

Prevention of relapse in older patients with major depressive disorder by escitalopram treatment

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INTRODUCTION

Epidemiological surveys have shown that approximately 13% of elderly persons manifest clinically relevant symptoms of depression and 2% have Major Depressive Disorder (MDD) (2). Nevertheless, only about one-third of elderly persons suffering from depression have a recorded diagnosis of depression and are properly diagnosed or receive appropriate treatment (1,3,5).

Clinical trial evidence suggests that older patients with MDD appear to benefit as much as middle-aged patients from treatment with antidepressants (6,7,8). There is however only limited evidence to support continuation treatment in elderly depressed patients who respond to antidepressant treatment.

Thus, there is a need for a properly designed study, conducted in elderly patients with recurrent as well as first episode depression, which could provide clear evidence of the relapse prevention efficacy of a well tolerated antidepressant such as escitalopram. There is a need for such a study also to be representative of the 'old-old' (age 75 years) as well as of the younger elderly population. The current study was conducted in 46 centres in 7 European countries and recruitment was monitored to ensure that at least one-third of the included patients were >75 years of age.

METHODS

This relapse prevention study started with a 12-week, open-label period; followed by 24 weeks of double-blind treatment. During the open-label period, patients received escitalopram 10mg during the first week, which could be increased to 20mg from week 2 at the clinician's discretion. From week 6, no further dose adjustment was allowed.

Patients in remission (prospectively defined as a MADRS total score < 12) were randomised to double-blind treatment in a 1:1 ratio. During the double-blind period, randomised patients were treated with escitalopram (10 or 20mg, retaining the dose determined during the first 6 weeks) or placebo.

Patients randomised to placebo after the open-label period had their escitalopram dose down-tapered from 20mg to 10mg one week before starting placebo.

Patients were in the double-blind period for 24 weeks (Figure 1).

Patients who completed the double-blind period, entered a one week double-blind taper period, where patients on escitalopram 20mg/day received 10mg/day for a week and then placebo and patients on escitalopram 10mg/day or placebo received placebo immediately.

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.

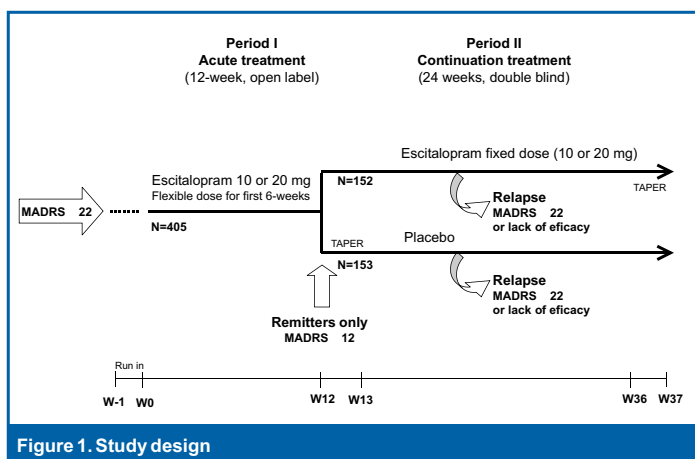


Figure 1. Study design

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 73 years, and more than one-third of the patients were > 75 years of age. The mean age of MDD onset was 56 years, the mean duration since the MDD diagnosis was made was 17.3 years, and the mean duration of the current episode was about 16 weeks.

Table 1. Baseline patient characteristics

	Open-label period		Double-blind period	
	Escitalopram (n=405)	Escitalopram (n=152)	Placebo (n=153)	
Mean age in years (range)	73 (64-91)	73 (64-86)	72 (65-90)	
Patients 75 years old	151 (37%)	50 (33%)	58 (38%)	
Sex (n, % women)	313 (77%)	119 (78%)	121 (79%)	
Race (% Caucasian)	99.8%	99.7%	100%	
BMI in kg/m ² (SD)	26.3 (4.1)	26.0 (4.0)	26.4 (4.2)	
Mean age at MDD onset in years (range)	56 (3-89)	55 (5-83)	55 (3-89)	

Of the 405 patients entering the open-label period, 305 patients (75%) were randomised to double-blind treatment: 152 patients to escitalopram and 153 patients to placebo. The ITT population thus comprised 305 patients (Figure 2).

