Annals of Clinical Psychiatry, 18[2]:83–89, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230600614447

Taylor & Francis

Escitalopram in the Long-term Treatment of Major Depressive Disorder

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Background. *Escitalopram has been proven safe and efficacious in the treatment of major depressive disorder (MDD) in short-term studies. The long-term clinical tolerability and response to treatment are presented from a 12-month open-label study with a total exposure time to escitalopram of 486 patient years.*
Methods. *Patients (n = 590) with MDD entered the study after completing one of two 8-week, double-blind, placebo-controlled, lead-in studies in primary care. Escitalopram was administered at doses of 10 or 20 mg/day (dose based on physician's clinical judgement) with an average exposure to escitalopram of 315 days. The primary efficacy parameter was the Montgomery Åsberg Depression Rating Scale (MADRS) total score.*
Results. *The overall withdrawal rate was 26%; and the withdrawal rate due to adverse events was 9%. The most common adverse events were headache, back pain, upper respiratory tract infection, rhinitis and nausea, with an incidence ranging from 11% to 17%. No new types of adverse events were seen after the acute period of 8 weeks, and the incidence declined with time. At baseline (entry into the 12-month study), patients had a mean MADRS total score of 14.2, which decreased to 10.5 after 8 weeks and 7.2 after 52 weeks (LOCF). The percentage of patients in remission (MADRS total score ≤12) increased from 46% at baseline to 65% by Week 8 and 86% by Week 52.*
Conclusions. *Escitalopram (10 to 20 mg/day) demonstrated a favorable safety and tolerability profile over 12-months treatment, with further improvement in patient response.*

Keywords Escitalopram, major depression, mood disorders

INTRODUCTION

Escitalopram is the most selective serotonin reuptake inhibitor (SSRI) (1) and has been shown to be efficacious and well tolerated in the short-term treatment of major depressive disorder (MDD) (2–4) and anxiety disorders (5–7).

Patients with depression face the possibility of relapsing and experiencing another depressive episode, even after achieving initial success with antidepressant treatment (8). Long-term treatment is required to prevent the relapse of depressive episodes when used as maintenance therapy (9). Tolerability issues are a concern during long-term treatment with antidepressants and long-term adverse effects such as weight gain and sexual dysfunction distinguish different classes of antidepressants (10).

The primary objective of this 12-month open-label study was to assess the safety and tolerability of escitalopram 10–20 mg/day in the long-term treatment of patients suffering from MDD in primary care. The secondary objective was to evaluate the clinical response to escitalopram during long-term treatment.

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METHODS

Study Design

This open-label, long-term extension study was conducted in primary care centers in 10 countries (Belgium, Canada, Estonia, Finland, France, The Netherlands, Norway, Sweden,

Switzerland, and The United Kingdom). Patients entered the study after completing one of two lead-in studies (3,4) where they received escitalopram (10 mg/day) or placebo in one study and escitalopram (10 to 20 mg/day), citalopram (20 to 40 mg/day), or placebo in the other study, for 8 weeks. All patients in this study started treatment with 10 mg/day escitalopram. After two weeks of treatment, the dose was flexibly adjusted (maximum 20 mg/day), based on the investigator's clinical judgment (Figure 1).

Patients

Outpatients between 18 and 65 years of age who fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) (8), criteria for a current episode of MDD and had a baseline Montgomery Åsberg Depression Rating Scale (11) (MADRS) total score ≥22 and ≤40 were eligible for the two lead-in studies for this extension study. Patients who had completed one of the lead-in studies could continue into the extension study if, in the judgment of the investigator, 12 months continuation of treatment with the antidepressant escitalopram was indicated.

