

Escitalopram and Paroxetine Compared to Placebo in the Treatment of Generalised Anxiety Disorder (GAD)

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INTRODUCTION

Generalised anxiety disorder (GAD) is defined by excessive anxiety and/or worry that persist for at least 6 months. The criterion of six months duration distinguishes GAD from the shorter, often self-limiting, situational anxiety, and more accurately reflects the serious, chronic, and unremitting nature of GAD.

Selective serotonin reuptake inhibitors (SSRIs) are now the mainstays of treatment for GAD¹. The efficacy of 10 or 20 mg/day escitalopram in GAD was established in 8-week, placebo-controlled, flexible-dose studies^{2,3}, and a 24-week, open-label extension study showed that patients continued to improve over time.

The present study investigated the efficacy and tolerability of 5, 10, and 20 mg escitalopram compared with placebo and the active reference compound paroxetine at the recommended daily dose of 20 mg, in patients with GAD.

OBJECTIVES

- To compare the acute efficacy of three fixed doses of escitalopram (5, 10, or 20mg/day) and the reference drug paroxetine (20mg/day) administered once daily to that of placebo during a 12-week treatment period in outpatients with GAD
- To assess the efficacy and tolerability of the two active products during the 12-week treatment period

STUDY DESIGN

This was a multinational, randomised, double-blind, parallel-group, placebo-controlled, active-reference (paroxetine), fixed-dose study in outpatients with GAD. The study consisted of a 1-week, single-blind placebo run-in period after which patients were randomised to 12 weeks of double-blind treatment with fixed doses of escitalopram (5, 10, or 20mg/day), paroxetine (20mg/day), or placebo. Patients who completed double-blind treatment entered a 2-week (1-week double-blind then 1-week single-blind) washout period.

MAIN SELECTION CRITERIA

- Outpatients between 18 and 65 years of age (extremes included)
- DSM-IV-TR criteria for a primary diagnosis of GAD (using the MINI to assist in the exclusion of disallowed co-morbidity)
- HAM-A total score ≥ 20 , MADRS 16
- A score ≥ 2 on HAM-A items 1 (anxious mood) and 2 (tension) at screening and at baseline

EFFICACY PARAMETERS

Primary efficacy variable

- HAM-A total score (change from baseline to Week 12 - LOCF)

Secondary variables

- HAM-A total score (change from baseline to each visit)
- Proportion of responders (patients with a CGI-I score ≤ 2) per visit
- Proportion of remitters (patients with a HAM-A total score ≤ 7) per visit

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs), vital signs, and weight/BMI
- Modified Discontinuation Emergent Sign and Symptoms (DESS47) checklist (for patients who completed the study)

STATISTICAL METHODS

The primary efficacy analysis was the adjusted mean change from baseline in HAM-A total score at Week 12, based on ITT (LOCF). Comparisons of the primary efficacy endpoint between escitalopram and placebo were made using analysis of covariance (ANCOVA) with treatment and centre as fixed factors, and with the baseline HAM-A total score as a covariate.

DISPOSITION AND DEMOGRAPHICS

The 681 patients in the five treatment groups showed no clinically relevant differences in patient demographics or baseline values (Tables 1 and 2).

Table 1: Baseline patient demography

	Placebo N=139	ESC 5 mg N=134	ESC 10 mg N=136	ESC 20 mg N=133	Paroxetine N=139
Women (%)	93 (67%)	78 (58%)	91 (67%)	92 (69%)	84 (60%)
Age (years) Mean \pm SD	41.8 \pm 11.6	40.7 \pm 11.9	41.8 \pm 12.8	41.0 \pm 12.2	41.7 \pm 12.0
Caucasian (%)	99.3	98.5	99.3	98.5	98.6
BMI (kg/m ²)	25.4	24.5	24.5	24.4	25.4

Table 2: Baseline values

	Placebo N=139	ESC 5 mg N=134	ESC 10 mg N=136	ESC 20 mg N=133	Paroxetine N=139
HAM-A total score	27.1	27.1	26.0	27.7	27.3
HAM-A score for item 1 (anxious mood)	2.81	2.79	2.77	2.78	2.85
HAM-A score for item 2 (tension)	2.81	2.75	2.67	2.73	2.79
CGI-S	4.62	4.57	4.51	4.57	4.60

EFFICACY RESULTS

HAM-A total score

Treatment with escitalopram 10mg ($p < 0.01$) and 20mg ($p < 0.05$) was statistically significantly superior to placebo at Week 12 (LOCF) for the primary efficacy analysis (adjusted mean change in HAM-A total score from baseline to last assessment)

Figure 1 shows the OC values over treatment time. Escitalopram 10mg and 20mg showed a statistically significant ($p < 0.05$ to 0.001) separation from placebo from Week 4 onwards. All doses of escitalopram were statistically significantly ($p < 0.05$) more effective than placebo at Week 12 (OC) and showed a clear dose-response relationship.

Paroxetine 20mg showed a statistically significant ($p < 0.05$) separation from placebo only at Week 10. Escitalopram 20mg was significantly ($p < 0.05$) superior to paroxetine 20mg at Week 12 (OC). Escitalopram 10mg was also significantly ($p < 0.05$) superior to paroxetine 20mg at last assessment (LOCF analysis).

