Research Article

ESCITALOPRAM IN THE TREATMENT OF ANXIETY SYMPTOMS ASSOCIATED WITH DEPRESSION

Borwin Bandelow, M.D., Ph.D.,[1]* Henning F. Andersen, MSc.,[2] and Ornah T. Dolberg, M.D.[2]

Most patients with depression have symptoms of anxiety associated with their illness. Our aim in this study was to investigate the efficacy of escitalopram, a proven antidepressant, on symptoms of anxiety in patients with major depressive disorder (MDD). Data from five placebo-controlled escitalopram studies in MDD were analyzed. Three of the studies also included a comparison with citalopram. In all studies, anxiety was assessed using the Inner Tension item (item 3) of the Montgomery–Åsberg Depression Rating Scale (MADRS). In three studies, anxiety symptoms were also specifically assessed, either continuously over time or at baseline and end point, by using the Hamilton Rating Scale for Anxiety (HAM-A), the Anxious Mood item of the HAM-A (item 1), the Psychic Anxiety subscale of the HAM-A (items 1-6 and 14), the Anxiety Psychic item (item 10) of the Hamilton Rating Scale for Depression (HAM-D-24), and the Anxiety/Somatization subfactor (items 10–13, 15, and 17) of the HAM-D-24. Escitalopram was significantly superior to placebo in all comparisons. Citalopram was also consistently better than placebo in all comparisons, except in the HAM-D-24 Anxiety/Somatization subfactor. In some comparisons with placebo, escitalopram showed a significantly earlier onset of action or an earlier separation. Escitalopram was significantly more effective compared to placebo in treating both anxiety symptoms and the entire depression in the total depressive population, as well as in depressive patients with a high degree of anxiety. Depression and Anxiety 24:53–61, 2007. © 2006 Wiley-Liss, Inc.

Key words: *escitalopram; anxiety; major depressive disorder; Montgomery–Åsberg Depression Rating Scale; Hamilton Depression Rating Scale; Hamilton Anxiety Rating Scale for Anxiety*

INTRODUCTION

Although major depressive disorder (MDD) and anxiety are two well-characterized diagnostic entities according to current diagnostic classifications, overlap between symptoms of depression and anxiety can be observed at both syndrome and symptomatology levels. Whereas anxiety is present in the majority of patients with major depression [Bandelow, 2003; Bolton et al., 1995; Fawcett and Kravitz, 1983; Kessler et al., 1996], patients with anxiety disorders often suffer from depression [Murphy et al., 2004; Wittchen et al., 1994]. Compared with noncomorbid cases, depressed patients with comorbid anxiety have a less favorable prognosis; increased incidences of alcohol and drug abuse, as well as suicide rates; higher health care utilization; and more social distress [Brown et al., 1996;

[1]Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany
[2]H. Lundbeck A/S, Copenhagen, Denmark

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*Correspondence to: B. Bandelow, Department of Psychiatry and Psychotherapy, University of Göttingen, von-Siebold-Str. 5, D-37085 Göttingen, Germany.
E-mail: sekretariat-bandelow@medizin-uni-goettingen.de

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Fawcett, 1992; Grunhaus et al., 1988; Kessler et al., 1996; Roy-Byrne et al., 2000; van Valkenburg et al., 1984; Vollrath and Angst, 1989].

Treatment with antidepressant drugs can improve both anxiety and mood symptoms. In the recent years, selective serotonin reuptake inhibitors (SSRIs) have been the first-line treatment of these conditions. The SSRI escitalopram has shown consistent efficacy and fast symptom relief in clinical trials in the treatment of MDD in four short-term studies [Burke et al., 2002; Lepola et al., 2003b; Ninan et al., 2003; Wade et al., 2002] and the short-term lead-in study to a relapse prevention trial [Rapaport et al., 2004].

Escitalopram has also shown efficacy in treatment of anxiety disorders and has been approved for the treatment of panic disorder (PD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD) in a number of countries. In a study with patients with PD, escitalopram-treated patients showed earlier separation from placebo in the Panic and Agoraphobia Scale total score than did citalopram-treated patients [Stahl et al., 2003]. Furthermore, in three double-blind, placebo-controlled studies in patients with GAD, escitalopram was also shown to be effective in reducing anxiety symptoms measured with the Hamilton Rating Scale for Anxiety [HAM-A; Goodman et al., 2004]. For patients suffering from SAD, escitalopram demonstrated its superiority to placebo in two acute studies [Kasper et al., 2005] and a relapse prevention study [Montgomery et al., 2005]. In a 24-week comparison with paroxetine, which has been used a reference drug for SAD in recent years, both drugs were superior to placebo, and at the end of the study, 20 mg/day escitalopram was superior to 20 mg/day paroxetine [Lader et al., 2004].