Patients were ineligible to participate in the lead-in studies if they met any of the following exclusion criteria: female of child-bearing potential who was pregnant, breast-feeding, or without adequate contraception at time of screening; met DSM-IV criteria for mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive–compulsive disorder, eating disorders, or mental retardation or any pervasive developmental or cognitive disorder; MADRS score ≥5 on item 10 (suicidal thoughts); treatment with antipsychotics, antidepressants, hypnotics, anxiolytics (except benzodiazepines for insomnia), antiepileptics, barbiturates, chloral hydrate, 5-HT receptor agonists; electroconvulsive treatment; treatment with behavior therapy or psychotherapy; treatment with any investigational drug within 30 days prior to entry; history of schizophrenia, psychotic disorder, or drug abuse (as defined by DSM-IV); history of severe drug allergy or hypersensitivity (including to citalopram); or lack of response to more than one antidepressant treatment (including citalopram) during present depressive episode.

Patients were withdrawn from this study: if the patient was at significant risk of suicide or had a score ≥5 points on item 10 of the MADRS; if the patient had a MADRS total score ≥40; if the patient became pregnant during the study; if, for safety and/or efficacy reasons, the investigator considered it to be in the best interests of the patient; or if the patient withdrew consent to participate. The patient could be withdrawn from the study; if a serious adverse event (SAE) occurred or if the patient was lost to follow-up. The study was approved by the local ethics committees and patients gave their written informed consent. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki (12).

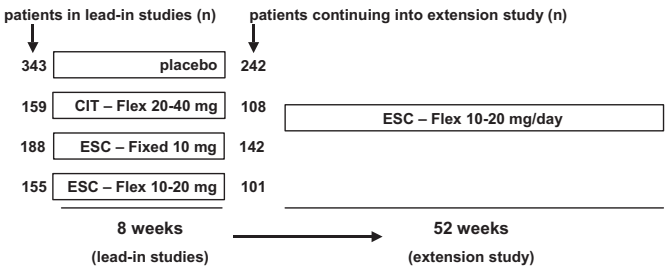

Figure 1 Schematic overview of study design. CIT: citalopram, ESC: escitalopram. Patient numbers are shown by treatment for the beginning and end of the lead-in studies.

Safety Measures

Safety and tolerability were evaluated at 4-week intervals on the basis of spontaneously reported treatment-emergent adverse events (TEAEs), SAEs (death, life-threatening conditions, hospitalization), clinical laboratory tests, and physical examination (including vital signs and weight measured at baseline and last visit).

Response to Treatment

Efficacy was assessed using the MADRS and Clinical Global Impressions – Severity (CGI-S) total scores. All measures were assessed at 4-week intervals. Additional analyses of efficacy included responders (≥50% improvement from baseline in the lead-in MADRS total score) and remitters (patients with a MADRS total score ≤12) (Montgomery, 1994).

Statistical Methodology

Safety analyses were performed on all patients treated with at least one dose of escitalopram. Point prevalence plots were made for TEAEs typical of SSRIs and bar graphs show the incidence for selected TEAEs. The incidence rate for a given time interval is the number of patients with a first reported occurrence of an AE in the time interval divided by the number of patients who entered the time interval and had not experienced the AE in any of the previous time intervals.

The response to treatment data for the intent-to-treat (ITT) population were analyzed using last observation carried forward (LOCF). Mean MADRS and CGI-S scores, and responder and remitter rates were calculated at each time point. Mean MADRS score was also calculated for patients receiving escitalopram in the lead-in studies, thereby adding 8 weeks of treatment for this subgroup.

RESULTS

Patient Disposition

A total of 590 patients were treated (Table 1), almost three-quarters of whom (437) completed the study. There was an approximately 3 to 1 ratio of women to men, and almost all the patients were Caucasian. The mean age was 42 ± 11 years (Table 2). Patients were exposed to escitalopram for a mean of 315 days, representing 486 patient years, with a mean daily dose of 13 mg at end of the study. A total of 183 patients (31%) were on 20 mg/day at their last efficacy assessment. Over 80% of the patients (480) were exposed to escitalopram for more than 6 months, and over one-third (212) of all the patients received escitalopram for more than 1 year.

