Escitalopram prevents relapse of obsessive-compulsive disorder
Naomi A. Fineberg, Brigitte Tonnoir, Ole Lemming, Dan J. Stein

1. Introduction

Obsessive-compulsive disorder (OCD) is a prevalent and disabling lifespan disorder. Wide-ranging epidemiological surveys repeatedly demonstrated high lifetime prevalence, amounting to 2–3% of the population worldwide, under DSM-III and DSM-III-R criteria (Robins et al., 1984; Weissman et al., 1994), although a recent analysis (Kessler et al., 2005a,b) suggested a lower estimate (12-month prevalence 1.0%; lifetime estimate 1.6%). Untreated OCD usually runs a chronic course, fluctuating in intensity but rarely disappearing. In a seminal follow-up study spanning several decades, Skoog and Skoog (1999) reported only a minority of patients had become symptom-free. Convincing evidence from large-scale placebo-referenced randomised controlled trials supports efficacy for the serotonin reuptake inhibitors (SRIs) clomipramine and selective serotonin reuptake inhibitors (SSRIs) fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram in the acute treatment of OCD. Response is characteristically partial with few patients achieving remission [defined as a Y-BOCS (Goodman et al., 1989) score ≤10]. Fixed-dose comparator studies provide evidence of a dose-response relationship with SSRIs (reviewed in Fineberg and Gale, 2005).

Abstract To examine the efficacy and tolerability of escitalopram in the prevention of relapse in patients with OCD, 468 patients with OCD were treated with open label escitalopram (10 mg or 20 mg) for 16 weeks, after which the 320 responders (Y-BOCS total score decrease ≥25%) were randomised to placebo or escitalopram (at the assigned dose) for 24 weeks double-blind treatment. The primary analysis (time to relapse) showed a significant advantage for escitalopram (p<0.001, log-rank test). The proportion of patients who relapsed was statistically significantly higher in the placebo group (52%) than in the escitalopram group (23%) (p<0.001, χ²-test). The risk of relapse was 2.74 times higher for placebo compared to escitalopram. Escitalopram was well tolerated and improvements in obsessive-compulsive symptoms reported during the open label period were sustained during the double-blind extension of treatment with active drug. These results demonstrate that escitalopram is effective for long-term treatment and relapse prevention in OCD.

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KEYWORDS
Obsessive-compulsive disorder; OCD; Escitalopram; Relapse prevention; Yale-Brown Obsessive Compulsive Scale; Y-BOCS
There have been fewer studies of long-term treatment and it remains less conclusively understood as to how well treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term. Studies of clomipramine (Katz et al., 1990), fluoxetine (Tollefson et al., 1994) and sertraline (Greist et al., 1995) investigated ‘responders’ from the acute treatment period and continued their previous treatment for up to 12 months including placebo. In all three trials, the authors concluded that the response to SRI was sustained, with no evidence of tolerance developing. In contrast, studies that have examined the discontinuation of active treatment and randomised patients to placebo have, in the main, demonstrated re-emergence of symptoms in the placebo-treated cohort. (Pato et al., 1988); (reviewed in Fineberg and Gale, 2005). Some, but not all relapse prevention studies investigating acute treatment-responders revealed a significant advantage for remaining on active medication. In the case of paroxetine, one published study of adult OCD (Hollander et al., 2003b) showed evidence supporting continuing the active drug compared with placebo, but a study on childhood OCD (Geller et al., 2003) and a small adulthood study (Bailer et al., 2005 – not peer reviewed) did not. In the fluoxetine relapse prevention trial, a significant advantage was restricted to the 60 mg fixed dose-level (Romano et al., 2001), whereas in the sertraline trial, efficacy was not established on the primary efficacy criterion but there was subsidiary evidence that sertraline reduced the occurrence of acute exacerbations of OCD and numbers of patients withdrawing prematurely from treatment due to relapse (Koran et al., 2002). There is some evidence to suggest that relapse after drug discontinuation is associated with increased resistance to resumed pharmacotherapy (Maina et al., 2001).

Escitalopram, an antidepressant that binds to both the primary site on the serotonin transporter as well as to the allosteric site, which has been shown to augment the efficiency of the inhibition of serotonin reuptake (Sánchez et al., 2004), is a new treatment for OCD. A recent placebo and reference controlled study of fixed doses of 10 mg and 20 mg escitalopram or 40 mg paroxetine showed efficacy for the 20 mg escitalopram dose-level compared with placebo at week 12, and efficacy for all active treatments at week 24 (Stein et al., 2006 – submitted for publication).