Based on the known and recognized frequent comorbid presence of both anxiety and depression, and because escitalopram has established efficacy within both major depression and anxiety indications, our aim was to investigate the effect of escitalopram in treating the symptoms of anxiety in patients suffering from major depression.

MATERIALS AND METHODS

PATIENTS

A post hoc analysis of rating scales measuring anxiety was performed on the five placebo-controlled studies of depressed outpatients [Burke et al., 2002; Lepola et al., 2003b; Ninan et al., 2003; Rapaport et al., 2004; Wade et al., 2002]. Table 1 summarizes the studies used in this analysis. Eligible participants were male or female outpatients, between 18 and 65 years of age. All studies included patients with MDD, as defined by DSM-IV. In Study 1, only patients with a score ≥ 25 on the 24-item Hamilton Rating Scale for Depression [HAM-D-24; Hamilton, 1960] were included. In Studies 2 and 4, patients were required to have a score between 22 and 40 on the Montgomery–Åsberg Depression Rating Scale [MADRS; Montgomery and Åsberg, 1979]. In Studies 3 and 5, patients were included if they had a minimum score of 22 on the MADRS and a minimum score of 2 on item 1 (Depressed Mood) of the HAM-D-24. In these studies, the depressive episode was required to be of at least 4 weeks' duration. Patients were excluded if there was evidence of active suicidal ideation or a recent suicide attempt, or if patients had any DSM-IV Axis I disorder other than MDD, any personality disorder, a history of substance abuse, a positive urine drug screen, or were being treated with psychopharmacologically active agents [except hypnotics for insomnia: zolpidem and zaleplon (Study 1); zolpidem (Studies 3 and 5) for insomnia at a maximum of 10 mg/day, no more than three times per week; and benzodiazepines used for insomnia in a stabilized dose within the last 6 months or used episodically in the lower part of the recommended dose range (Studies 2 and 4)]. Women who were not pregnant or breast-feeding and utilizing adequate contraception were eligible to participate. The institutional ethics committees for all participating study centers approved the study protocols, and all subjects provided written informed consent.

STUDY DESIGN

All studies used a multicenter, randomized, 8-week, double-blind, placebo-controlled design and began with 1 week of single-blind placebo treatment that followed an initial screening visit. At the end of the single-blind lead-in period, patients who remained eligible were randomized to receive 8 weeks of double-blind treatment with the active drug (escitalopram or citalopram) or placebo. All studies compared escitalopram with placebo, and in Studies 3–5, citalopram was included as active reference. Three studies used a fixed-dose design, whereas in the other two studies, dosing was flexible and could be increased based on clinical response. In the latter trials, dose could subsequently be decreased to the initial dose (i.e., the minimum recommended dose) when adverse events emerged. Studies 1, 3, and 5 were conducted in specialist settings, whereas the other two studies were conducted in primary care settings.

ASSESSMENT

All evaluations were conducted after 1, 2, 4, 6, and 8 weeks of double-blind treatment. In all five studies, we evaluated depressive symptoms using the MADRS. Anxiety symptoms were evaluated with the Inner Tension item of the MADRS (item 3). In Studies 1, 3, and 5, anxiety symptoms were also assessed continuously at all visits (Study 1) or only at baseline and end point (Study 3 and 5) with the HAM-A [Hamilton, 1959], the Anxious Mood item of the HAM-A (item 1), the Psychic Anxiety subscale of the HAM-A (items 1–6 and 14), the Anxiety Psychic item

TABLE 1. Summary of studies

Study	Reference	Comparison, dosage range	Dose	Setting
1	Ninan et al., 2003	Escitalopram 20 mg/day versus placebo	Fixed	Specialist
2	Wade et al., 2002	Escitalopram 10 mg/day versus placebo	Fixed	Primary care
3	Burke et al., 2002	Escitalopram 10 or 20 mg/day versus citalopram 40 mg/day and placebo	Fixed	Specialist
4	Lepola et al., 2003b	Escitalopram 10–20 mg/day versus citalopram 20–40 mg/day and placebo	Flexible	Primary care
5	Rapaport et al., 2004, Forest Labs (unpublished data)	Escitalopram 10–20 mg/day versus citalopram 20–40 mg/day and placebo	Flexible	Specialist

(item 10) of the HAM-D-24, and the Anxiety/Somatization subfactor (items 10–13, 15, and 17) of the HAM-D-24.