Patient Withdrawals

The overall withdrawal rate was 25.9% (Table 1). Expressed as a percentage of the ITT population in the lead-in studies (n = 845), 51.7% of those patients completed this extension study, although patients were not obliged to enter the extension study upon completion of the lead-in studies, and some centers did not participate in the extension. Adverse events were the most common primary reason for withdrawal (8.8%), followed by withdrawal of consent (7.6%) (Table 1). The TEAEs most frequently leading to withdrawal were pregnancy (1.0%), weight increase (1.0%), nausea (0.8%), decreased libido (0.7%), suicide attempt (0.7%), and aggravated depression (0.5%). There were no deaths.

Table 1 Patient Disposition

	n	(%)
Patients included	593	
Patients treated	590	
Patients withdrawn	153	(25.9)
Patients completing	437	(74.1)
Primary reason for withdrawal:		
Adverse events	52	(8.8)
Withdrawal of consent	45	(7.6)
Lost to follow-up	17	(2.9)
Lack of efficacy	13	(2.2)
Administrative or other reasons(s)	16	(2.7)
Protocol violation	9	(1.5)
Non-compliance with study product	1	(0.2)

Table 2 Summary of Patient Characteristics at Baseline of Extension Study ± SD

	n = 590
Mean age, range (years)	42 (18–65)
Gender (% female)	75
Race (% Caucasian)	99
Mean weight (kg)	72 ± 16
Mean height (cm)	167 ± 8
BMI (kg/m^2)	26 ± 6
Mean baseline MADRS	14.2 ± 8.2
CGI-S	2.7 ± 1.1

Adverse Events

The most frequent treatment-emergent adverse events (TEAEs) with an incidence ≥5% in the lead-in studies and in the extension study are shown in Table 3. TEAEs that were reported by more than 10% of patients in the extension study were headache, back pain, upper respiratory tract infection, rhinitis, and nausea. Patients switched from placebo to escitalopram treatment reported transient levels of some TEAEs resulting from acute treatment, such as nausea. The majority of the TEAEs were considered by the investigator to be mild or moderate. No new types of adverse events were seen after the acute period of 8 weeks.

The incidence of selected TEAEs was plotted over time periods of 90 days, and is presented in Figure 2. Nausea, as a TEAE typically seen in patients treated for depression with SSRIs, was plotted as a point prevalence graph for those patients treated with escitalopram in the lead-in studies and starting from the first day of treatment in those studies (Figure 3). The prevalence of nausea was highest in the first weeks and subsequently decreased to <1%.

TEAEs related to sexual function included impotence (4.1%), ejaculation disorder (2.8%), and ejaculation failure (2.8%) for men, and decreased libido (3.4%), anorgasmia (1.7%), and abnormal sexual function (1.0%) for both sexes. Sexual dysfunction was the primary reason for withdrawal of 9 patients (1.5%).

Table 3 Adverse Events with an Incidence ≥5% in One Treatment Group in the Lead-in

	Weeks 1–8 (lead-in studies)			Weeks 9–60*
Preferred Term	Escitalopram	Citalopram	Placebo	Escitalopram
Patients treated	346	160	343	590
Patient years of exposure	49.7	23.9	48.8	486
Patients with TEAEs	63.6%	65.0%	57.4%	80.5%
Headache	12.1%	13.8%	12.8%	17.1%
Nausea	12.7%	14.4%	6.1%	10.5%
Diarrhoea	4.6%	7.5%	3.2%	6.4%
Influenza-like symptoms	5.2%	5.0%	4.1%	8.5%
Upper respiratory tract infection	5.5%	2.5%	5.8%	11.9%
Rhinitis	3.2%	6.9%	3.5%	11.5%
Insomnia	5.5%	4.4%	3.2%	8.3%
Increased sweating	5.5%	5.6%	0.9%	5.1%
Dry mouth	2.3%	7.5%	0.9%	2.9%

*extension study.