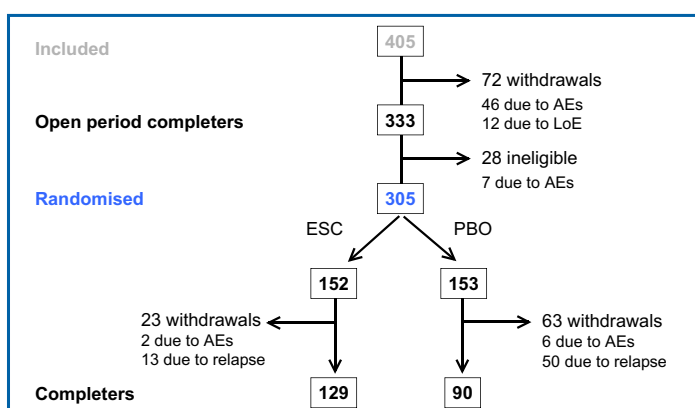


Figure 2. Patient disposition (AE, adverse events; LoE, lack of efficacy)

Open-label Period

The effect of the 12-week open-label treatment was reflected in a decrease from the start of the open-label period in the mean MADRS total score (LOCF) [from 31.1 to 9.7] (Figure 3) and in the CGI-S [from 4.84 to 2.22]. At Week 12, 81.0% (328/405) of the patients were MADRS responders, and 79.5% had achieved remission (MADRS < 12).

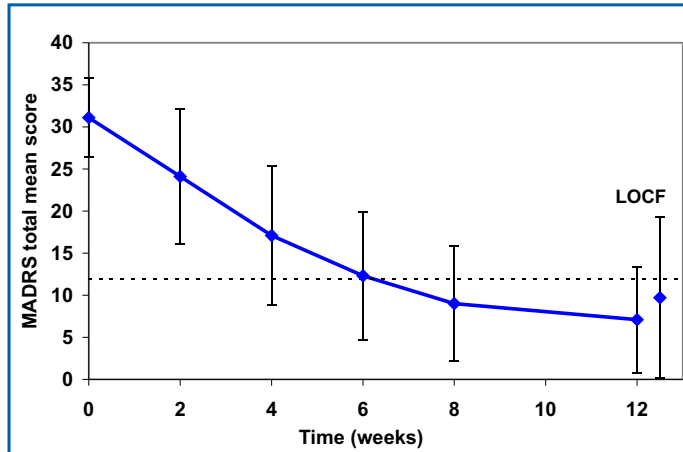


Figure 3. MADRS total scores during open-label treatment with escitalopram 10 to 20 mg/day. Values are \pm SD, n=405

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=405) \pm SD	Start of double-blind period		Change after 24 weeks double-blind treatment*		Treatment difference mean [95% CI]
		Escitalopram (n=152) \pm SD	Placebo (n=153) \pm SD	Escitalopram (n=130)	Placebo (n=91)	
MADRS total score	31.1 4.7	5.3 3.4	5.3 3.4	-0.9	+0.8	-1.22 [-2.28 to -0.17]*
CGI-S	4.84 0.7	1.62 0.7	1.7 0.7	-0.15	+0.10	-0.33 [-0.53 to -0.12]*
CGI-I [†]	3.08 1.0	1.25 0.5	1.32 0.5	-0.04	+0.04	-0.64 [-1.55 to +0.26]

ITT: intent to treat, OC: observed cases, SD: standard deviation, *change relative to score at the start of double-blind period, [†]Measured at Week 2, *p<0.05 ANCOVA, CI: confidence interval

Double-blind Period

The results of the primary analysis showed a beneficial effect of escitalopram relative to placebo on the time to relapse of MDD (log-rank test, p<0.001) (Figure 4), relapse being defined (*a priori*) as either a MADRS total score \geq 22, or lack of efficacy, or as judged clinically by the investigator.