STATISTICAL METHODS

Efficacy analyses were conducted for a modified intent-to-treat population (ITT), which included all randomized patients who took at least one dose of double-blind study medication and had at least one postbaseline efficacy assessment. For all comparisons, we used analysis of covariance (ANCOVA), adjusting for baseline values and center. For all variables analyses, we used both last-observation-carried-forward (LOCF) and observed cases (OC) data.

RESULTS

DEMOGRAPHICS

Table 2 shows the demographic characteristics of the patients at baseline. Patients in the different treatment groups did not differ significantly with regard to demographic variables or illness severity.

Main efficacy and safety analyses of these studies have been published previously [Burke et al., 2002; Lepola et al., 2003b; Ninan et al., 2003; Rapaport et al., 2004; Wade et al., 2002]. The results of primary efficacy end points of the different studies are shown in Table 2.

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MADRS total score in anxious patients. In the three citalopram-controlled trials (Studies 3–5), the MADRS total score in the subgroup of patients with high initial anxiety (baseline MADRS item 3 score ≥ 4) was examined. In order to have comparable doses from the studies, the data from the escitalopram 10 mg/day group of Study 3 were excluded from this analysis. Our main finding was that in the escitalopram group there was a significantly ($P<.01$ to $P<.001$) superior effect compared to placebo as of week 1 (Fig. 1). In addition, at weeks 1, 6, and 8, there was also a statistically significant difference between the escitalopram and the citalopram groups ($P<.05$), indicating an earlier onset of action and a more evident effect for escitalopram on anxiety symptoms in these patients.

MADRS item 3 (Inner Tension). When the MADRS item 3 data from all five studies were pooled, the escitalopram group demonstrated a highly significant ($P<.01$ to $P<.001$) and early separation from placebo that was evident from week 1 onward (Fig. 2). In addition, it was interesting to note that in all five studies individually, escitalopram was significantly superior to placebo, starting from week 1 (Study 3) to week 4 (Study 1), and throughout the study period (Table 3).

At end point, after 8 weeks of treatment, the differences in MADRS item 3 between escitalopram and placebo were significant in all studies ($P<.01$ to $P<.001$), indicating an effect on symptoms of anxiety in these various study populations (Table 4).

In Study 3, there was a statistical significance between the escitalopram 20 mg/day and citalopram 40 mg/day groups at week 1 ($P<.01$; Table 4). Also in Study 5, there was a statistical significance between the escitalopram and citalopram groups at week 1 ($P<.05$; Table 4).

HAM-D-24 Anxiety/Somatization factor (items 10–13, 15, and 17). In Study 1, escitalopram demonstrated superior efficacy based on the HAM-D-24 Anxiety/Somatization subscale compared with placebo, a difference that was significant at 2 weeks and onward ($P<.05$ to $P<.001$; Table 4). In Study 3, both doses of escitalopram showed a statistically significant difference versus placebo for this subscale from week 4 onward (Table 4). Treatment with citalopram was also superior to treatment with placebo; this difference was noticeably significant at 2 ($P<.01$), 4, and 8 weeks ($P<.05$; Table 4). In Study 5, there were no significant differences between the active treatment groups and placebo, except for the citalopram group at week 8 (Table 4).

HAM-D-24 Anxiety Psychic (item 10). In Study 1, escitalopram demonstrated superior efficacy based on the HAM-D-24 Anxiety Psychic (item 10) versus placebo, a difference that was significant at 2 weeks and onward ($P<.01$ to $P<.001$; Table 4). In Study 3, both doses of escitalopram were more efficacious than placebo; it was noted that the escitalopram 10 mg/day

TABLE 2. Sample characteristics, baseline scores of rating scales, and results of primary efficacy end points

