Research Article

ESCITALOPRAM IN THE TREATMENT OF GENERALIZED ANXIETY DISORDER: DOUBLE-BLIND, PLACEBO CONTROLLED, FLEXIBLE-DOSE STUDY

Jonathan R.T. Davidson, M.D.,1* Anjana Bose, Ph.D.,2 Andrew Korotzer, Ph.D.,2 and Hongjie Zheng, Ph.D.2

Escitalopram has been shown in clinical trials to improve anxiety symptoms associated with depression, panic disorder, and social anxiety disorder. This study was designed to evaluate the efficacy and tolerability of escitalopram in the treatment of generalized anxiety disorder (GAD). Outpatients (18 years or older) who met DSM-IV criteria for GAD, with baseline Hamilton Rating Scale for Anxiety (HAMA) scores ≥18, were randomly assigned to double blind treatment with escitalopram (10 mg/day for the first 4 weeks and then flexibly dosed from 10–20 mg/day) or placebo for 8 weeks, following a 1-week, single-blind, placebo lead-in period. The primary efficacy variable was the mean change from baseline in total HAMA score at Week 8. The escitalopram group (N = 158) showed a statistically significant, and clinically relevant, greater improvement at endpoint compared with placebo (N = 157) in all prospectively defined efficacy parameters. Significant improvement in HAMA total score and HAMA psychic anxiety subscale score for the escitalopram-treated group vs. the placebo-treated group was observed beginning at Week 1 and at each study visit thereafter. Mean changes from baseline to Week 8 on the HAMA total score using a last-observation-carried-forward (LOCF) approach were −11.3 for escitalopram and −7.4 for placebo (P < .001). Response rates at Week 8 were 68% for escitalopram and 41% for placebo (P < .01) for completers, and 58% for escitalopram and 38% for placebo LOCF values (P < .01). Treatment with escitalopram was well tolerated, with low rates of reported adverse events and an incidence of discontinuation due to adverse events not statistically different from placebo (8.9% vs. 5.1%; P = .27). Escitalopram 10–20 mg/day is effective, safe, and well tolerated in the treatment of patients with GAD. Depression and Anxiety 19:234–240, 2004. © 2004 Wiley-Liss, Inc.

Key words: escitalopram; placebo; generalized anxiety disorder; GAD; efficacy; safety; tolerability

INTRODUCTION

Generalized anxiety disorder (GAD) has a lifetime prevalence in the United States of approximately 5% [Kessler et al., 1994]. GAD is characterized by excessive, pervasive, and uncontrollable worry that causes debilitating psychic and somatic symptoms, including irritability, restlessness, concentration difficulties, clammy hands, dry mouth, sweating, nausea, and diarrhea [American Psychiatric Association, 1994; Brown, 1997]. It is a chronic, recurrent disorder and is

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Contract grant sponsor: Forest Laboratories, Inc.

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Received for publication 5 February 2003; Accepted 29 September 2003

DOI 10.1002/da.10146
Published online 10 June 2004 in Wiley InterScience (www.interscience.wiley.com)

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unlikely to remit spontaneously [Yonkers et al., 1996]. Untreated GAD produces significant impairment in daily functioning, elevated medical utilization, and increased morbidity and mortality [Massion et al., 1993; Zajecka, 1997]. Epidemiological surveys indicate that GAD is often comorbid with other psychiatric disorders, including depression [Brawman-Mintzer and Lydiard, 1996, 1997; Brawman-Mintzer et al., 1993].

Benzodiazepines traditionally have been used to treat anxiety disorders [Brawman-Mintzer and Lydiard, 1997; Dubovsky, 1990] but their usefulness is limited by their lack of efficacy for comorbid depression, as well as concerns about the potential for dependence and withdrawal symptoms in longer-term use [Roy-Byrne et al., 1993; Shader and Greenblatt, 1993]. Buspirone is less likely to lead to dependence or withdrawal; however, it is associated with a limited spectrum of action, a need for multiple daily doses and careful dose titration, and concerns about efficacy and patient satisfaction in clinical practice [Ninan et al., 1998; Schweizer, 1995]. Tricyclic antidepressants such as imipramine have been shown to be effective in the treatment of GAD, but their side effect profiles can limit compliance [Hoehn-Saric et al., 1988; Rickels et al., 1993]. Other antidepressants such as trazadone and nefazodone also may be effective for GAD, but supporting data are limited [Hedges et al., 1996; Rickels et al., 1993]. More recently, the selective serotonin reuptake inhibitor (SSRI), paroxetine [Pollack et al., 2001], and the extended-release formulation of the serotonin and norepinephrine reuptake inhibitor (SNRI), venlafaxine [Davidson et al., 1999], have been shown to be effective in the treatment of GAD, suggesting serotonergic involvement in the pathogenesis of GAD. The racemic SSRI antidepressant citalopram (which is composed of the isomers escitalopram and R-citalopram) also has been shown to have anxiolytic activity [Joubert and Stein, 1999; Leinonen et al., 1999; Rosenberg et al., 1994; Stahl, 2000] and to be effective in treating panic disorder [Leinonen et al., 2000; Lepola et al., 1998; Wade et al., 1997] and obsessive-compulsive disorder [Joubert and Stein, 1999; Montgomery et al., 2001a].