The primary objective of the current study was to compare the efficacy of escitalopram 10 mg or 20 mg/day with that of placebo in preventing relapse during 24 weeks in outpatients with OCD who had responded to 16 weeks prior open label treatment with escitalopram. The secondary objectives were to assess long-term efficacy and tolerability of escitalopram (10 and 20 mg/day) in outpatients with OCD during sustained treatment with escitalopram.

2. Experimental procedures

The study was conducted at 62 centres in 14 countries, in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) (WMA, 1964). The study was approved by local ethics committees and all patients gave written, informed consent.

2.1. Study design

This relapse prevention study started with a 16-week open label period that was followed by a 24-week, randomised, double blind treatment period (Fig. 1). During the open label period, patients received escitalopram 10 mg/day for the first week, after which the dose could be increased to 20 mg/day at a scheduled visit in case of lack of efficacy, and could be decreased to 10 mg/day in case of dose-limiting adverse events. After week 12, the dose was fixed. Patients who had responded (≥25% decrease from baseline in Yale-Brown Obsessive Compulsive Scale [Y-BOCS] total score) by the end of the 16 week open label period were eligible to randomisation to either escitalopram (fixed dose of 10 or 20 mg/day) or placebo in a 1:1 ratio. Non-responders left the study and were treated at the investigator’s discretion.

During the double-blind period, patients randomised to placebo who were on 20 mg/day escitalopram during the open label period received 10 mg/day escitalopram for one week before dose tapering. Patients randomised to escitalopram were titrated to the 10 or 20 mg/day dose levels that they had tolerated during the open label period.

During the double-blind period, patients randomised to placebo who were on 20 mg/day escitalopram during the open label period received 10 mg/day escitalopram for one week before dose tapering. Patients randomised to escitalopram were titrated to the 10 or 20 mg/day dose levels that they had tolerated during the open label period.
week (week 1) and then placebo for the remainder of the study. Patients randomised to escitalopram continued on the same fixed dose (10 or 20 mg/day) as they had received at the end of the open label period until the 1-week double-blind taper period (Week 25), during which patients on 20 mg/day escitalopram received 10 mg/day, while patients on 10 mg/day escitalopram or placebo received placebo. Throughout the 24-week double-blind period (until taper), the investigators evaluated relapse symptoms. Relapse was defined as either an increase in the Y-BOCS total score of ≥5 points from the time of randomisation, or an unsatisfactory treatment effect (lack of efficacy) as judged by the investigator. Patients who relapsed were withdrawn from the study.

2.2. Allocation to treatment

Study medications were tablets for oral administration, of identical appearance, taste or smell. The oxalate salt of escitalopram was used. After the open label period, eligible patients were assigned to escitalopram or placebo treatment according to a computer-generated randomisation list. The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available in blocks of four. All study personnel and participants were blinded to treatment assignment for the entire duration of the study.

2.3. Patients

Patients were enrolled from psychiatric practices, special-ized clinical centres, psychiatric hospital departments, or general practice. Patients eligible for this study were outpatients between 18 and 65 years of age (extremes included), with a primary diagnosis of OCD (current episode) according to DSM-IV-TR (APA, 1994) without other primary psychiatric disorders or significant somatic morbidity and with a Y-BOCS total score ≥20 (moderately to severely ill patients). The duration of the OCD had to be at least 1 year and the OCD should have been stable for at least 6 months, according to clinical judgement.

