

Escitalopram for prevention of relapse in generalised anxiety disorder (GAD)

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ABSTRACT

Escitalopram is efficacious in the treatment of generalised anxiety disorder (GAD). The present study investigated the effect of escitalopram in the long-term prevention of relapse in patients who had responded to acute treatment with escitalopram.

A total of 491 adult patients with a primary diagnosis of GAD (according to DSM-IV criteria) and a Hamilton Anxiety (HAM-A) total score ≥ 20 , received 12-week, open-label escitalopram 20mg/day. Of these, 375 patients responded to treatment (HAM-A total score ≤ 10) and were randomly assigned to 24-76 weeks of double-blind treatment with escitalopram 20mg/day (n=187) or placebo (n=188). The primary efficacy parameter was the time to relapse, defined as either an increase in HAM-A total score to 15 or more, or lack of efficacy as judged by the investigator.

The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, $p < 0.001$). The risk of relapse was 4.04 [95%CI: 2.75 to 5.94] times higher for placebo- than for escitalopram 20mg-treated patients ($p < 0.001$). Significantly fewer escitalopram-treated patients relapsed compared with placebo (19% versus 56%, $p < 0.001$). Escitalopram was well tolerated, with placebo levels of overall withdrawals as well as withdrawals due to adverse events. The discontinuation rate, excluding relapses, was 21% for both escitalopram and placebo. Thus, escitalopram was effective in preventing relapse and well tolerated in the long-term treatment of GAD.

INTRODUCTION

Generalised anxiety disorder (GAD) is characterised by excessive anxiety and uncontrollable worry that persist for more than six months. The efficacy of escitalopram 10mg to 20mg daily in GAD was established in three 8-week, placebo-controlled, flexible-dose studies and an open-label extension study (Davidson et al., 2004; Goodman et al., in press; Stein et al., in press; Bielski et al., in press). In addition, escitalopram has recently shown dose-dependent efficacy, in the treatment of GAD over 12 weeks (Baldwin et al., 2004). The primary objective of this study was to evaluate the effect of escitalopram (20mg/day) versus that of placebo on the prevention of relapse of GAD in patients who had responded to treatment with escitalopram.

METHODS

- This relapse prevention study started with a 12-week, open-label period; followed by at least 24 weeks of double-blind treatment. During the open-label period, patients received escitalopram 10mg during the first week, and 20mg during the remaining 11 weeks.
- Responders to treatment during the open-label period were defined as patients with a decrease in the Hamilton Anxiety Scale (HAM-A) (Montgomery and van Zwieten-Boot, 2002) total score to 10 or less. Non-responders left the study and were treated at the physician's discretion.
- Patients who responded to treatment were randomised to double-blind treatment in a 1:1 ratio. During the double-blind period, randomised patients were treated with either escitalopram 20mg or placebo.
- Patients randomised to placebo had their escitalopram dose down-tapered from 20mg to 10mg one week before starting placebo.
- Patients who completed the double-blind period, entered a two week double-blind down-tapering period, where patients on escitalopram received 10mg/day for a week and placebo for the second week and patients on placebo continued on placebo.
- Patients were in the double-blind period for a minimum of 24 weeks and a maximum of 76 weeks, depending on when in the recruitment period they entered the study, as all patients were to complete the double-blind period simultaneously (Figure 1).
- The primary efficacy analysis used a two-tailed log-rank test to compare the time to relapse for patients treated with escitalopram versus placebo. In addition, Kaplan-Meier survival curves were produced and the Cox proportional hazard model for survival data was used to estimate hazard ratios. A chi-square test was used to compare the crude proportions of relapsed patients.

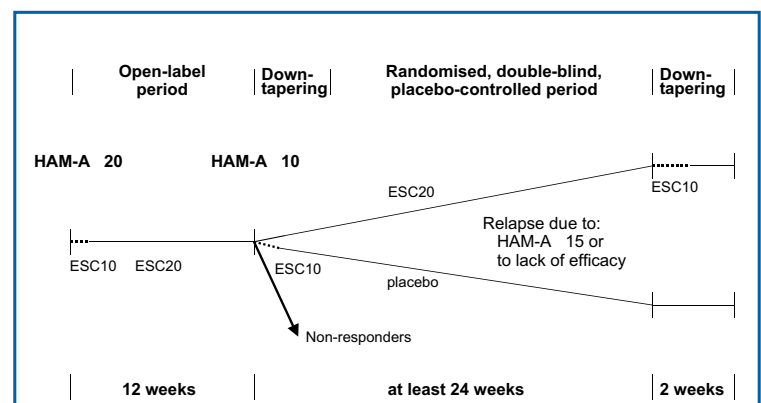


Figure 1. Study design

RESULTS

Patient demography at inclusion and at randomisation revealed no significant differences between patients treated with escitalopram or placebo (Table 1). The average age was 41 years, the mean age of GAD onset was 36 years, and the mean duration of GAD was 5.6 years.