	1[a]		2[b]		3[c]			
Study	Placebo	ESC 20 mg	Placebo	ESC 10 mg	Placebo	CIT 40 mg	ESC 10 mg	ESC 20 mg
N	153	147	189	191	122	125	119	125
Female (%)	65	57	78	74	59	62	71	67
Age (mean)	39.0±11.5	37.8±11.6	40±12	41±11	40.3±10.6	40.0±11.5	40.6±12.3	39.6±12.1
MADRS (mean)	30.5±4.1	30.4±4.0	28.7±3.7	29.2±4.2	29.5±5.0	29.2±4.5	28.0±4.9	28.9±4.6
HAM-D-24 (mean)	29.7±3.6	30.4±4.1	—	—	25.8±5.9	25.9±5.9	24.3±6.2	25.8±5.7
HAM-A (mean)	17.7±5.0	17.0±4.8	—	—	16.9±6.1	16.9±5.3	15.4±5.4	17.2±5.4
Primary efficacy end point (LOCF)[§]	−10.0	−13.3**	−13.6	−16.3**	−9.4	−12.0*	−12.8**	−13.9**
Primary efficacy end point (OC)	−10.7	−14.8**	−14.7	−17.4**	−10.0	−13.5*	−14.0**	−16.1**

	4[d]			5[e]		
Study	Placebo	CIT 20–40 mg	ESC 10–20 mg	Placebo	CIT 20–40 mg	ESC 10–20 mg
N	154	160	155	127	123	125
Female (%)	72	69	75	58	49	52
Age (mean)	43±12	44±11	43±11	42.2±12.5	42.1±12.7	41.4±11.9
MADRS (mean)	28.7±4.0	29.2±4.2	29.0±4.3	28.8±5.0	28.3±5.0	28.7±4.3
HAM-D-24 (mean)	—	—	—	25.0±5.3	25.0±5.5	24.8±5.4
HAM-A (mean)	—	—	—	15.6±4.7	16.1±4.8	15.1±4.9
Primary efficacy end point (LOCF)[§]	−12.1	−13.6	−15.0**	−11.2	−13.0	−12.9
Primary efficacy end point (OC)	−13.5	−14.6	−15.9**	−11.8	−14.1*	−15.1*

[§]Adjusted mean difference from baseline in MADRS total score.
*$P<.05$ versus placebo; **$P<.01$ versus placebo.
[a]Ninan et al., 2003.
[b]Wade et al., 2002.
[c]Burke et al., 2002.
[d]Lepola et al., 2003b.
[e]Rapaport et al., 2004.
CIT, citalopram; ESC, escitalopram.

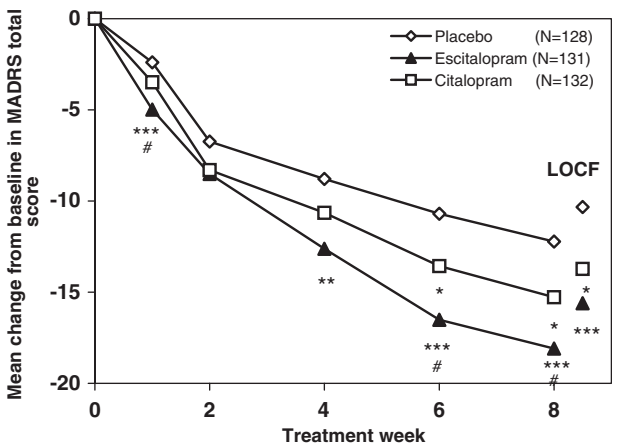

Figure 1. Change from baseline in mean MADRS total score in the subgroup of patients with high initial anxiety (baseline MADRS item 3 score ≥4) from three citalopram-controlled studies (Studies 3–5) (baseline value 31.43) by visit (ITT, OC) and week 8 (LOCF). *$P<.05$, **$P<.01$ versus placebo, ***$P<.001$ versus placebo, #$P<.05$ versus citalopram.

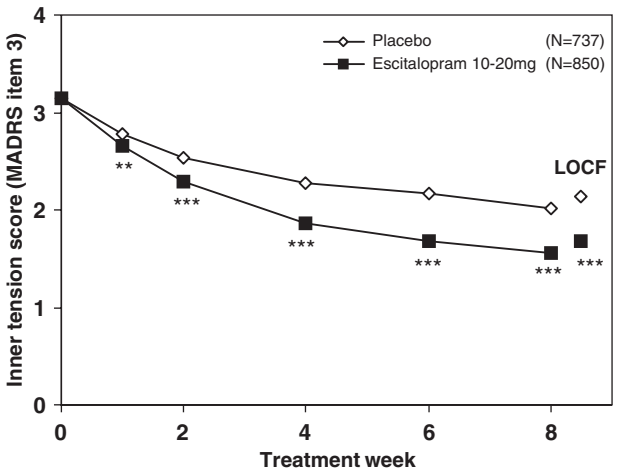

Figure 2. Change from baseline in mean MADRS Item 3 (Inner Tension) score by visit (ITT, OC) and week 8 (LOCF) for the five studies pooled (baseline value 3.14).