Patients with any of the following DSM-IV disorders were excluded: current or past history (considered as the primary disorder in the previous 6 months) of major depressive disorder, panic disorder, generalised anxiety disorder, post-traumatic stress disorder, eating disorder, body dysmorphic disorder, schizotypal personality disorder, any cognitive disorder (including dementia), mental retardation or any pervasive developmental disorder, alcohol or drug (other than nicotine) abuse-related disorder or any history of mania or any bipolar disorder, schizophrenia or psychotic disorder (or psychotic features), motor/verbal tic disorder (including Tourette’s) or any personality disorder judged by the investigator to jeopardise the evaluation of the treatment for primary OCD. Patients were also excluded if they were at risk of suicide according to the investigator, or had a rating ≥5 points on item 10 (suicidal thoughts) of the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), or a MADRS total score ≥22. Patients were also excluded if they had recently used any of the following therapies: electroconvulsive therapy within the last 6 months, formal psychotherapy of any kind, prophylactic treatment with any anticonvulsant drug, or psychotropics (other than zolpidem, zopiclone, or zaleplon prescribed episodically for insomnia). Disallowed drugs within the last 2 weeks prior to screening were: antipsychotics and mood stabilisers including lithium (6 months for depot preparations), monoamine oxidase inhibitors (also reversible), psychoactive herbal remedies, dopamine antagonists for any indication, or serotonergic agonists, or any other antidepressant (fluoxetine, 5 weeks) or drug used for the treatment of OCD. In addition, patients with a history of severe drug allergy or hypersensitivity, or known hypersensi-tivity to citalopram and/or escitalopram, patients with current depressive symptoms, patients that had not responded to 3 well-conducted OCD treatments (SSRIs or clomipramine, for at least 12 weeks), and patients who had demonstrated a lack of response to previous treatment with citalopram or escitalopram (including current episode) were also excluded.

2.4. Assessments

Only those investigators who had actively participated in rater training sessions prior to inclusion of patients into the study were allowed to rate patients. Rater training was undertaken to increase inter-rater reliability, and was chaired by an experienced psychiatrist. Patient ratings were assessed by the same investigator at each visit, whenever possible. Efficacy and tolerability parameters were assessed after 1 and 2 weeks, and then every 2 weeks during open label treatment. For patients randomised to double-blind treatment, efficacy and tolerability parameters were assessed 2, 4, 6, 8, and 12 weeks after randomisation and then every 4 weeks until their last dose of double-blind treatment (Week 24).

Efficacy assessments at each study visit were: Y-BOCS, National Institute of Mental Health-Obsessive-Compulsive Scale (NIMH-OCS) (Insel et al., 1983) and Clinical Global Impressions–Severity of Illness (CGI-S) and Improvement of illness (CGI-I) (Guy, 1976). MADRS measurements were also made during both the open label and the double-blind period.

The prospectively defined primary analysis of efficacy was the time to relapse from the start date of double-blind treatment. Relapse was defined as an increase in the Y-BOCS total score of ≥5 points, or lack of efficacy as judged by the investigator. The prospectively defined secondary efficacy parameters included proportion of relapsed patients, change in scores for the total Y-BOCS, Y-BOCS obsessive and compulsive subscores, NIMH-OCS, CGI-S and CGI-I and the proportion of patients fulfilling criteria for clinical response (≥25% decrease from baseline in Y-BOCS total score) and remission (Y-BOCS score ≤10).

Tolerability and safety evaluations were based on spontaneously reported adverse events (AEs), vital signs, body weight, and physical examination. Discontinuation symptoms were assessed by evaluation of AEs during the
first 2 weeks after randomisation (tapering of escitalopram for patients randomised to the placebo arm).

2.5. Statistical analysis

The sample size and power calculations were based on analysis of time to relapse in the double-blind period. Assuming a relapse hazard ratio of 3.3 (placebo relative to escitalopram), and further assuming that withdrawal due to reasons other than relapse would occur at a rate of 0.001 per week in both treatment groups, a total of 240 patients (120 patients per treatment group) randomised to the double-blind period would provide 85% power to find a statistically significant difference between escitalopram and placebo, using a two-tailed, log-rank test at the 5% level of significance. It was anticipated that approximately 40 to 60% of the patients enrolled in the open label period would be eligible for the double-blind period. This meant that approximately 500 patients needed to be enrolled in the open label period.

All efficacy analyses in the double-blind treatment period were conducted using the intention-to-treat (ITT) population, which consisted of all randomised patients who took at least one dose of trial medication and had at least one post-randomisation efficacy assessment. The primary efficacy analysis used a two-tailed log-rank test to compare the time to relapse for patients treated with escitalopram versus placebo, using SAS version 9.1 as statistical software. In addition, Kaplan-Meier survival curves were calculated and the Cox proportional hazard model for survival data was used to estimate hazard ratios. A χ²-test was used to compare the crude proportions of relapsed patients.