Table 1. Patient demography at the start of open-label treatment and at randomisation to double-blind treatment

	Open-label period		Double-blind period	
	Escitalopram (n=491)	Escitalopram (n=187)	Placebo (n=188)	
Mean age in years (range)	41 (18-65)	41 (18-65)	42 (18-64)	
Sex (% women)	59	60	60	
Race (% Caucasian)	99	100	97	
BMI (kg/m ²)	25.5	25.5	25.3	
Mean age at GAD onset in years (range)	36 (7-66)	37 (9-66)	37 (7-65)	
Mean duration of GAD in years (range)	5.6 (0-56)	4.6 (0-47)	5.5 (0-56)	

Of the 491 patients entering the open-label period, 375 patients (77%) were randomised to double-blind treatment: 187 patients to escitalopram 20mg/day and 188 patients to placebo. The ITT population comprised 373 patients, since two patients were randomised despite being non-responders. Patient disposition for the open label period and the randomised double-blind period of the study (Weeks 24 to 76) is shown in Figure 2. Patients who relapsed include all patients withdrawn due to lack of efficacy, plus other patients who fulfilled the relapse criteria.

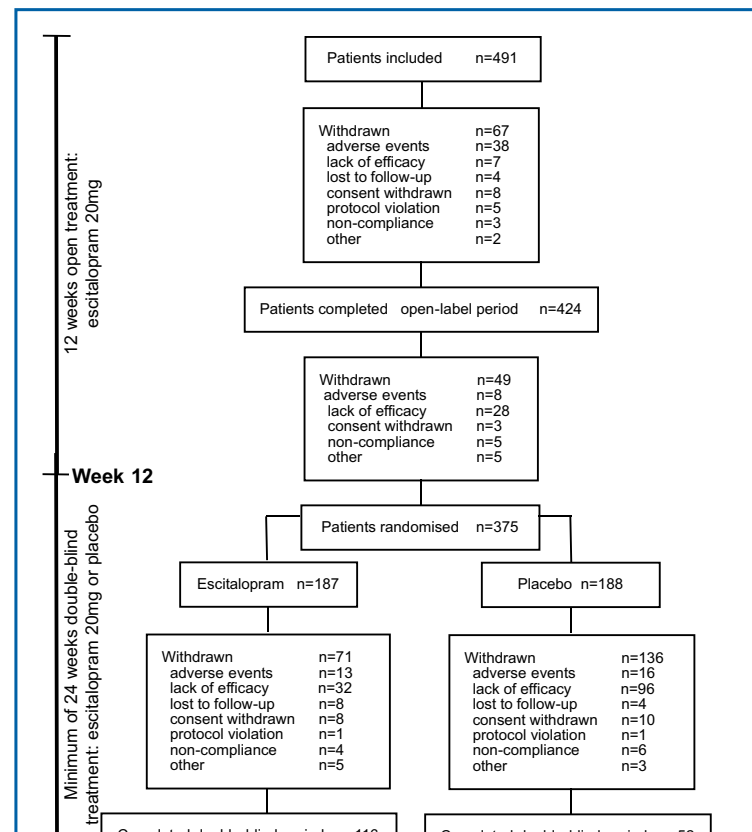


Figure 2. Patient disposition

Open-label Period

The effect of the 12-week open-label treatment was reflected in a substantial improvement from the start of the open-label period in the HAM-A total and subscale scores (psychic anxiety and somatic anxiety), CGI-S score, HAD anxiety score, SDS scores, and the MADRS total score (Table 2).

Table 2. Secondary efficacy measures - change from randomisation to Week 24 of the double-blind period (ITT, OC)

Efficacy Parameter	Start of open-label period (n=491) \pm SD	Start of double-blind period		Change after 24 weeks of double-blind treatment		
		Escitalopram (n=186) \pm SD	Placebo (n=187) \pm SD	Escitalopram (n=133)	Placebo (n=65)	Treatment difference mean [95% CI]
HAM-A total	27.3 \pm 4.4	5.7 \pm 2.9	5.0 \pm 3.1	-0.83	+0.39	-1.22 [-2.28 to -0.17]*
HAM-A psychic anxiety	14.5 \pm 2.4	3.1 \pm 2.0	2.8 \pm 2.0	-0.30	+0.58	-0.88 [-1.57 to -0.20]*
HAM-A somatic anxiety	12.8 \pm 3.3	2.6 \pm 1.9	2.3 \pm 1.8	-0.54	-0.21	-0.33 [-0.88 to +0.23]
CGI-S	4.6 \pm 0.7	1.9 \pm 0.7	1.7 \pm 0.7	-0.31	+0.02	-0.33 [-0.53 to -0.12]*
HAD anxiety	13.8 \pm 3.4	5.5 \pm 3.4	5.3 \pm 3.5	-0.78	-0.14	-0.64 [-1.55 to +0.26]
SDS - work	6.0 \pm 2.1	1.5 \pm 1.6	1.4 \pm 1.6	-0.46	+0.02	-0.48 [-0.91 to -0.05]*
SDS - social life	6.0 \pm 2.2	1.6 \pm 1.7	1.3 \pm 1.6	-0.19	+0.44	-0.63 [-1.08 to -0.17]*
SDS - family life	5.6 \pm 2.1	1.4 \pm 1.5	1.3 \pm 1.7	-0.33	+0.12	-0.45 [-0.84 to -0.06]*
MADRS total score	11.1 \pm 3.2	3.5 \pm 2.7	3.3 \pm 2.7	-0.37	+0.38	-0.75 [-1.61 to +0.11]