TABLE 3. Mean scores and statistical analyses of clinical results with escitalopram

Scale	Study	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Last assessment
MADRS total	1–5 (PBO)	29.0	25.2	22.7	19.7	18.5	17.5	—
MADRS total	1–5 (ESC)	29.0	24.6*	21.4***	17.6***	15.6***	14.5***	—
MADRS item 3≥4	3–5 (PBO)	31.43	29.04	24.69	22.64	20.73	19.21	21.10
MADRS item 3≥4	3–5 (CIT)	31.43	27.94	23.13	20.79	17.86*	16.16*	17.71*
MADRS item 3≥4	3–5 (ESC)	31.43	26.44***‡	22.92	18.81**	14.92***‡	13.34***‡	15.82***
MADRS item 3	3–5 (PBO)	3.14	2.78	2.53	2.27	2.17	2.01	2.14
MADRS item 3	3–5 (ESC)	3.14	2.65**	2.29***	1.87***	1.68***	1.55***	1.68***
MADRS item 3	1 (PBO)	3.20	2.78	2.63	2.46	2.41	2.16	2.27
MADRS item 3	1 (ESC)	3.20	2.77	2.40	2.00***	1.81***	1.68**	1.84**
MADRS item 3	2 (PBO)	3.29	2.89	2.60	2.16	2.15	1.90	2.06
MADRS item 3	2 (ESC)	3.29	2.74	2.35**	1.76***	1.72***	1.56**	1.67***
MADRS item 3	3 (PBO)	3.02	2.72	2.55	2.34	2.24	2.29	2.38
MADRS item 3	3 (CIT 40)	3.02	2.73	2.25*	1.85**	1.68**	1.71***	1.89**
MADRS item 3	3 (ESC 10)	3.02	2.50	2.18*	1.82**	1.67**	1.66***	1.81***
MADRS item 3	3 (ESC 20)	3.02	2.39*‡	2.07**	1.84**	1.65***	1.61***	1.78***
MADRS item 3	4 (PBO)	3.26	2.92	2.53	2.34	2.13	1.99	2.14
MADRS item 3	4 (CIT)	3.26	2.81	2.51	2.13	1.92	1.80	1.88*
MADRS item 3	4 (ESC)	3.26	2.82	2.38	2.03*	1.78**	1.62**	1.70***
MADRS item 3	5 (PBO)	2.86	2.42	2.34	2.03	2.04	1.96	2.07
MADRS item 3	5 (CIT)	2.86	2.62	2.17	1.68*	1.51**	1.46**	1.65*
MADRS item 3	5 (ESC)	2.86	2.30‡	2.19	1.73	1.47***	1.42**	1.60**
HAM-D-24 items 10–13, 15, 17	1, 3, 5 (PBO)	6.47	5.64	5.29	4.73	4.40	4.23	4.45
HAM-D-24 items 10–13, 15, 17	1, 3, 5 (ESC)	6.47	5.55	4.92**	4.10***	3.64***	3.54***	3.93***
HAM-D-24 items 10–13, 15, 17	1 (PBO)	7.83	6.60	6.32	5.77	5.23	4.82	5.04
HAM-D-24 items 10–13, 15, 17	1 (ESC)	7.83	6.55	5.78*	4.82***	4.26**	4.05*	4.44
HAM-D-24 items 10–13, 15, 17	3 (PBO)	5.97	5.21	5.03	4.52	4.14	4.14	4.36
HAM-D-24 items 10–13, 15, 17	3 (CIT 40)	5.97	5.31	4.26**	3.78**	3.68	3.51*	3.92
HAM-D-24 items 10–13, 15, 17	3 (ESC 10)	5.97	5.11	4.60	3.81*	3.48*	3.62*	3.78*
HAM-D-24 items 10–13, 15, 17	3 (ESC 20)	5.97	5.17	4.56	3.80*	3.20**	3.12***	3.53**
HAM-D-24 items 10–13, 15, 17	5 (PBO)	6.05	5.37	4.70	4.01	3.90	3.79	4.11
HAM-D-24 items 10–13, 15, 17	5 (CIT)	6.05	5.24	4.39	3.98	3.47	3.15*	3.76
HAM-D-24 items 10–13, 15, 17	5 (ESC)	6.05	5.28	4.69	3.77	3.54	3.32	3.80
HAM-D-24 item 10	1, 3, 5 (PBO)	2.03	1.78	1.70	1.54	1.41	1.39	1.45
HAM-D-24 item 10	1, 3, 5 (ESC)	2.03	1.62**	1.43***	1.15***	1.04***	1.09***	1.19***
HAM-D-24 item 10	1 (PBO)	2.21	1.88	1.82	1.67	1.51	1.44	1.49
HAM-D-24 item 10	1 (ESC)	2.21	1.76	1.51***	1.20***	1.12***	1.13**	1.20**
HAM-D-24 item 10	3 (PBO)	2.02	1.73	1.73	1.66	1.40	1.40	1.44
HAM-D-24 item 10	3 (CIT 40)	2.02	1.69	1.47*	1.11***	1.12**	1.09**	1.25
HAM-D-24 item 10	3 (ESC 10)	2.02	1.58	1.54	1.17***	1.06**	1.25**	1.24
HAM-D-24 item 10	3 (ESC 20)	2.02	1.58	1.41**	1.21***	1.01**	1.08**	1.19**
HAM-D-24 item 10	5 (PBO)	1.89	1.76	1.63	1.38	1.39	1.36	1.38
HAM-D-24 item 10	5 (CIT)	1.89	1.60	1.55	1.27	1.06**	1.00**	1.09*
HAM-D-24 item 10	5 (ESC)	1.89	1.60	1.41*	1.17	1.08**	1.01**	1.10*
HAM-A total	1 (PBO)	17.33	15.02	14.29	12.8	11.84	11.38	11.9
HAM-A total	1 (ESC 20)	17.33	14.78	13.37	11.12**	9.94**	9.42**	10.39*
HAM-A item 1	1 (PBO)	2.00	1.84	1.72	1.65	1.54	1.44	1.48
HAM-A item 1	1 (ESC 20)	2.00	1.65*	1.50*	1.23***	1.16**	1.10**	1.14***
HAM-A items 1–6, 14	1 (PBO)	11.52	10.11	9.73	8.73	8.10	7.60	7.95
HAM-A items 1–6, 14	1 (ESC 20)	11.52	9.61	8.84*	7.12***	6.52**	6.16**	6.71**