The proportion of patients who relapsed within 24 weeks was significantly higher in the placebo group (33%; 50 patients) than in the escitalopram group (9%; 13 patients) (χ^2 test, p<0.001). Thus 91% of patients treated with escitalopram remained relapse-free versus 67% of placebo-treated patients.

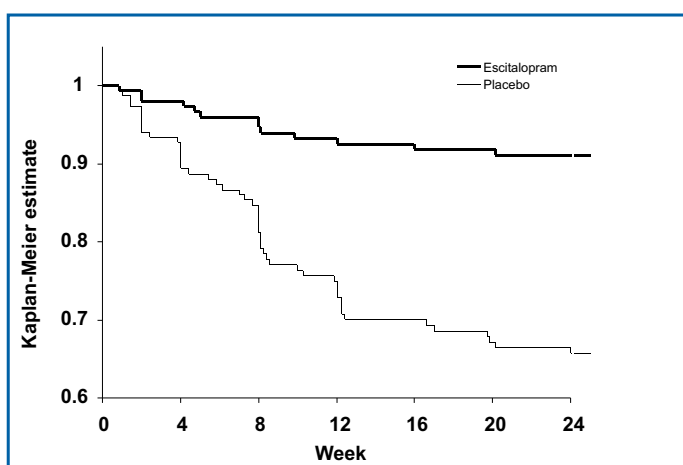


Figure 4. Kaplan Meier survival analysis of relapse over 24 weeks. Time to relapse showed a significant advantage for patients treated with escitalopram compared to patients treated with placebo (p<0.001; log-rank test).

The secondary analysis of time to relapse, based on the Cox proportional hazard model, the estimated hazard ratio was 4.44 (95% confidence interval: 2.41 to 8.17; p<0.001). Thus, the risk of relapse was 4.44 times higher for placebo-treated patients than for escitalopram-treated patients.

The effect of long-term treatment as measured by the MADRS total score was stable over time for the escitalopram group. A similar pattern was seen for all secondary measures (Table 2).

The percentage of MADRS responders decreased from 100% to 66.7% in the placebo group, but only to 90.8% in the escitalopram group (LOCF, p<0.001) (Figure 5).

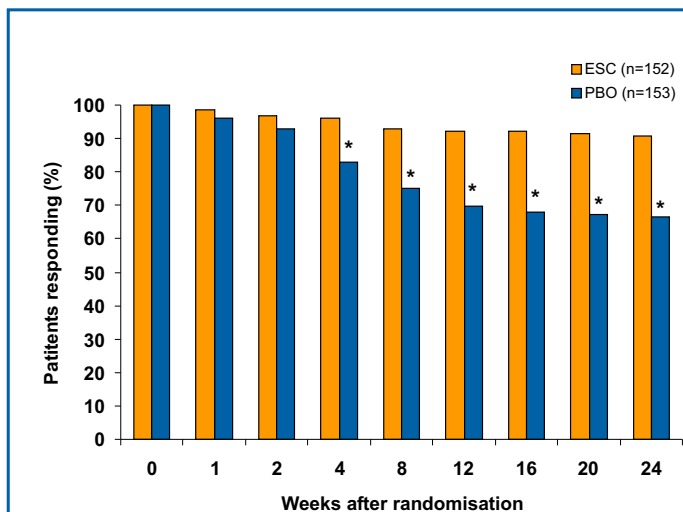


Figure 5. MADRS responders (50% decrease from baseline score) during the double-blind treatment period.

The percentage of MADRS remitters decreased from 100% to 59.5% in the placebo group, and to 88.2% in the escitalopram group (LOCF, p<0.001) (Figure 6).