ITT: intent to treat, OC: observed cases, SD: standard deviation, *p<0.05 ANCOVA, CI: confidence interval

Double-blind Period

The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, $p < 0.001$) (Figure 3). The proportion of patients who relapsed was significantly higher in the placebo group (56%; 105 patients) than in the escitalopram group (19%; 35 patients) ($p < 0.001$, chi-square test). The proportion of patients who relapsed within 24 weeks was significantly higher in the placebo group (52%; 98 patients) than in the escitalopram group (18%; 34 patients) ($p < 0.001$, chi-square test).

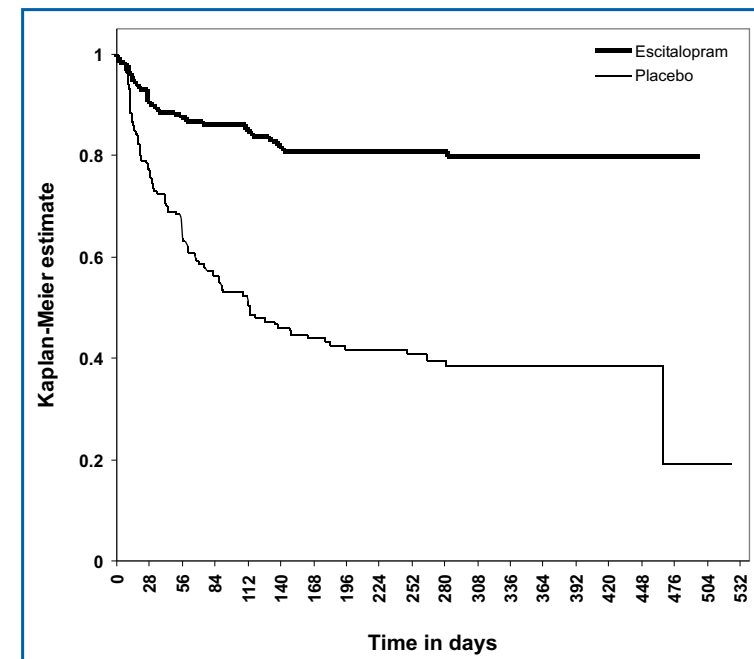


Figure 3. Kaplan-Meier survival analysis of relapse, time to relapse showed a significant advantage for patients treated with escitalopram compared to patients treated with placebo ($p < 0.001$).

CONCLUSIONS

- The risk of relapse was 4.04 times higher in patients treated with placebo versus escitalopram 20mg/day, demonstrating the advantage of long-term treatment of GAD.
- There was a significant reduction in the incidence of relapse with escitalopram versus placebo in patients with GAD responding to acute treatment.
- The superiority of escitalopram versus placebo was shown on the primary survival analysis of time to relapse, as well as on all of the prospectively defined secondary measures.

In the secondary analysis of time to relapse, based on the Cox proportional hazard model, the hazard ratio was 4.04 (95% Confidence Interval: 2.75 - 5.94), that is, the risk of relapse was 4.04 times higher with placebo than with escitalopram ($p < 0.001$; chi-square test).

The effect of long-term treatment as measured by the HAM-A total score (ITT, OC) was stable over time for the escitalopram group and showed a slight deterioration in the placebo group during the double-blind period. A similar pattern was seen for all secondary measures (HAM-A subscales, CGI-S, HAD-anxiety, SDS, and MADRS) (Table 2). Based on an LOCF analysis, these differences in favour of escitalopram were statistically significant for both primary and all secondary measures.

Tolerability

Analysis of clinical safety laboratory tests, vital signs, revealed no clinically relevant mean changes either from baseline within the two treatment groups or between the two treatment groups.