*$P<.05$ versus placebo; **$P<.01$ versus placebo; ***$P<.001$ versus placebo;
‡$P<.05$ versus citalopram; ‡‡$P<.05$ versus citalopram.
PBO, placebo; ESC, escitalopram; CIT, citalopram.
Scores from pooled studies in bold—used only to indicate results from all patients from more than one trial.

TABLE 4. Studies 3 and 5: adjusted mean anxiety ratings at baseline and end point (OC)

		End point (Study 3)				End point (Study 5)			
Group	Baseline[a]	Placebo	CIT 40 mg	ESC 10 mg	ESC 20 mg	Baseline[b]	Placebo	CIT 20–40 mg	ESC 10–20 mg
HAM-A total score	16.63	11.62	10.13	10.06	8.94**	15.62	10.54	8.58**	8.82*
HAM-A anxious mood (item 1)	1.90	1.40	1.13*	1.13*	1.03**	1.79	1.25	0.96*	0.89**
HAM-A psychic anxiety	11.55	7.94	6.95	6.55*	5.81***	10.76	7.07	5.49**	5.76*

*$P<.05$ versus placebo, **$P<.01$ versus placebo, ***$P<.001$ versus placebo.
[a]Burke et al., 2002.
[b]Rapaport et al., 2004.
CIT, citalopram; ESC, escitalopram.

group showed a significant ($P<.01$ to $P<.001$) difference versus placebo after 4 and 6 weeks of treatment (Table 4). Furthermore, the group treated with escitalopram 20 mg/day demonstrated a significant ($P<.05$ to $P<.001$) difference versus placebo from week 2 onward (Table 4). The citalopram group also demonstrated superior efficacy compared with placebo, a difference that was significant ($P<.05$ to $P<.001$) at weeks 2, 4, and 6, but not at week 8 (Table 4). In Study 5, the escitalopram group demonstrated a significant ($P<.05$ to $P<.001$) difference versus placebo in this HAM-D-24 item from weeks 2, 6, and 8 (Table 4). The citalopram group also demonstrated superior efficacy compared with placebo, a difference that was significant ($P<.05$ to $P<.01$) at weeks 6 and 8 (Table 4).