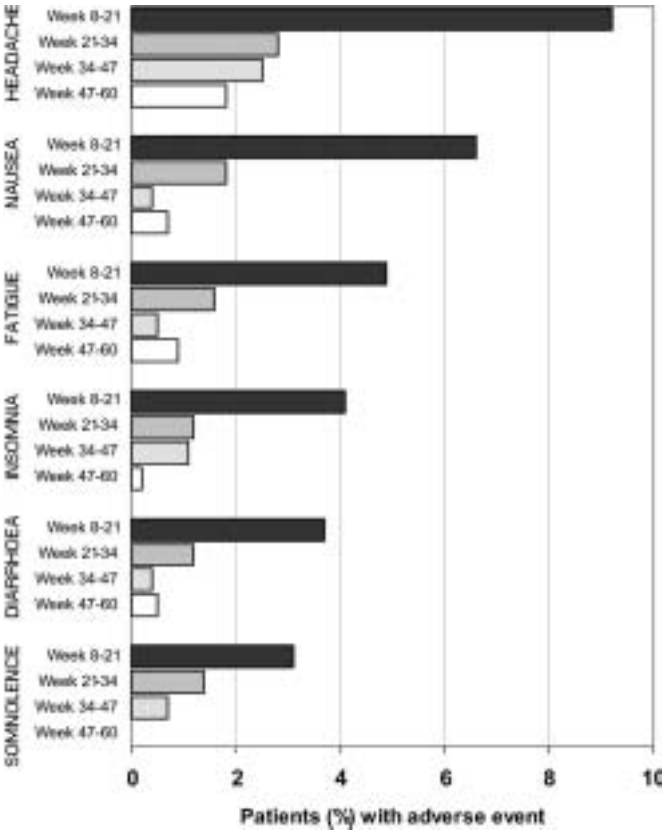

Figure 2 Bar plot showing the incidence of selected treatment-emergent adverse events over 90-day periods from entry into the extension study.

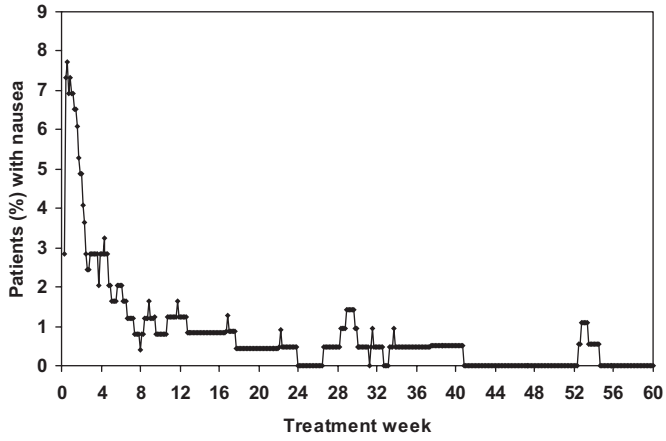

Figure 3 Point prevalence plot (%) for nausea for escitalopram-treated patients. These data start from the time of entry of these patients into the lead-in studies.

Vital Signs

There were no clinically significant safety findings with respect to changes in mean values for vital signs, weight, or clinical laboratory values. There were 105 patients who had potentially clinically significant weight increases (≥7% of body weight) and 19 with potentially clinically relevant weight decreases (≥7% of body weight). Six patients withdrew due to weight increase, and one because of weight decrease, as an AE. Mean weight increased from 71.8 kg at baseline to 74.1 kg at the last assessment, corresponding to a mean weight gain of 2.3 kg over the course of the extension study. The patients with potentially clinically significant weight increase weighed on average 4.6 kg less than the other patients at entry into this extension study (67.9 kg versus 72.5 kg), and weighed on average 1.6 kg more than them at the last assessment.