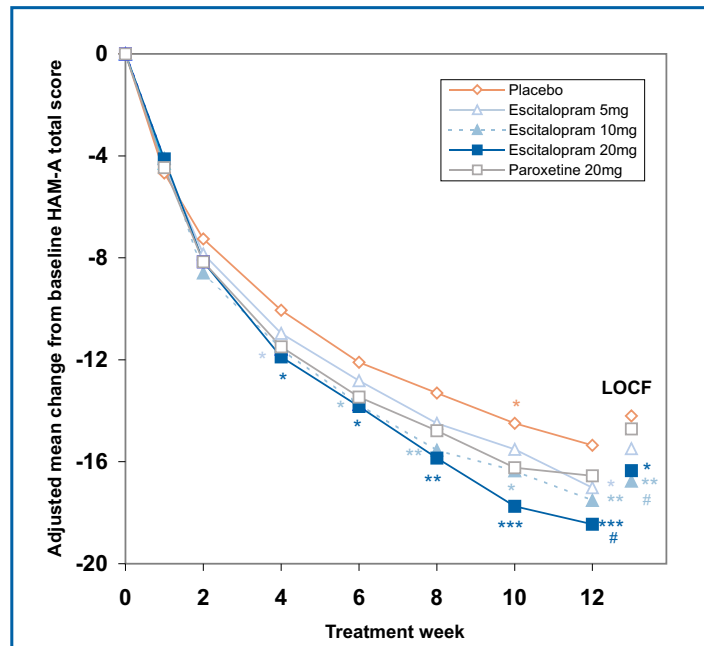


Figure 1. Mean changes from baseline in HAM-A total scores by visit (ITT, OC) and last assessment (LOCF). Difference vs. placebo * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Difference vs. paroxetine # $p < 0.05$.

Responders

In the LOCF analysis at Week 12, the proportion of responders (patients with a CGI-I score ≤ 2) in the escitalopram 10mg group was statistically significantly ($p < 0.05$) superior to the paroxetine 20mg group.

At Week 12, the proportion of responders in the escitalopram 10mg group (78%, LOCF and 83%, OC) and in the escitalopram 20mg group (84%, OC) was statistically significantly ($p < 0.05$ to 0.01) larger than in the placebo group (63%, LOCF and 69%, OC) (Figure 2).

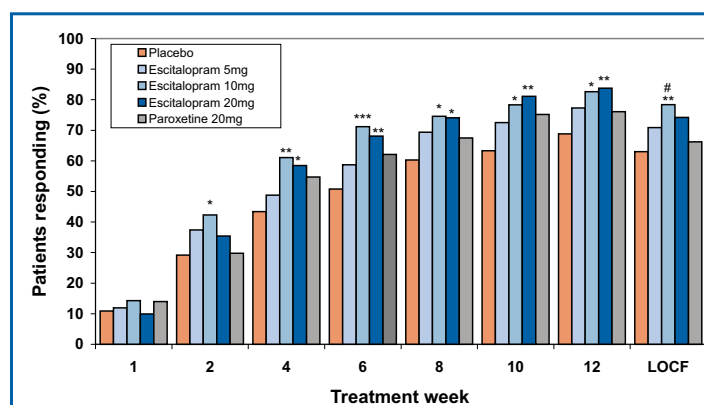


Figure 2. Proportion of patients with a CGI-I score of 1 or 2 (FAS, OC) and at last assessment (LOCF). Difference vs. placebo * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Difference vs. paroxetine # $p < 0.05$.

Remitters

In the LOCF analysis of the proportion of patients in remission (HAM-A total score ≤ 7) at Week 12, all three doses of escitalopram were statistically significantly ($p < 0.05$ to 0.01) superior to placebo, and 10mg escitalopram (47.8%) was significantly ($p < 0.05$) superior to 20mg paroxetine (33.1%).

In the OC analysis, the proportion of patients in remission was statistically significantly larger in the escitalopram 5mg group at Week 12 and in the escitalopram 10mg and escitalopram 20mg groups at Week 8 onwards compared with the placebo group ($p < 0.05$ to 0.01 ; Figure 3).

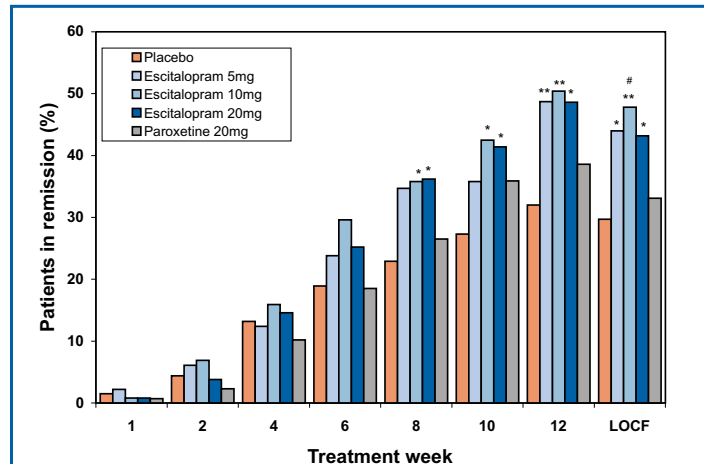


Figure 3. Proportion of patients with a HAM-A total score ≤ 7 by visit (ITT, OC) and last assessment (LOCF). Difference vs. placebo * $p < 0.05$; ** $p < 0.01$. Difference vs. paroxetine # $p < 0.05$.