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HAM-A total score. Anxiety ratings were performed continuously at all visits (Study 1) or only at baseline and end point (Studies 3 and 5). In Study 1, escitalopram 20 mg/day demonstrated superior efficacy in the total HAMA score compared with placebo, a difference that was significant after 4 weeks and onward ($P<.05$ to $P<.01$; Table 4). In Study 3, at end point, only those patients treated with escitalopram 20 mg/day ($P<.01$) showed a significantly better effect compared to those on placebo (Table 4). In Study 5, both the escitalopram ($P<.05$) and citalopram ($P<.01$) groups were superior to the placebo group in HAM-A total score (Table 4).

HAM-A Anxious Mood (item 1). In Study 1, escitalopram 20 mg/day demonstrated a superior efficacy in the HAM-A Anxious Mood item compared with placebo, a difference that was significant from 1 week onward ($P<.05$ to $P<.001$; Table 4). In Studies 3 and 5, at end point, all active treatments were significantly superior to placebo (Table 4).

HAM-A Psychic Anxiety (items 1–6 and 14). In Study 1, escitalopram demonstrated superior efficacy in the HAM-A Psychic Anxiety item compared with placebo, a difference that was significant from 2 weeks onward ($P<.05$ to $P<.001$; Fig. 7). In Studies 3 and 5, at end point, all treatment groups except citalopram 40 mg/day in Study 3 showed a statistically significant difference versus placebo (Table 4).

ADVERSE EVENTS

Both escitalopram and citalopram were generally well tolerated at all dosages. The most common adverse events included nausea, diarrhea, and increased sweating, which is consistent with findings of previous studies. For the three studies that included citalopram (Studies 3–5), the total withdrawal rates were 17.0% (69/405) for escitalopram, 15.7% for citalopram (64/408), and 16.9% for placebo (68/403). The corresponding withdrawal rates due to adverse events were 6.9% (28/405) for escitalopram, 5.4% for citalopram (22/408), and 2.5% for placebo (10/403). When all five studies were pooled, the total withdrawal rates were 17.0% for escitalopram (155/862) and 16.0% for placebo (119/745), and adverse events withdrawal rates were 6.0% for escitalopram (52/862) and 1.7% for placebo (13/745). Treatment with escitalopram was not associated with more side effects than treatment with citalopram. In particular, the incidence of treatment-emergent anxiety, a symptom often occurring during the initial treatment phase with SSRIs, did not differ among the treatment groups: Study 1, 1.3% for placebo and 1.4% for escitalopram 10–20 mg/day; Study 2, 3.2% for placebo and 1.6% for escitalopram 10 mg/day; Study 3, 1.6% for placebo, 4.0% for citalopram 40 mg/day, 1.7% for escitalopram 10 mg/day, and 4.0% for escitalopram 20 mg/day; Study 4, 0.6% for placebo, 1.9% for citalopram 20–40 mg/day, and 2.6% for escitalopram 10–20 mg/day; and Study 5, 0.8% for placebo, 2.4% for citalopram 20–40 mg/day, and 0.0% for escitalopram 10–20 mg/day. When all studies were pooled, the incidences were 1.6% for placebo, 2.7% for citalopram, and 1.9% for escitalopram.

DISCUSSION

In this study, the efficacy of escitalopram in treating the symptoms of anxiety associated with major depression was evaluated on the basis of five placebo-

controlled, double-blind studies in patients with major depression. Exclusion criteria precluded patients with concomitant diagnosable anxiety disorders; however, no structured interviews were performed, and this is perhaps the basis for the presence of patients with comorbid anxiety disorders and anxiety symptoms included in this pooled analysis.

Epidemiological studies have long noted the frequent comorbidity of depression and anxiety; more than half of those diagnosed with a depressive disorder have an anxiety disorder, and anxiety disorders tend to precede depression by several years [Wittchen et al., 1994]. The probability that depression will be comorbid with a well-defined anxiety syndrome is twice as high as the probability that depression will be comorbid with alcohol dependence [Möller, 2002]. Clinicians have been well aware of this in their daily practice; the characteristic patient entering the clinic diagnosed with depression is much more likely to have symptoms of anxiety, if not a full-blown syndromatic anxiety disorder, than to suffer from depressive symptoms alone [Kaufman and Charney, 2000].