The SSRI antidepressant escitalopram has demonstrated anxiolytic activity in several validated animal models. The duration of stress (e.g., footshock)-induced ultrasonic vocalization in rats, an index of anxiolytic activity, is reduced by escitalopram [Sanchez, 2001]. In the light/dark box model, the natural aversion of rats to exploring the light portion of the box is typically overcome by anxiolytic agents such as benzodiazepines. Escitalopram, but not R-citalopram, increases the amount of time rats spend in a light environment instead of a dark environment [Sanchez, 2001]. Finally, electrical or chemical stimulation of the dorsal periaqueductal gray matter in the rat leads to a panic-like aversive reaction that is considered one of the most reliable models of panic anxiety. Hogg demonstrated that escitalopram potently reduced aversion induced by dPAG stimulation in the rat [Hogg and Jessa, 2002].

Escitalopram is responsible for the therapeutic effect of the racemate citalopram [Burke et al., 2002; Hyttel et al., 1992; Owens et al., 2001; Sanchez and Brennum, 2000]. Clinically, escitalopram has been shown to have a broad spectrum of anxiolytic activity. For example, in several trials, escitalopram consistently improved anxiety symptoms associated with major depression [Burke et al., 2002; Gorman et al., 2002]. It also is safe and effective in the treatment of panic disorder [Stahl et al., 2002] and social anxiety disorder [Kasper et al., 2002]. Although R-citalopram has no serotonin-reuptake inhibiting activity, R-citalopram inhibits escitalopram-induced increases in extracellular serotonin levels [Mork et al., 2002], leading to the prediction of better clinical efficacy for escitalopram when administered alone than as a component of racemic citalopram.

These considerations motivated the present examination of the safety and efficacy of escitalopram vs. placebo in the treatment of generalized anxiety disorder.

**PATIENTS AND METHODS**

This was a randomized, double-blind, placebo-controlled, multicenter, flexible-dose study of 315 U.S. outpatients with generalized anxiety disorder.

**PATIENT SELECTION**

Male or female outpatients between 18 and 80 years of age who met DSM-IV [American Psychiatric Association, 1994] criteria for GAD and had a normal physical and laboratory examination, and ECG results at the screening visit were eligible for inclusion. Patients were required to have a minimum score of 18 on the Hamilton Rating Scale for Anxiety (HAMA) and a minimum score of 2 on the HAMA tension and anxiety items [Hamilton, 1959]. Patients with Hamilton Depression Rating Scale (HAM-D) [Hamilton, 1960] scores of 17 or greater and patients with lower scores on the Covi Anxiety Scale [Lipman, 1982] than the Raskin Depression Scale [Lipman, 1982] were excluded. Also excluded were patients who met DSM-IV criteria for any of the following: current bipolar disorder, schizophrenia or any psychotic disorder, obsessive compulsive disorder, mental retardation or any pervasive developmental disorder or cognitive disorder; principal diagnosis for any DSM-IV-defined Axis I disorder other than GAD; history of psychotic disorder or psychiatric features; and substance abuse or dependence within the past 6 months.

Use of psychoactive medications prior to study entry that precluded participation included depot neuroleptics within 6 months; any neuroleptic, antidepressant, or anxiolytic within 2 weeks (5 weeks for fluoxetine); daily benzodiazepine therapy within 1 month; and concomitant treatment with any psychotropic drug (except zolpidem for sleep) or any drug with a
psychotropic component. Also excluded were women who were pregnant or breastfeeding, or of childbearing potential and not practicing a reliable method of birth control. All participants provided written informed consent prior to study entry. The study protocol was approved by the local Institutional Review Board (IRB) of all participating sites or, where appropriate, by a central IRB.