TOLERABILITY RESULTS

Withdrawals

A total of 98 patients (14%) withdrew from the study during the 12-week, double-blind period (Table 3). The most common reasons for withdrawal were adverse events in the active treatment groups, and lack of efficacy in the placebo group.

The proportion of patients who withdrew due to adverse events was low. Significantly more patients (chi-square test, $p < 0.05$) in the 20mg escitalopram and 20mg paroxetine groups withdrew due to adverse events compared to the placebo group. Withdrawal rates due to lack of efficacy in the 5mg escitalopram, 20mg paroxetine, and placebo groups were comparable.

CONCLUSIONS

- Escitalopram (10 and 20 mg/day) was effective and well tolerated in the treatment of GAD for 12 weeks.
- A dose-response relationship was seen among the patients completing the trial (OC), with escitalopram 20mg giving the highest response.
- Escitalopram 10mg was statistically superior to paroxetine 20mg for the change from baseline to Week 12 (LOCF) based on HAM-A and CGI-I.
- Patients who stopped treatment with escitalopram 10mg had fewer discontinuation effects than those who stopped treatment with paroxetine 20mg.

Table 3. Primary reasons for withdrawal during the 12-week study period

	Placebo N=139	ESC 5 mg N=134	ESC 10 mg N=136	ESC 20 mg N=133	Paroxetine N=139
Patients completed	89%	87%	87%	84%	81%
Total with drawn	11%	13%	13%	16%	19%
Adverse events	3%	5%	6%	11%*	9%*
Lack of efficacy	4%	4%	0%*	2%	3%

* $p < 0.05$ (chi-square test) versus placebo

Treatment-emergent adverse events (TEAEs)

There was no statistically significant difference in the number of patients with TEAEs across the treatment groups (Table 4).

Table 4. Treatment-emergent adverse events with an incidence of $\geq 10\%$ in any group during the treatment period

Preferred Term	Placebo N=139	ESC 5 mg N=133	ESC 10 mg N=136	ESC 20 mg N=133	Paroxetine N=139
Patients with TEAEs	63.3%	65.7%	69.1%	70.7%	72.7%
Nausea	12%	15%	21%	21%	22%
Fatigue	3%	8%	10%*	17%*	9%
Headache	17%	16%	25%	16%	9%
Insomnia	2%	9%*	13%*	11%*	11%*
Dizziness	6%	4%	10%	9%	6%

* $p < 0.05$ versus placebo

Analysis of vital signs, weight, and BMI revealed no clinically relevant changes in mean values from baseline.

Discontinuation emergent signs and symptoms (DESS)

The mean total scores on the modified DESS checklist for the paroxetine 20mg group, and escitalopram 5 and 10mg groups were at a maximum after 7 days of washout treatment (Figure 4). The number of new or worsened DESS items was statistically significantly higher in the 20mg paroxetine group (4.2, $p < 0.001$) than in the placebo group (0.4) at Day 7. The discontinuation symptoms were transient and, after a further 7 days of washout treatment, returned to a level only slightly higher than that before starting washout treatment. (The escitalopram 20mg group received escitalopram 10mg for the first 7 days, and data are therefore not presented.)

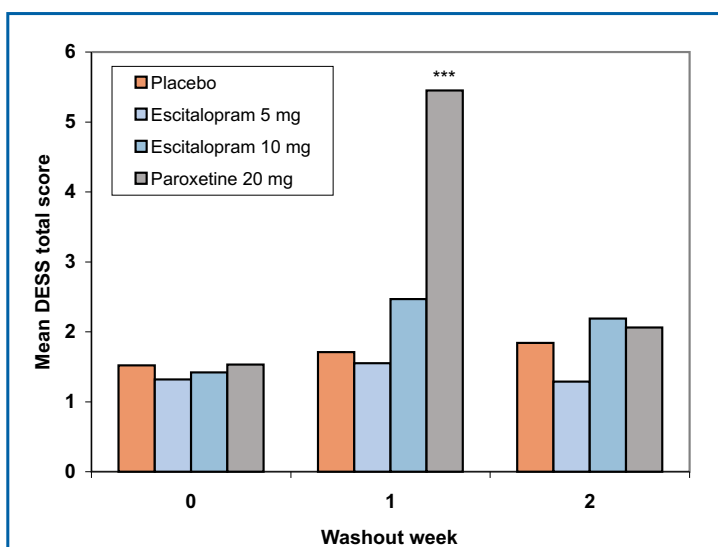


Figure 4. Modified DESS total score for completers. Difference vs. placebo *** $p < 0.001$.

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