Comparisons between escitalopram and placebo with respect to the secondary efficacy parameters were performed using analysis of covariance (ANCOVA) with treatment group and country as factors, and with the score at randomisation as a covariate. In order to exclude potentially confounding discontinuation effects, the influence of discontinuation symptoms on the primary analysis was investigated in four analyses, in which relapses occurring during the first 7 and 14 days after randomisation were censored.

3. Results

3.1. Patient characteristics at inclusion and at randomisation

Of the 468 patients entering the open label period, 320 patients (69%) were randomised to double-blind treatment: 163 patients to escitalopram and 157 patients to placebo. The ITT population comprised 320 patients due to the exclusion of

![Figure 2](https://example.com/figure2.png)

Figure 2  Patient disposition and analysis sets for the open label period and the randomised double-blind period of the study.

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two patients that were randomised without having met the Y-BOCS response criterion during the open label period (Fig. 2). Although the majority of patients were Caucasian, there was a broad mixture of other ethnicities in the study population (Table 1). At study entry, patients were roughly equally divided between males and females; the mean age was approximately 36 years with stable DSM-IV OCD that had been symptomatic for an average of 5 years (range 1–52 years).

The mean baseline Y-BOCS total score was approximately 26 (Table 2), representing moderate to severe OCD. The mean baseline NIMH-OCS total score was approximately 9, representing clinical obsessive-compulsive behaviour. CGI-S was approximately 5 indicating a markedly ill population. The mean MADRS total score was approximately 10, reflecting low levels of comorbid depressive symptoms. There were no differences in demographics and clinical parameters between the two treatment groups in the randomisation period. In the double-blind period, 133 of the 163 patients (82%) in the escitalopram group received 20 mg/day escitalopram.

### 3.2. Efficacy

The primary efficacy analysis showed a statistically significantly superior effect of escitalopram relative to placebo on the time to relapse of OCD (Fig. 3, log-rank test, \( p < 0.001 \)); the proportion of patients who relapsed was statistically significantly higher in the placebo group (81 out of 157 patients; 52%) than in the escitalopram group (38 out of 163 patients; 23%) (Fig. 2; \( \chi^2 \)-test, \( p < 0.001 \)). The Y-BOCS relapse criterion accounted for almost all of the relapses (116 out of 119 patients, 97%). The Cox proportional hazards model gave an estimated hazard ratio of 2.74 (\( p < 0.001 \)); that is, the risk of relapse was 2.74 times higher for placebo-treated patients than for escitalopram-treated patients. In post-hoc analyses based only on the Y-BOCS relapse criterion, the proportion of patients who relapsed was 50% in the placebo group (79 out of 157 patients) and 23% in the escitalopram group (37 out of 163 patients; \( \chi^2 \)-test, \( p < 0.001 \)), with an estimated hazard ratio of 2.73 (\( p < 0.001 \)). The robustness of the conclusions from the primary efficacy analysis was confirmed by the secondary analysis of time to relapse using the per-protocol set (comprising the subpopulation of the ITT with no major protocol deviations during the double-blind period). In analyses using the ITT and a 7- or 14-day relapse cut-off period after randomisation, during which relapses were censored to discount the possible effect of discontinuation symptoms, escitalopram was significantly superior to placebo. Subgroup analyses did not reveal any difference for

### Table 1 Patient demographics and OCD history

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Escitalopram (n = 468)</th>
<th>Placebo (n = 157)</th>
<th>Escitalopram (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n %)</td>
<td>239 (51.1%)</td>
<td>82 (52.2%)</td>
<td>80 (49.1%)</td>
</tr>
<tr>
<td>Age in years Mean ± SD</td>
<td>35.8 ± 11.4</td>
<td>35.8 ± 11.1</td>
<td>35.4 ± 12.4</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>374 (79.9%)</td>
<td>125 (76.7%)</td>
<td>126 (80.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (0.4%)</td>
<td>0</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>85 (18.2%)</td>
<td>28 (17.8%)</td>
<td>35 (21.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (1.5%)</td>
<td>3 (1.9%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Age at onset Mean ± SD</td>
<td>22.5 ± 10.9 (n = 465)</td>
<td>22.1 ± 10.3</td>
<td>23.6 ± 11.8</td>
</tr>
<tr>
<td>Years since onset Mean ± SD</td>
<td>13.9 ± 10.6 (n = 465)</td>
<td>14.2 ± 10.5</td>
<td>12.5 ± 10.5</td>
</tr>
<tr>
<td>Duration of current symptoms</td>
<td>4.9 ± 6.8 (n = 465)</td>
<td>4.8 ± 6.5 (n = 157)</td>
<td>4.8 ± 7.6 (n = 162)</td>
</tr>
</tbody>
</table>