STUDY FLOW

Patients who continued to meet all entry criteria at the baseline visit following a 1-week, single-blind, placebo lead-in period were randomly assigned to 8 weeks of double-blind treatment with placebo or escitalopram. Study visits were subsequently conducted after 1, 2, 4, 6, and 8 weeks of double-blind treatment. Patients were treated continuously through the study with 1 tablet/day of double-blind medication. For the first 4 weeks, patients received escitalopram 10 mg/day or matching placebo. At the Week-4 or -6 visit, if the investigator judged therapeutic response to be insufficient, patients were dispensed double-blind medication from a separate bottle containing either escitalopram 20 mg tablets or matching placebo and were told to continue taking 1 tablet per day. Patients could be returned to the starting dose thereafter if necessary for tolerability reasons.

EFFECTACY VARIABLES AND SAFETY ASSESSMENTS

The primary efficacy measurement was change in HAMA total score, and assessments were performed at screening, baseline and all subsequent visits. Secondary measures of efficacy were performed using the Clinical Global Impressions (CGI) Scale [Guy, 1976], [with CGI Severity (CGI-S) measurements obtained at baseline and all subsequent visits, and CGI Improvement (CGI-I) assessments performed at all visits after baseline], the patient-rated Hospital Anxiety and Depression (HAD) Scale (baseline, Week 4, and endpoint) [Zigmond and Snaith, 1983], the Covi and Raskin scales (baseline, Week 4, and endpoint) [Lipman, 1982], and a quality of life (QOL) scale that consisted of 16 items of the Quality of Life Enjoyment and Satisfaction Questionnaire (baseline and endpoint) [Endicott et al., 1993]. Additional protocol-defined endpoints included the HAMA psychic anxiety and somatic anxiety subscales, and the HAMA anxiety and tension items.

Safety assessments included adverse events, vital signs, 12-lead electrocardiogram, and laboratory tests. All end of study assessments were performed upon early termination.

STATISTICAL ANALYSIS

Efficacy analyses were based on the intent-to-treat (ITT) population that comprised all patients who took at least one dose of study medication and had at least one post-baseline efficacy assessment on the HAMA. All patients who took at least one dose of double-blind study medication were included in the safety analyses. Comparisons between treatment groups were carried out using an analysis of covariance (ANCOVA) model with treatment and study center as factors, and the baseline score as covariate. CGI-I scores were analyzed by analysis of variance (ANOVA) with treatment and study center as factors. Between group comparison of CGI-I responders (defined as CGI-I score of 1 or 2) and HAMA remitters (defined as HAMA ≤ 7) were performed using a Cochran-Mantel-Haenszel test controlling for study center. Rates of discontinuation due to adverse events were compared between groups using Fisher's exact test. All tests were two-sided, with a 5% significance level for main effects. All efficacy analyses used the last-observation-carried-forward (LOCF) approach, unless otherwise noted.

RESULTS

A total of 315 patients (158 in the escitalopram group and 157 in the placebo group) who completed the 1-week placebo lead-in phase and received at least one dose of double-blind medication were included in the safety analysis. Of these, 307 patients (154 in the escitalopram group and 153 in the placebo group) had at least one post-baseline HAMA assessment. These patients formed the intent-to-treat (ITT) population and were included in the efficacy analysis. Demographic and baseline clinical characteristics of the safety population are shown in Table 1. No significant differences between the treatment groups were observed.

At baseline, mean efficacy scores were indicative of a patient population with moderate to severe GAD (Table 1). Prior GAD pharmacotherapy was reported by 34% of placebo-treated patients and 40% of escitalopram-treated patients; most of these were either nonresponders or intolerant to prior treatment. Overall, 77% of patients (75% of escitalopram-treated patients and 78% of placebo-treated patients) completed the study. The most common reasons for discontinuation were loss to follow-up (7.6%) and adverse events (7.0%). The mean daily dose of escitalopram in this study was 12.3 mg, and 58% of escitalopram-treated patients had a mean daily dose exceeding 10 mg.