Serious Adverse Events

The number of SAEs (38) corresponded to one event per 13 patient years. One event, severe gastritis, in a 52-year-old man who had been taking ibuprofen for fibromyalgia, was considered by the investigator to be possibly related to escitalopram. The symptoms stopped 2 weeks before last dose with escitalopram. Serious adverse events reported by more than one patient included attempted suicide (n = 5), aggravated depression (n = 3), and accidental injury (n = 2), none of which were considered by the investigator to be related to escitalopram treatment. Included in the SAE reports were 3 pregnancies (out of a total of 6) that ended in induced abortion. The 5 suicide attempts, which included suicidal behavior/thoughts and no fatal outcomes, correspond to 1 attempt per 97 patient-years exposure to escitalopram. Four of the five attempts led to withdrawal from the study.

Efficacy

Patients entered this extension study after 8 weeks of treatment with placebo, citalopram, or escitalopram, with a mean MADRS baseline total score of 14.2 (Table 2). Baseline MADRS total scores were 15.2 for patients previously treated with placebo, 14.6 for patients previously treated with citalopram, and 13.2 for patients previously treated with escitalopram, i.e., after 8 weeks of treatment in the lead-in studies. Their MADRS total score continued to decrease with time during long-term treatment. The treatment in the lead-in studies did not significantly affect the mean MADRS total scores during the extension study.

The mean MADRS total scores improved throughout the study, from a baseline value of 14.2 to 7.2 by Week 52 (LOCF) (5.8; OC) (Figure 4). By Week 4 of this extension study, the mean MADRS total score was <12 and 60% of patients were in remission (MADRS total score ≤12). The decrease subsequently observed, both in the LOCF and OC analyses, suggested that the reduction in depressive symptoms was not due to the withdrawal of patients with higher than average MADRS total scores, but instead to a continued improvement in the severity of depressive symptoms.

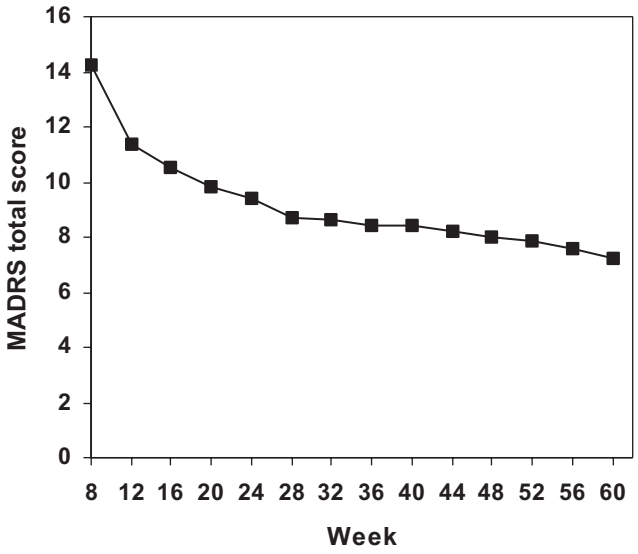

Figure 4 Mean Montgomery Åsberg Depression Rating Scale (MADRS) total scores over time for all patients (ITT) from entry into this extension study (LOCF).

Table 4 Patients in Remission (Defined as MADRS Total Score ≤12) during the 12-Month Extension Study (OC)

Visit week	Total number of patients	Number of patients withdrawn	Number of patients in remission	Patients in remission (%)
0	588	0	269	45.7
2	582	6	304	52.2
4	579	3	345	59.6
8	564	15	365	64.7
12	538	26	376	69.9
16	523	15	378	72.3
20	513	10	401	78.2
24	498	15	383	76.9
28	489	9	372	76.1
32	486	3	373	76.7
36	471	15	378	80.3
40	463	8	374	80.8
44	454	9	380	83.7
48	439	15	373	85.0
52	438	1	377	86.1