| SD: standard deviation. |

### Table 2 Secondary efficacy measures at end of open label and double-blind period (ITT, LOCF, ANCOVA)

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Randomisation</th>
<th>24 weeks after randomisation</th>
<th>ESC (n = 468)</th>
<th>PBO (n = 157)</th>
<th>ESC (n = 163)</th>
<th>PBO (n = 157)</th>
<th>ESC (n = 163)</th>
<th>Adjusted mean change from randomisation (PBO versus ESC)</th>
<th>Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-BOCS total</td>
<td>26.4 ± 3.7</td>
<td>15.0 ± 8.5</td>
<td>11.2 ± 5.3</td>
<td>10.8 ± 5.4</td>
<td>14.8 ± 7.5</td>
<td>10.7 ± 7.3</td>
<td>−3.67***</td>
<td>−4.91 to −2.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsessional subscale</td>
<td>13.3 ± 2.2</td>
<td>7.6 ± 4.4</td>
<td>5.8 ± 2.7</td>
<td>5.4 ± 2.8</td>
<td>7.9 ± 4.0</td>
<td>5.6 ± 4.0</td>
<td>−1.94***</td>
<td>−2.66 to −1.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsive subscale</td>
<td>13.0 ± 2.2</td>
<td>7.4 ± 4.4</td>
<td>5.5 ± 3.0</td>
<td>5.4 ± 2.9</td>
<td>6.9 ± 3.9</td>
<td>5.1 ± 3.7</td>
<td>−1.74***</td>
<td>−2.37 to −1.12</td>
<td></td>
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</tr>
<tr>
<td>NIMH-OCS total</td>
<td>9.2 ± 1.7</td>
<td>5.8 ± 2.9</td>
<td>4.5 ± 2.0</td>
<td>4.5 ± 2.0</td>
<td>5.8 ± 2.7</td>
<td>4.4 ± 2.6</td>
<td>−1.39***</td>
<td>−1.89 to −0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-I</td>
<td>3.8 ± 0.7b</td>
<td>2.3 ± 1.2</td>
<td>1.8 ± 0.7</td>
<td>1.7 ± 0.6</td>
<td>2.5 ± 1.3</td>
<td>1.9 ± 1.1</td>
<td>−0.61***</td>
<td>−0.87 to −0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.7 ± 0.8</td>
<td>3.3 ± 1.3</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 1.0</td>
<td>3.2 ± 1.2</td>
<td>2.6 ± 1.2</td>
<td>−0.60***</td>
<td>−0.82 to −0.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS totalb</td>
<td>10.0 ± 5.3</td>
<td>5.9 ± 5.2</td>
<td>4.6 ± 3.9</td>
<td>4.9 ± 4.2</td>
<td>5.3 ± 5.3</td>
<td>4.2 ± 5.1</td>
<td>−1.66***</td>
<td>−2.88 to −0.43</td>
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</tr>
</tbody>
</table>

| aObserved cases for MADRS (Montgomery-Åsberg Depression rating Scale), bMean score at open label period Week 1; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; ESC, escitalopram; LOCF, last observation carried forward; NIMH-OCS, National Institute of Mental Health-Obsessive-Compulsive Scale; PBO, placebo; Y-BOCS, Yale-Brown Obsessive Compulsive Scale. |

**p < 0.01, ***p < 0.001, difference versus placebo.**

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age, gender, baseline total Y-BOCS score, duration of OCD or previous treatment of OCD. Both the 10 mg and 20 mg escitalopram subgroups were statistically significantly superior to the corresponding placebo subgroups in the analysis of time to relapse.

During the open label period, treatment with escitalopram resulted in a substantial decrease in the mean scores on the Y-BOCS total, the Y-BOCS obsessional and compulsive subscales, the CGI-S, and CGI-I (Table 2). The proportion of responders after 16 weeks of open label treatment was 74%, based upon the Y-BOCS.