EFFECTACY

Results at endpoint are presented in Table 2 for all prospectively defined efficacy measures. Compared with placebo treatment, escitalopram treatment had significantly superior effects on all measures, reflecting comprehensive improvement in patients’ condition. Results from Observed Cases analyses at endpoint were qualitatively similar to those of the LOCF analyses,
TABLE 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=157)</th>
<th>Escitalopram (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.5±13.1</td>
<td>39.5±12.1</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>52.9%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Race, % Caucasian</td>
<td>71.3%</td>
<td>70.9%</td>
</tr>
<tr>
<td>Duration of GAD disorder, years</td>
<td>9.05±10.0</td>
<td>10.70±12.3</td>
</tr>
<tr>
<td>HAMA scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>23.2±4.2</td>
<td>23.6±4.6</td>
</tr>
<tr>
<td>Somatic Anxiety Subscale</td>
<td>9.9±3.1</td>
<td>10.0±3.2</td>
</tr>
<tr>
<td>Anxiety Item</td>
<td>2.6±0.6</td>
<td>2.6±0.5</td>
</tr>
<tr>
<td>Tension Item</td>
<td>2.6±0.5</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>HAD Anxiety Subscale</td>
<td>12.2±3.9</td>
<td>12.7±3.8</td>
</tr>
<tr>
<td>HAD Depression Subscale</td>
<td>7.3±3.7</td>
<td>7.7±4.0</td>
</tr>
<tr>
<td>HAMD score</td>
<td>11.9±3.7</td>
<td>12.4±3.6</td>
</tr>
<tr>
<td>HAMD Anxiety Subscale</td>
<td>5.3±2.2</td>
<td>5.3±1.8</td>
</tr>
<tr>
<td>CGI Severity</td>
<td>6.9±1.7</td>
<td>7.0±1.8</td>
</tr>
<tr>
<td>Raskin Depression Scale</td>
<td>2.8±1.4</td>
<td>3.0±1.4</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>51.7±8.4</td>
<td>49.5±9.0</td>
</tr>
<tr>
<td>CGI Severity</td>
<td>4.2±0.5</td>
<td>4.3±0.5</td>
</tr>
</tbody>
</table>

Values are presented as mean ± sd, or as percentages. Baseline efficacy values are based on the ITT population (placebo, N=153; escitalopram, N=154).

TABLE 2. Efficacy results at week 8 (LOCF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=153)</th>
<th>Escitalopram (N=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMA scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>−7.4±0.6</td>
<td>−11.3±0.6**</td>
</tr>
<tr>
<td>Psychic Anxiety Subscale</td>
<td>−3.8±0.4</td>
<td>−6.4±0.3**</td>
</tr>
<tr>
<td>Somatic Anxiety Subscale</td>
<td>−3.6±0.3</td>
<td>4.8±0.3*</td>
</tr>
<tr>
<td>Anxiety Item</td>
<td>−0.7±0.1</td>
<td>−1.2±0.1**</td>
</tr>
<tr>
<td>Tension Item</td>
<td>−0.8±0.1</td>
<td>−1.2±0.1***</td>
</tr>
<tr>
<td>CGI Severity</td>
<td>−0.8±0.1</td>
<td>−1.4±0.1**</td>
</tr>
<tr>
<td>CGI Improvement score</td>
<td>2.8±0.1</td>
<td>2.4±0.1**</td>
</tr>
<tr>
<td>HAD Anxiety Subscale</td>
<td>−1.7±0.3</td>
<td>−4.4±0.4**</td>
</tr>
<tr>
<td>HAMD Anxiety Subscale</td>
<td>−0.7±0.2</td>
<td>−1.9±0.2**</td>
</tr>
<tr>
<td>CGI Anxiety Scale</td>
<td>−1.9±0.2</td>
<td>−3.2±0.2**</td>
</tr>
<tr>
<td>Raskin Depression Scale</td>
<td>−0.4±0.2</td>
<td>−1.3±0.1**</td>
</tr>
<tr>
<td>HAMD score</td>
<td>1.4±0.4</td>
<td>−4.4±0.5**</td>
</tr>
<tr>
<td>HAD Depression Subscale</td>
<td>−0.8±0.3</td>
<td>−2.7±0.4**</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>1.7±0.7</td>
<td>8.4±0.9**</td>
</tr>
</tbody>
</table>

Mean ± SEM changes from baseline, except for CGI-I, where values represent mean ± SEM values at endpoint. Mean changes are not adjusted for baseline levels.