Of the patients continuing from the lead-in studies to the extension study, 53.6% had responded (≥50% improvement in baseline MADRS total score) at the end of the lead-in studies, and 4.2% (25/590 patients) were still severely depressed (MADRS≥30). By the end of the study, the proportion of responders had markedly increased (99.5% OC; 98.1% LOCF). Consistent with the continued improvement during long-term treatment with escitalopram was an increase in the percentage of patients in remission, which increased from 46% at baseline to 86% (OC) at Week 52 (Table 4). The MADRS total score was transiently >12 for 102 of the original 270 (37.8%) patients in remission at the beginning of this extension study, and persistently >12 for 18 patients (6.7%). Expressed as a percentage of the ITT population (588), 79.4% of patients had achieved remission at Week 52. This included 91 patients in remission who had withdrawn from the study. These patients had been in remission for an average of 129 days before withdrawal.

An analysis of the effect on patient outcome (remission) based on response at the end of the lead-in studies (Week 8) and completion of maintenance treatment with escitalopram is shown in Figure 5. Of the 437 patients who completed the extension study, 212 (48.5%) had responded by 8 weeks and achieved remission after 12 months, with an average MADRS total score of 2.9, and 164 had not responded by 8 weeks but achieved remission, with an average MADRS total score of 5.3. Of the 151 patients who did not complete the extension study, 63 had responded by 8 weeks and achieved remission, with an average MADRS total score of 4.7, and 28 had not responded by 8 weeks but achieved remission, with an average MADRS total score of 6.9.

The clinical relevance of these long-term efficacy results was confirmed by the results from analysis of the CGI-S scores. CGI-S scores decreased throughout the study from 2.7 at baseline to 1.6 at last assessment (OC). At baseline, 55% of patients had a CGI-S score of 3 or more (mildly ill, or worse), decreasing to 37% by Week 8, and 14% by Week 52. The percentage of patients with a total MADRS ≥22 also decreased with time, from 20.2% to 2.1% (9 patients; OC) after 12 months.

DISCUSSION

Depression is a common chronic illness, which is generally treated by primary care physicians using antidepressant drugs. Many patients have a poor treatment outcome often due to the short duration of treatment that most receive. One of the factors contributing to poor long-term compliance is the tolerability profile of many antidepressants. The current study was primarily designed to document the tolerability of escitalopram used in a primary care environment but, nevertheless, allows us to draw some conclusions about its potential efficacy in long-term use in general practice.

Over 80% of all patients entering this long-term study completed at least six months of treatment and would have more than adequately complied with World Health Organization treatment guidelines for depression. The withdrawal rate from the study (26% over 12 months) was lower than that seen with other modern antidepressants in medium to long-term use (13). This presumably reflects good tolerability and patient acceptability, as indicated by the decrease with time of the incidence of the most common TEAEs reported during acute treatment.

Of those patients withdrawing from the study, 34% (52/153) cited TEAEs as the primary reason although, as can be seen from Figure 2, the incidence of reported TEAEs fell after the first three months. This reduction in TEAE incidence was not due to withdrawals from the study, which continued at a low constant level throughout the 12 months (Table 4).