The anti-OCD effect of escitalopram was maintained during the double-blind period with statistically significant differences in mean change from randomisation in Y-BOCS, NIMH-OCS total, CGI-I and CGI-S (Table 2, p < 0.001). From week 4 of double-blind treatment onwards, there was a sustained, statistically significant between-group difference in Y-BOCS total score, both in last-observation-carried-forward (LOCF) (Fig. 4a) and OC (Fig. 4b) analysis. There was also a significant separation in favour of escitalopram in the proportion of Y-BOCS responders (Fig. 5) and remitters (Fig. 6).

### 3.3. Safety

A total of 94 out of 468 patients (20%) withdrew during the 16-week open label period, 28 due to AEs (Fig. 2). 54 patients who completed the open label period were not randomised, 1 of whom because of AEs (Fig. 2). AEs during the open label period are shown in Table 3, almost all of which were mild to moderate. There were no deaths in the study. One patient (in the open label period) was withdrawn due to suicidal ideation. In the open label period (including safety follow-up), 6 patients had 9 serious AEs (SAEs) (all considered by the investigator not related to treatment). In the double-blind period, none of the patients in the escitalopram group had SAEs; 3 patients in the placebo group had 3 SAEs (all considered by the investigator not related to treatment). There were 2 unintended pregnancies, both of which led to withdrawal from the study. Both women gave birth to healthy children.
The balance between acute treatment phase (Tollefson et al., 1994; Greist et al., 1990), the number of such studies is still rather few (Fineberg and Gale, 2005). In this relapse prevention study, escitalopram was found to be effective, safe, and generally well tolerated for long-term treatment for OCD. Although most studies that have looked at continuation treatment have found an advantage for comparison with either clomipramine (100–300 mg) or placebo for 10 weeks, after which the 124 responders continued with a year long double-blind extension period. The superiority of clomipramine over placebo was demonstrated to the extent that OCD was no longer compromising the lives of half the clomipramine-treated patients. However, 23% of the patients treated with clomipramine withdrew early due to adverse events. In the study by Pato et al. (1988), 21 patients successfully treated with clomipramine for 5–27 months were given placebo for 7 weeks, with 18 patients completing placebo treatment and 16 of them relapsed. Given the chronic, sometimes refractory nature of OCD and the associated serious disability, an effective and well-tolerated treatment that keeps those who responded, well, is a valuable addition to our current treatment armamentarium.

In the present study, the proportion of patients who relapsed was 52% in the placebo group and 23% in the escitalopram group after 24 weeks of double-blind treatment. This compares with 59% (30/51) for placebo versus 38% (20/53) (and a Hazard Ratio of 2.7) for paroxetine after 6 months of double-blind treatment (Hollander et al., 2003b), and 18% (4/22) for placebo and 0% (0/19) for paroxetine after 6 months of double-blind treatment (Bailer et al., 2005 – not peer reviewed). Koran et al. (2002) reported relapse rates of 24% (27/114) for placebo and 9% (10/109) for sertraline after 28 weeks of double-blind treatment. The lower relapse rates in the studies by Koran et al. (2002) and Bailer et al. (2005) may be due to the longer open label periods (12 months and 6–12 months, respectively) and differences in relapse criteria.

Compared to placebo, both 10 mg and 20 mg escitalopram were effective on all a priori primary and secondary outcome measures of preventing relapse, with a statistically significantly superior effect relative to placebo on the time to relapse of OCD and a hazard ratio of 2.74. The anti-OCD effect of escitalopram seen during the 16-week open label period was maintained during the double-blind period, with significant differences in mean symptom scores (Y-BOCS, NIMH-OCS, CGI, MADRS) between the escitalopram and placebo groups. The proportion of responders and remitters was also significantly greater in the escitalopram group. The definition of clinical response (≥ 25% improvement in baseline total Y-BOCS score) was chosen to indicate clinically

### Table 3 Treatment-emergent adverse events (TEAEs) with an incidence of 5% or more during open label treatment or double-blind treatment