*P<.01
**P<.001

The mean changes from baseline were significantly greater for the escitalopram-treated group than for the placebo-treated group at every time point starting at Week 1, as well as at endpoint, for the HAMA total score (primary efficacy variable; Fig. 1) and the HAMA psychic anxiety subscale (Fig. 2). Similar outcomes were observed for clinician rated global measures: by visit, LOCF values were significantly superior for escitalopram-treated patients vs. placebo by Week 2 for the CGI-I, an effect observed at each subsequent time point.

A significantly greater proportion of escitalopram-treated patients than placebo-treated patients were responders (CGI-I score of 1 or 2) by Week 2. Half the patients completing 4 weeks of escitalopram treatment and 68% of patients completing 8 weeks of escitalopram treatment were responders (Fig. 3; LOCF values at endpoint were 58% escitalopram, 38% placebo; P<.01). There was no gender effect on response rates (data not shown). More than twice as many escitalopram-treated patients than placebo-treated patients who completed this trial were in remission (HAMA ≤ 7) at Week 8 (36% vs. 16%; P<.01).

Further analyses of the Week 4 time point (prior to up-titration) were conducted to assess the efficacy of the 10 mg/day escitalopram dose. Table 3 presents the
HAD Depression Subscale
Raskin Depression Scale
Covi Anxiety Scale
HAD Anxiety Subscale
CGI Improvement score 3.1
CGI Severity score
HAMA scores
scores), at the week-4 visit.
in depression scores (HAD depression subscale, Raskin
subscales, HAMA anxiety and tension items, CGI-I,
placebo in the HAMA, HAMA psychic anxiety
mg/day led to significant improvement relative to
results from each instrument for which an assessment
was scheduled at the end of Week 4. Escitalopram 10
mg/day led to significant improvement relative to
placebo in the HAMA, HAMA psychic anxiety
subscale, HAMA anxiety and tension items, CGI-I,
CGI-S, HAD anxiety subscale, and the Covi, as well as
in depression scores (HAD depression subscale, Raskin
scores), at the week-4 visit.

SAFETY AND TOLERABILITY

Escitalopram treatment was safe and well tolerated.
The rate of discontinuation due to adverse events was
not significantly different between the escitalopram
and placebo groups (8.9% escitalopram vs. 5.1%
placebo; \( P = .27 \)). Only four adverse events were
reported with an incidence exceeding 10%: headache,
nausea, somnolence, and upper respiratory tract infec-
tion (Table 4). Three sexual adverse events were
reported with a frequency exceeding 5%: decreased
libido (7% escitalopram and 3% placebo), ejaculation
disorder (7% escitalopram and 3% placebo), and
anorgasmia (6% escitalopram and 0 placebo). Mean
changes in laboratory, vital sign, body weight, and
ECG values were small in magnitude and clinically
unremarkable.

TABLE 4. Most frequent adverse events*

<table>
<thead>
<tr>
<th></th>
<th>Placebo, ( N = 157 )</th>
<th>Escitalopram, ( N = 158 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>17.8%</td>
<td>23.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.9%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5.7%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.6%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

*Incidence was at least 10% in both treatment groups.

DISCUSSION

The present study demonstrates the efficacy and
safety of escitalopram in the treatment of generalized
anxiety disorder. Escitalopram led to significant
improvement relative to placebo in all prospectively
defined efficacy parameters. The broad benefit of
escitalopram on both psychological and somatic
symptoms of GAD is worthy of note. In addition to
producing a robust anxiolytic effect, escitalopram led
to significant global improvements in patients’ condi-
tions. Escitalopram-treated patients rated their quality
of life as significantly improved relative to placebo-
treated patients. Depressive symptoms were also
significantly improved by escitalopram. A total of
68% of patients completing 8 weeks of escitalopram
treatment were responders. Remission occurred in
36% of subjects following 8 weeks of escitalopram
treatment, a finding that stands in contrast to the
reported remission rate of only 38% after 5 years in a
naturalistic setting [Yonkers et al., 1996]. In a previous
study of paroxetine and placebo in GAD [Pollack et al.,
2001], remission rates were 42.5% for drug and 26.3%
for placebo, i.e., a 16.2% difference, which is compar-
able to our findings.