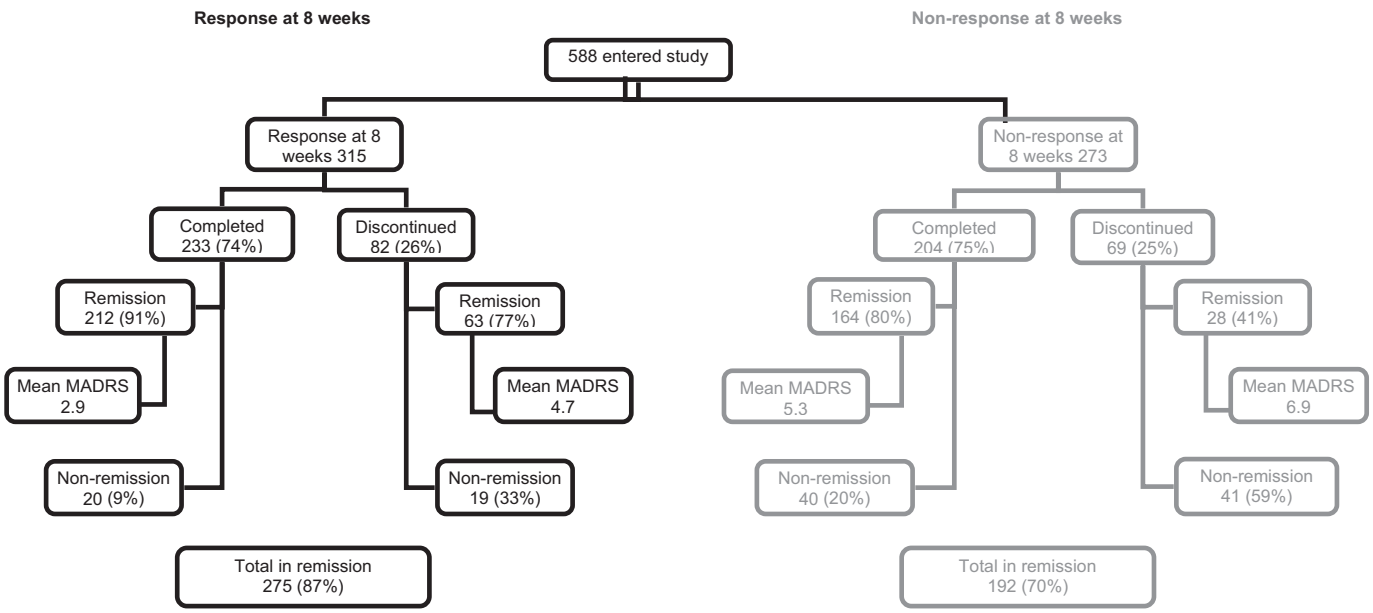

Figure 5 Analysis of patients in remission (MADRS total score ≤12) based on response at week 8 of the lead-in studies and completion of the extension period.

No specific measure of sexual function was incorporated in this study, the incidence quoted being in response to an open question from the investigator. Inevitably this leads to an underreporting of sexual side effects. Nevertheless both the low withdrawal rate from the study and the low reported incidence of sexual problems indicate that in the primary care environment sexual dysfunction may be less of a problem with escitalopram than has been reported with other SSRIs (14).

SSRIs have been associated with weight increase in long-term use, although this has not been a consistent finding in all studies. The mechanism for this weight gain is not clear and has been observed during a background of generally increasing weight, possibly reduced initial weight due to depression and stable or reduced weight during short-term studies (15). In this study, the mean weight gain was 2.3 kg over the course of the extension period. In the absence of a placebo control group, it is unclear if this weight gain is due to escitalopram, or to weight recovery following successful treatment of depression (16). It is notable however, that the initial mean weight of patients with ≥7% weight increase (67.9 kg) was significantly lower than that of patients without a potentially clinically significant weight gain (72.5 kg). Only six patients cited weight increase as the principal reason for withdrawal from the study.

The aim of depression treatment should be to achieve stable remission and to then maintain the patient well for a reasonable length of time. Residual symptoms result in both reduced quality of life and the potential for relapse (17,18). It is thought that short-term response to antidepressant treatment is a predictor of outcome in the long term. As there were no specific criteria for progression from the short-term study to this long-term extension study, it was possible to examine the influence of response (defined as a ≥50% reduction in MADRS) at eight weeks on both adherence and outcome.

Approximately 74% (233/315) of patients who responded during the short-term study completed the long-term extension study, compared to 75% (204/273) who had not responded. Response at eight weeks was thus not a predictor of adherence.