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Open label ESC (n = 468)</th>
<th>DB Weeks 0–2 PBO (n = 157)</th>
<th>ESC (n = 163)</th>
<th>DB Week 2–24 PBO (n = 157)</th>
<th>ESC (n = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AEs, n (%)</td>
<td>330 (70.5%)</td>
<td>47 (29.8%)</td>
<td>23 (14.1%)***</td>
<td>50 (31.8%)</td>
<td>64 (39.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>93 (19.9%)</td>
<td>9 (5.7%)</td>
<td>1 (0.6%)***</td>
<td>1 (0.6%)</td>
<td>5 (3.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>85 (18.2%)</td>
<td>7 (4.4%)</td>
<td>3 (1.8%)</td>
<td>7 (4.4%)</td>
<td>7 (4.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (10.9%)</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>40 (8.5%)</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>35 (7.5%)</td>
<td>25 (15.9%)</td>
<td>1 (0.6%)***</td>
<td>1 (0.6%)</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>32 (6.8%)</td>
<td>5 (3.2%)</td>
<td>1 (0.6%)</td>
<td>4 (2.5%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>31 (6.6%)</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>24 (5.1%)</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>24 (5.1%)</td>
<td>&lt;2%</td>
<td>&lt;2%</td>
<td>2 (1.3%)</td>
<td>7 (4.3%)</td>
</tr>
</tbody>
</table>

DB, double-blind period; PBO, placebo; ESC, escitalopram. **p < 0.01, ***p < 0.001, difference versus placebo.
significant improvement and is similar to that used in other efficacy studies of SSRIs (Montgomery et al., 2001; Hollander et al., 2003a).

The concept of remission for OCD is more debatable and there is no universally accepted definition. It has been described as a brief period during which sufficient improvement has occurred that the individual no longer suffers with OCD (Simpson et al., 2006). For this study we chose a relatively conservative criterion of Y-BOCS ≤ 10 for remission status. Patients with this level of illness were still likely to fulfill some of the DSM-IV criteria for OCD. Other studies have chosen remission criteria ranging from Y-BOCS <16 to Y-BOCS ≤ 7 (Simpson et al., 2006; Hollander et al., 2003b; Eddy et al., 2004; Van Oppen et al., 1995; McLean et al., 2001; Cottroux et al., 2001). The analysis by Simpson et al. (2006) found that a Y-BOCS threshold score of 7 did not discriminate between active and control treatments, whereas a threshold score of 12 did.

The strength of the effect of escitalopram versus placebo was evident across all subgroups without any evident difference regarding age, sex, years since onset of OCD, previous treatments or dose. Although fewer escitalopram responders were receiving 10 mg than 20 mg doses at the 16-week randomisation point, suggesting a preferential initial response to 20 mg escitalopram, 10 mg/day of escitalopram was equally as effective as 20 mg/day at preventing relapse. Not only did patients on placebo relapse significantly more frequently than patients on either dose of escitalopram, but also patients on placebo withdrew from the trial due to lack of efficacy nearly 2.5 times as often.

Previous relapse prevention studies have cited discontinuation effects in the placebo-treated group as a possible confound (e.g., Hollander et al., 2003b). In the present study, discontinuation effects were minimised by down-titrating the 20 mg dose to 10 mg for one week before switching to placebo. Examination of adverse events occurring exclusively in the 1 to 4-week period following randomisation demonstrated only a modest increase within the placebo group relative to escitalopram, and dizziness and nausea alone were significantly over represented relative to patients still receiving escitalopram, consistent with previous reports with escitalopram (Baldwin et al., in press). Adverse events in patients randomised to placebo were mainly mild in severity and did not lead to increased rates of leaving the study early. Moreover, when the survival analysis excluded withdrawals during the 1- to 2-week period following randomisation, the advantage for escitalopram remained just as strong, suggesting discontinuation effects are not responsible for the benefits associated with remaining on escitalopram.

A risk-benefit profile depends not only on measures of efficacy but also on those of tolerability. Adverse events during the double-blind period were few, and only in 2 patients (versus 3 on placebo) were they of such intensity to be the primary cause of withdrawal.

Acquisition of a substantial proportion of patients from primary care sites (“general practice”) could have increased the degree of treatment responsiveness in the sample. A sample drawn entirely from tertiary care sites, or sites specializing in OCD might have had a lower remission rate because more treatment-resistant patients are seen at such sites. At entry to the study, the mean Y-BOCS score was 26.4 (±3.7), representing moderate-severe OCD. A total of 74% patients achieved a clinical response during the 16-week open label escitalopram treatment period, by the end of which the mean Y-BOCS score for the ‘intent-to-treat cohort’ had reduced to 15.0 (±8.5), representing moderate OCD.

Secondary remission criteria of OCD also improved on open label escitalopram. These results are in line with the results from a 24-week dose-finding study reporting anti-OCD efficacy for 10 mg and 20 mg escitalopram (Stein et al., 2006 — submitted for publication), and with studies using different designs showing long-term efficacy for other SSRIs such as sertraline (Greist et al., 1995), fluoxetine (Tollefson et al., 1994), and paroxetine (Hollander et al., 2003b).