Because significantly more placebo patients were withdrawn during the double-blind period, the difference in the extent of patient exposure (excluding the two down-taper periods) and the down-taper period at the end of the study should be considered when interpreting the withdrawal results (Table 3). During the double-blind period, 8.5% of the patients in the placebo group and 7.0% of the patients in the escitalopram group withdrew due to adverse events. In both groups, the majority of the TEAEs during the double-blind period were mild to moderate. During down taper after randomisation to double-blind treatment, the incidence of TEAEs was similar in the escitalopram group (30.5%) and in the placebo group (33.5%). During down-taper at the end of the study, more escitalopram patients (28.4%) than placebo patients (11.5%) reported TEAEs, particularly dizziness and nervousness.

Table 3. Treatment-emergent adverse events (TEAEs) with an incidence $\geq 5\%$ in any treatment group

Preferred Term	Open-label period	Double-blind period (up to 76 weeks)				Down-taper at completion	
	Escitalopram (n=491) 103 PYE	Escitalopram (n=187) 7.0 PYE	Placebo* (n=188) 6.6 PYE	Escitalopram (n=187) 112.3 PYE	Placebo (n=188) 63.0 PYE	Escitalopram* (n=116) 4.4 PYE	Placebo (n=52) 2.0 PYE
Patients with TEAEs	382 (77.8%)	57 (30.5%)	63 (33.5%)	105 (56.1%)	61 (32.4%)	33 (28.4%)	6 (11.5%)
Nausea	119 (24.2%)	4 (2.1%)	6 (3.2%)	4 (2.1%)	1 (0.5%)	5 (4.3%)	0
Headache	82 (16.7%)	9 (4.8%)	9 (4.8%)	21 (11.2%)*	7 (3.7%)	2 (1.7%)	1 (1.9%)
Ejaculation failure (men)	24 (4.9%)	<1%	<1%	0	0	<1%	<1%
Dizziness	57 (11.6%)	4 (2.3%)	23 (12.2%)*	7 (3.7%)	6 (3.2%)	11 (9.5%)*	0
Fatigue	55 (11.2%)	1 (0.5%)	3 (1.6%)	9 (4.8%)	5 (2.7%)	4 (3.4%)	1 (1.9%)
Insomnia	54 (11.0%)	4 (2.1%)	12 (6.4%)	7 (3.7%)	7 (3.7%)	2 (1.7%)	0
Dry mouth	53 (10.8%)	<1%	<1%	3 (1.6%)	2 (1.1%)	<1%	<1%
Somnolence	48 (9.8%)	<1%	<1%	0	0	<1%	<1%
Diarrhoea	47 (9.6%)	0	3 (1.6%)	7 (3.7%)	5 (2.7%)	<1%	<1%
Increased sweating	39 (7.9%)	2 (1.1%)	0	3 (1.6%)	0	3 (2.6%)	0
Decreased libido	31 (6.3%)	<1%	<1%	1 (0.5%)	1 (0.5%)	<1%	<1%
Anorexia	28 (5.7%)	<1%	<1%	1 (0.5%)	2 (1.1%)	<1%	<1%
Rhinitis	27 (5.5%)	9 (4.8%)*	2 (1.1%)	26 (13.9%)*	11 (5.9%)	2 (1.7%)	0
Upper resp tract infection	19 (3.9%)	2 (1.1%)	1 (0.5%)	13 (7.0%)	5 (2.7%)	<1%	<1%
Back pain	13 (2.6%)	2 (1.1%)	2 (1.1%)	11 (5.9%)	8 (4.3%)	<1%	<1%
Nervousness	7 (1.4%)	2 (1.1%)	3 (1.6%)	1 (0.5%)	2 (1.1%)	7 (6.0%)	0

PYE: patient years of exposure
 *patients down-tapering from escitalopram 20mg to 10mg to placebo;
 *p<0.05, not adjusting for differences in PYE

REFERENCES

- Baldwin DS, Huusom AKT, Mæhleum E. Escitalopram and paroxetine compared to placebo in the treatment of generalised anxiety disorder (GAD). Eur Neuropsychopharmacol 2004;14(Suppl 3):S311-S312.
- R Bielski, A Bose, C-C Chang. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychol, in press
- Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: a double-blind, placebo controlled, flexible dose study. Depress Anx 2004; 19: 234-240.
- Goodman, W. K., Bose, A., & Wang, Q. Treatment of generalized anxiety disorder with escitalopram: Pooled results from double-blind, placebo-controlled trials. J Affect Dis, in press
- Montgomery S, van Zwieten-Boot B. ECNP Consensus Meeting March 2000 Guidelines for Investigating Efficacy in GAD. Eur Neuropsychopharmacol 2002; 12: 81-87.
- Stein D, Andersen HF, Goodman W. Escitalopram for the treatment of GAD: efficacy across different subgroups and outcomes. Ann Clin Psychol, in press.

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