Significant improvement relative to placebo in
HAMA total scores and HAMA psychic anxiety
subscale scores were observed at the end of the first
week of escitalopram treatment, a finding that is
consistent with the results of multiple studies of
escitalopram in major depressive disorder [Burke et al.,
2002; Gorman et al., 2002; Montgomery et al.,
2001b; Wade et al., 2002]. This trial also provides
support for the effectiveness of escitalopram 10 mg/day
in the treatment of GAD. The daily dose of escitalo-
pram was fixed at 10 mg/day for the first 4 weeks of

TABLE 3. Efficacy results at week 4 (LOCF)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo ( N = 153 )</th>
<th>Escitalopram ( N = 154 )</th>
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</thead>
<tbody>
<tr>
<td>HAMA scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>(-6.3 \pm 0.5)</td>
<td>(-8.8 \pm 0.5**)</td>
</tr>
<tr>
<td>Psychic Anxiety Subscale</td>
<td>(-3.3 \pm 0.3)</td>
<td>(-4.9 \pm 0.3**)</td>
</tr>
<tr>
<td>Somatic Anxiety Subscale</td>
<td>(-3.0 \pm 0.3)</td>
<td>(-3.9 \pm 0.3*)</td>
</tr>
<tr>
<td>Anxiety Item</td>
<td>(-0.6 \pm 0.1)</td>
<td>(-0.8 \pm 0.1**)</td>
</tr>
<tr>
<td>Tension Item</td>
<td>(-0.6 \pm 0.1)</td>
<td>(-0.9 \pm 0.1**)</td>
</tr>
<tr>
<td>CGI Severity score</td>
<td>(-0.6 \pm 0.1)</td>
<td>(-1.0 \pm 0.1**)</td>
</tr>
<tr>
<td>CGI Improvement score</td>
<td>(3.1 \pm 0.1)</td>
<td>(2.7 \pm 0.1**)</td>
</tr>
<tr>
<td>HAD Anxiety Subscale</td>
<td>(-1.4 \pm 0.3)</td>
<td>(-3.2 \pm 0.3**)</td>
</tr>
<tr>
<td>Covi Anxiety Scale</td>
<td>(-1.6 \pm 0.2)</td>
<td>(-2.4 \pm 0.2**)</td>
</tr>
<tr>
<td>Raskin Depression Scale</td>
<td>(-0.3 \pm 0.1)</td>
<td>(-1.0 \pm 0.1**)</td>
</tr>
<tr>
<td>HAD Depression Subscale</td>
<td>(-0.8 \pm 0.2)</td>
<td>(-1.8 \pm 0.3**)</td>
</tr>
</tbody>
</table>

\(^1\)Mean \pm SEM changes from baseline, except for CGI-I, where values
represent mean \pm SEM values at week 4. Mean changes are not
adjusted for baseline levels.

\( *P < .05 \)

\( **P < .01 \)

\( ***P < .005 \)
treatment. The observed onset of effect after 1 week of treatment and the significant improvements in GAD symptomatology noted at the end of week 4 is therefore consistent with the efficacy of the 10 mg/day dose.

The effectiveness of escitalopram 10 mg/day was also a consistent finding in the depression trials [Burke et al., 2002; Wade et al., 2002] and escitalopram is indicated for the treatment of major depressive disorder at a dose of 10 mg/day [“Prescribing information for Lexapro (escitalopram oxalate)” 2002]. GAD and major depression are frequently comorbid [Angst, 1993; Brawman-Mintzer and Lydiard, 1996, 1997; Brawman-Mintzer et al., 1993] but this study did not address comorbid GAD and depression (depressed patients were excluded). Additional study would be worthwhile to determine whether escitalopram at 10 mg/day would be effective in comorbid depression and GAD.

Escitalopram was well tolerated in this study, with a rate of discontinuation due to adverse events not different than for placebo. This finding has been observed for effective doses of escitalopram in several depression trials [Burke et al., 2002; Wade et al., 2002] and in one panic disorder trial [Stahl et al., 2002]. The tolerability profile of escitalopram in treating GAD compares favorably to other treatments indicated for GAD, particularly with regard to the incidence of the most common adverse events [Davidson et al., 1999; Gelenberg et al., 2000; Pollack et al., 2001].

In conclusion, this study demonstrates that escitalopram is effective and well-tolerated in generalized anxiety disorder, as determined by both clinician- and patient-rated outcome measures. Further studies to evaluate the comparative safety and efficacy of escitalopram relative to other established GAD treatments appear warranted.

REFERENCES


Montgomery SA, Kasper S, Stein DJ, Bang Hedegaard K, Lemming OM. 2001a. Citalopram 20 mg, 40 mg and 60 mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. Int Clin Psychopharmacol 16:75–86.