Regulatory clinical trials examining the efficacy of certain drugs in depression are traditionally designed toward including patients with a specific, narrow cluster of symptoms and a single diagnosis of either depression or anxiety to demonstrate efficacy in a specific indication. More and more trials now examine how specific pharmacological interventions will affect patients with a combination of symptoms—depression and anxiety, either symptomatic or a diagnosable anxiety disorder [Davidson et al., 2002; De Nayer et al., 2002; Dunner et al., 2003; Fava et al., 2000; Hoehn-Saric et al., 2000; Lepola et al., 2003a; Ravindran et al., 1997; Russell et al., 2001; Silverstone and Salinas, 2001]. The importance of this lies in the fact that not only are these patients more representative of the patients seen in clinical practice than the "pure" depressed or anxious type of patient, but that these patients are also actually more difficult to treat. It has been shown that the presence of comorbid symptoms confers a less favorable prognosis and poorer outcomes, and that these patients express higher levels of social distress, have higher suicide rates, have increased incidence of alcohol and drug abuse, and use health care services to a greater extent [Belzer and Schneier, 2004; Brown et al., 1996; Fawcett, 1992; Fawcett and Kravitz, 1983; Grunhaus et al., 1988; Roy-Byrne et al., 2000; van Valkenburg et al., 1984; Vollrath and Angst, 1989]. Therefore, a drug producing a robust antidepressant effect, together with a significant reduction in anxiety symptoms, would make a worthwhile clinical contribution.

Citalopram is a racemate, consisting of equal amounts of an S (sinister)- and an R (rectus)-enantiomer. The serotonin reuptake inhibitor activity of the racemate resides almost exclusively in the S-enantiomer, escitalopram [Hyttel et al., 1992]. It has been demonstrated in preclinical investigations that in the racemate, the R-enantiomer counteracts these effects [Sánchez, 2003; Sánchez and Kreilgaard, 2004; Sánchez et al., 2003a, b]. This may explain why escitalopram has stronger anxiolytic and antidepressant effects than citalopram at twice the dose. Indeed, the preclinical data are consistent with findings from clinical trials in patients with depression and anxiety disorders, in which escitalopram bestowed an additional benefit compared to "equivalent" doses of citalopram [Lepola et al., 2004]. In addition, in these trials, it was found that the beneficial effects of escitalopram were not compromised by a higher incidence of adverse events.

In light of this, it was important to examine the efficacy of escitalopram in treating the symptoms of anxiety as associated with major depression. This was evaluated on the basis on a number of different assessments in the population from five placebo-controlled, double-blind studies in patients with major depression. The assessment parameters can be divided into two large groups: anxiety items appearing in ratings scales for depression, and anxiety-specific scales, including total scores and selected subscores.

When examining the effect of escitalopram on anxiety symptoms as they are incorporated in rating scales for depression, MADRS item 3 was examined for all patients, both in each study separately and in pooled data from all five studies. In the pooled analysis, escitalopram demonstrated an early and highly significant separation from placebo from week 1 onward. Based on the total MADRS score in patients with high initial anxiety, escitalopram was significantly superior to placebo from week 1 and in some time points, also to citalopram. With the HAM-D-24 anxiety factors, included in three studies, the results were more varied, but escitalopram was superior to placebo on this factor in some of the studies. On the HAM-D-24 Anxiety Psychic, item 10, escitalopram was consistently superior to placebo in all three trials included, and on some parameters, so was citalopram, taking into account that the HAM-D-24 is a scale less sensitive in detecting weekly changes.

The anxiety-specific scales included the HAM-A total score, Anxious Mood item (i.e., HAM-A Item 1), and the Psychic Anxiety subscale. Based on the HAM-A total score, escitalopram 20 mg was superior to placebo in two of three studies. Comparable findings were noted for the Anxious Mood item and for Psychic Anxiety items.

CONCLUSION

In summary, although comorbidity of anxiety and depression is more the rule than the exception in daily clinical practice, clinical studies often do not reflect this phenomenon, because patients with either depression or anxiety disorders are enrolled. This fact is also a limitation of the present analysis. Despite this

limitation, the data do show that escitalopram is consistently very effective in treating both anxiety symptoms and the entire depression in the total depressive population, as well as in depressive patients with a high degree of anxiety.

However, more studies are needed to address patients with prospectively defined comorbid anxiety and depression.

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