CONCLUSIONS

- This study demonstrate that continuation treatment with escitalopram significantly reduces the risk of relapse of depressive episodes in older patients; 91% of escitalopram-treated patients versus 67% of placebo-treated patients remained relapse free.
- The risk of relapse was 4.44 times higher in patients treated with placebo versus escitalopram 10 to 20mg/day, demonstrating the advantage of long-term treatment of older patients with MDD.
- The superiority of escitalopram versus placebo was statistically significant and was shown on the primary efficacy endpoint of time to relapse, as well as on all of the prospectively defined secondary measures.
- Escitalopram 10 to 20mg/day was well tolerated in older patients.

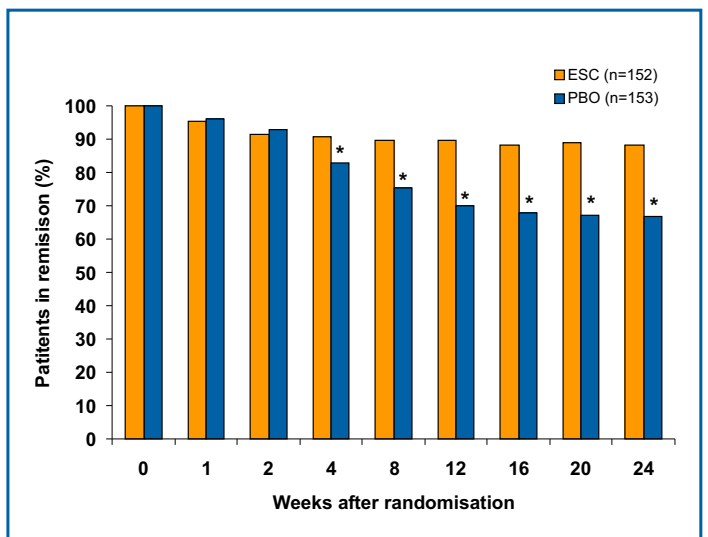


Figure 6. MADRS remitters (MADRS < 12) during the double-blind treatment period.

Tolerability

In the open-label period, 217 patients (53.6%) reported at least one adverse event. The most common adverse events were nausea (12.1%), headache (9.4%), dizziness (6.7%), and diarrhoea (5.2%). A total of 53 patients (13.1%) withdrew due to adverse events.

During taper after randomisation to double-blind treatment, the incidence of adverse events was similar in the escitalopram group (30.5%) and in the placebo group (33.5%). During the double-blind period, 3.9% of the patients in the placebo group and 1.3% of the patients in the escitalopram group withdrew due to adverse events. In both groups, the majority of the adverse events during the double-blind period were mild to moderate.

The incidence of adverse events was higher in the placebo group (17.6%) than in the escitalopram group (9.2%) during the first 2 weeks after randomisation to double-blind treatment, the most common adverse events being nausea, headache, dizziness, and diarrhoea (Table 5). During the one-week taper at the end of double-blind treatment, more placebo patients (24.4%) than escitalopram patients (18.1%) reported adverse events.

Table 5. Adverse events (AEs) with incidence \geq 5% in any treatment group

Preferred Term	Open-label period		Double-blind period (24 weeks)			
	Escitalopram (n=405)	Placebo (n=153)	Taper after randomisation (Week 0 to 2)	From Week 2 until completion	Escitalopram* (n=127)	Placebo (n=90)
Patients with AEs	215 (53.1%)	14 (9.2%)	27 (17.6%)	53 (34.9%)	54 (35.3%)	23 (24.4%)
Nausea	49 (12.1%)	0	4 (2.6%)	0	0	0
Headache	38 (9.4%)	5 (3.3%)	6 (3.9%)	4 (2.6%)	5 (3.3%)	2 (1.6%)
Dizziness	27 (6.7%)	2 (1.3%)	5 (3.3%)	7 (4.6%)	5 (3.3%)	7 (5.5%)
Diarrhoea	21 (5.2%)	0	0	5 (3.3%)	4 (2.6%)	0

*patients tapering from escitalopram to placebo

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