.3 ± 0.1	4.3 ± 0.1	–1.6 ± 0.1	–1.6 ± 0.1	–2.1 ± 0.2	–1.8 ± 0.2
QOL	47.1 ± 1.3	48.9 ± 1.3	10.2 ± 1.2	6.7 ± 1.6	10.2 ± 1.4	7.5 ± 1.7
Response Rate	–	–	65.0%	55.7%	78.3%	62.3%

Presented are mean ± SEM baseline values and mean ± SEM changes from baseline. (Mean ± SEM values at Weeks 8 and 24 are presented for CGI-I. Response rate was defined as CGI-I of 1 or 2).

Table 3 Adverse Events with an Incidence ≥ 10% in Either Treatment Group during the 24-Week Double-blind Treatment Period

	Escitalopram (N=61)	Paroxetine (N=62)
Ejaculation disorder[a]	14.8%	30.0%
Anorgasmia[b]	5.9%	26.2%
Insomnia	14.8%	25.8%
Decreased libido	4.9%	22.6%
Headache	11.5%	21.0%
Somnolence	13.1%	16.1%
Dry mouth	13.1%	16.1%
Constipation	1.6%	14.5%
Nausea	14.8%	12.9%
Inflicted injury	4.9%	11.3%
Increased sweating	3.3%	11.3%
Diarrhea	21.3%	8.1%
Fatigue	11.5%	8.1%
Upper respiratory tract infection	14.8%	4.8%

[a]Based on percentage of male patients (n = 27 escitalopram, 20 paroxetine).
[b]Based on percentage of female patients (n = 34 escitalopram, 42 paroxetine).

mean weight increased by 3.5 ± 6.9 lbs and 5.5 ± 6.6 lbs for the escitalopram and paroxetine groups, respectively. However, a total of 18.0% of paroxetine-treated patients and 8.3% of escitalopram-treated patients experienced a 7% or greater increase over baseline weight.

During the down-titration period, the proportion of paroxetine-treated patients reporting dizziness and paresthesia were 9.7% and 6.5%, respectively. None of the escitalopram-treated patients reported these adverse events during the down-titration period. No adverse event was reported by more than one escitalopram-treated patient during the down-titration period.

DISCUSSION

Substantial data exist to support the use of both paroxetine (10–12) and escitalopram (7–9)in the treatment of GAD. The data presented in this report confirm these findings. Similar proportions of patients in both groups completed 24 weeks of double-blind treatment. Both drugs led to substantial improvements in every efficacy measure, including core GAD symptoms, depression symptoms, and quality of life.

Beyond that, however, clinically important differences emerged between escitalopram and paroxetine.

In this trial, escitalopram was better tolerated than paroxetine, as indicated by at least three measures. Firstly, there were significantly fewer premature discontinuations due to adverse events in the escitalopram group than in the paroxetine group. Secondly, there were fewer reports of treatment-emergent adverse events for the escitalopram group than for the paroxetine group. Finally, the incidence of the majority of the most frequent adverse events were lower for the escitalopram group than for the paroxetine group. This was especially the case for sexual adverse events (ejaculation disorder, anorgasmia, and decreased libido), insomnia, and constipation, where the rates observed in this trial for these events were consistent with previously reported values associated with these agents (23–26). In contrast, reports of diarrhea and upper respiratory tract infection were notably more frequent for the escitalopram group than for the paroxetine group.

Weight gain and discontinuation syndromes have been associated with the use of certain SSRIs (27–32), and so it was of interest to compare the incidence of weight gain during double-blind treatment, and the emergence of adverse events during the down-titration period for the two drugs. Symptoms consistent with a discontinuation syndrome, such as dizziness and paresthesia (31), were observed during the down-titration period for several paroxetine treated patients despite the dose taper-down design. Discontinuation symptoms were not noted for any escitalopram treated patients during the down-titration phase, though it should be noted that escitalopram was not down-titrated from 10 mg/day during this period.

Regarding weight gain, the mean increase (5.5 lbs) for the paroxetine treated group was somewhat greater than what had been reported in an earlier placebo-controlled trial of paroxetine in the long-term treatment of GAD, in which mean weight gain among paroxetine treated patients was 2.9 lbs (12). There are some differences in the design of these studies that might account for the differential outcomes with respect to weight gain. For example, the placebo-controlled trial evaluated the efficacy of paroxetine in preventing relapse among patients who had responded to 8 weeks of single-blind treatment with the drug. Thus patients who entered the long-term phase of the trial presumably were able to tolerate paroxetine during the 8-week single-blind treatment phase. Second, during the placebo-controlled phase of that trial, the paroxetine dose was fixed at the dose that was being received at the end of the single-blind phase, whereas in the present trial, patients receiving less than 50 mg/day paroxetine could be up-titrated further in the event of insufficient therapeutic response. It is of note that the relative frequency of clinically significant weight gain (i.e., an increase over baseline weight of 7% or greater) was lower for the escitalopram group than for the paroxetine group (8% vs. 18%).

In this trial, escitalopram treatment was shown to be at least as effective as paroxetine on most outcome measures. Two aspects of this trial limit the interpretation of the efficacy results: the lack of a placebo treatment arm, and the small group sizes; this study was not designed to establish the statistical superiority of one of the active treatment groups relative to the other. Even though no placebo treatment arm was included, the magnitude of the improvement in HAMA scores for both treatment groups was consistent with those reported from placebo-controlled trials (7–8, 10–11).

For conditions such as GAD, which require long-term treatment, prescribing choices need to take into account both acute effects on efficacy and tolerability, as well as outcomes from continuation treatment. In this trial, escitalopram treatment was better tolerated and at least as effective as paroxetine treatment, and should be considered a first-line option by clinicians for the treatment of GAD.

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