Almost 91% (212/233) of patients who were in response at eight weeks and also completed 12 months within the study achieved remission (MADRS ≤12), compared to 80% (164/204) of patients with had not responded by eight weeks. Adherence to medication for 12 months combined with response at 8 weeks, predict improved patient outcome. In addition, the mean MADRS total score of patients in remission after 12 months from the 8-week responder group was lower than that of the non-responders (2.9 vs. 5.3) suggesting a more stable remission, with fewer residual symptoms.

While early response to treatment appears to be an indicator of both good and stable outcome, it is notable that even in this group, 102 of the original 270 patients (37.8%) in remission at the beginning of this study had an MADRS score >12 at some time during the 12 months.

Of patients discontinuing study before 12 months, 77% of the 8-week responder group were in remission when last seen, compared to 41% of the nonresponders. The outcome for 8-week nonresponders discontinuing before 12 months and the early discontinuers was poor.

These outcomes support the conclusions that patients benefit from up to 12 months continued treatment with escitalopram, even when initial response is slow. The long-term adverse event profile of escitalopram was similar to that observed during acute treatment and no new safety findings were noted in long-term use. Escitalopram is a safe, well-tolerated, and efficacious long-term treatment for patients with depression.

ACKNOWLEDGMENTS

AGW has received research grants, consultancy fees and lecture fees from most pharmaceutical companies in the area of CNS development. This includes H. Lundbeck A/S, the manufacturers of escitalopram. ND and HER are full time employees of Lundbeck A/S. This study was sponsored by H. Lundbeck A/S.

We gratefully acknowledge the investigators in each of the 97 primary care centers in the study: Belgium: Francis Vandebuerie, Peter Van Langenhove, Guido Mehuys. Canada: Stephen John Coyle, Donald K. Taylor/Douglas Tweel, Daniel A. Landry, A.V. Ravindran, Robin T. Reesal, Paul Latimer. Estonia: Siiri Vään, Andres Sild, Ants Puusild, Kadri Jaanson. Finland: Ulla Lepola, Pekka Tamminen, Jukka Penttinen, Pekka Rundelin, Raija Kerätär, Kirsti Pakkala, Ritva Tanskanen, Mauno Vanhala, Juha Teirilä, Hannu Koponen. France: Alain Chaleon, Didier Sacareau, Francois Grivet, Philippe Marmor, Charles Lousqui, Jean-Rene Auriault, Jean-Luc Gabrielli, Philippe Dumond, Michel Bismuth, Marc Bouet, Christian Fabié, Pierre Fuchs, Bruno Gay, Gérard Rouviere, Olivier Decloux, Laurent Goepfert, Jean-Louis Huberschwiller, Jean-Claude Haus, Francois Lacoin, Michèle Pithon, Georges Binet, Hervé Vilarem, Jean-Michel Lerouge, Jean Yves Vogel, Christian Aliotti, Gilles Cebe, Pierre Darmé, Francois Dejean, André Delachienne, Bernard Ducournau, Gérard Duroux, Gérard Forcada, Christian Francois, Louis Herlet, Didier Herman, Patrick Jehl, Jean-Michel Larrode, Maxime Maurel, Gérald Mongin, Jean-Louis Navarre, Daniel Parent, Jean-Pierre Peynaud, Victor Ratsianoharana, Patrice Sauveur, Michel Vigens. Netherlands: Norbert Vogel, Pauline de Graaf-Pernot, Thomas Ehling, Lena de Schipper. Norway: Ragnar Rabe, Morten Bastøe, Mikkel Mundal, Trond Hatlebrekke, Helge Johan Helgesen, Tore Eikeland, Britta Spies. Sweden: Rolf Adolfsson. Switzerland: Blajo Blajev, Roman Vogt. United Kingdom: Alan Wade, Andrew J. Smithers, Peter R. Harvey, Richard Pool, Alun H. Jones, Andrew Cowie, Peter James Davies, Martin Adler, Jeremy Simmons, Trevor Gooding, Robin Lal-Sarin, Sohail Butt, Dayantha S. Fernando, Bhavest Bodalia, Roger Cranfield.

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