By the end of the double-blind period, 54% of patients treated with escitalopram had achieved remission (Y-BOCS ≤ 10). This is a relatively high proportion, as remission in OCD, albeit not well defined, is still relatively rare among patients with this chronic, refractory disorder. It should be noted that in the relapse prevention period only the 68% of patients who had responded (≥ 25% decrease from baseline in Y-BOCS total score) in the open label period were included.

While the relapse rate with escitalopram was significantly lower than with placebo, 23% of escitalopram-treated patients did relapse during the 24 weeks randomisation period with an estimated median time of 10 months. The Y-BOCS relapse criterion accounted for the majority of relapses (97%). Relapse was defined in the present study as an increase in the Y-BOCS total score by at least 5 points from randomisation. The definition of relapse (an increase of 5 points from randomisation in the Y-BOCS score) has been used in other studies (e.g., Koran et al., 2002). We considered a 5-point change to be clinically relevant for this study since we anticipated it would approximate to a 50% loss of pre-randomisation improvement. The choice of the relapse criterion affects the numbers of qualified relapses (Simpson et al., 2005) and the power of the study to detect drug-placebo differences. Some studies (Romano et al., 2001; Koran et al., 2002) used more stringent, multiple relapse criteria that resulted in lower relapse rates due to high number of patients not meeting the criteria. In the study by Koran et al. (2002), which did not discriminate between sertraline and placebo on the primary analysis of relapse probability, but did show an advantage for continuing active treatment on other measures, the authors considered their use of multiple relapse criteria (worsening by 5 points on Y-BOCS plus Y-BOCS total score ≥ 10 for remission) to be conservative. The relapse prevention study by Hollander et al. (2003b), that demonstrated efficacy for paroxetine, defined relapse as a return of the Y-BOCS score to baseline or an increase by one point on the CGI-S scale.

Patients were withdrawn from the present study if relapse criteria were present at a single visit. Thus, patients classified as relapsed could have experienced a transient exacerbation of illness. This could explain why the relapse rate for escitalopram was intermediate between that reported for sertraline (9%), in a study (Koran et al., 2002) in which determination of relapse required worsening over three consecutive visits, and paroxetine (38%) in a study (Hollander et al., 2003b) that allowed an arguably laxer relapse criterion of worsening by 1 point on the CGI-S scale at any one rating time point.
This was a large study by any standard, conducted in 62 centres in 14 countries. It benefited by testing escitalopram in a broad range of cultures and ethnicities. However, some centres recruited only small numbers of patients and the capacity for variability between centres was high. To minimise this problem, all centres met stringent quality criteria before recruitment was allowed, including strict tests of inter-rater reliability on rating instruments. In order to enter this study, patients were required to have been substantially and stably unwell for prolonged periods in order to minimise random fluctuations. It remains to be established whether long-term treatment with escitalopram is effective in mild or fluctuating forms of OCD. In addition, patients with relevant DSM-IV Axis I or II comorbidities that may have confounded the response to escitalopram were not allowed to participate. Specifically, significant depression was disallowed. In the clinical situation, comorbidity between OCD, anxiety disorders, and affective disorders is common and may affect relapse and response rates. In the relapse prevention study of childhood OCD (Geller et al., 2003), comorbid illness was associated with a reduced initial response to paroxetine and an increased risk of relapse following withdrawal from treatment. Further studies are needed to address long-term treatment and relapse in patients with coexisting disorders.

In summary, these results support the effectiveness and tolerability of escitalopram in daily doses of 10 mg or 20 mg in maintaining symptom-relief and preventing relapse for up to 24 weeks in patients with OCD who are not suffering from comorbidities causing substantial additional distress or impairment and who have not failed to respond to three well-conducted SRI treatment trials.

5. Conclusions

This study shows that escitalopram at a dose of 10 mg or 20 mg/day significantly reduced the risk of relapse in the patients with OCD who met the inclusion criteria. Escitalopram at a dose of 10 mg or 20 mg/day was well tolerated by patients with OCD and had an anti-OCD effect during 16 weeks of open label treatment and a significant relapse preventing effect during continued treatment up to 24 weeks.

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References


