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Escitalopram for the Treatment of GAD: Efficacy Across Different Subgroups and Outcomes

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Background. *Generalized anxiety disorder (GAD) is characterized by anxiety, and also frequently associated with depressive symptoms. Benzodiazepines have commonly been used in the treatment of GAD, but are not effective antidepressant agents. In this study, we determined whether the selective serotonin reuptake inhibitor escitalopram, was effective across different subgroups and outcomes (anxious symptoms, depressive symptoms, and quality of life).*
Methods. *Three randomized, placebo controlled studies of escitalopram in GAD have employed a similar design, allowing for pooling of the data. The primary efficacy measure was the Hamilton Anxiety Scale (HAMA). General linear models were used to determine the efficacy of escitalopram across different subgroups and outcomes.*
Results. *Escitalopram was efficacious for GAD on a range of measures of both anxiety and depression, and improved the associated impairment in quality of life. There was no significant interaction of effects on the HAMA with demographic or clinical variables. Furthermore, escitalopram was efficacious on both primary and secondary scales in the subgroup of subjects with above-median severity of depressive symptoms at baseline (HAMD-17>12).*
Conclusions. *Escitalopram reduces anxiety and depressive symptoms in GAD, and improves quality of life. It is equally effective in GAD patients, with an above-median level of depressive symptoms. Further research is needed to determine whether these results can be extrapolated to GAD patients with comorbid major depression.*

INTRODUCTION

Generalized anxiety disorder (GAD), a disorder characterized by anxious expectation and by psychic and somatic tension, is increasingly recognized as an important psychiatric disorder. With the highest prevalence of all anxiety disorders in primary practice, it is both persistent and disabling, and is associated with significant morbidity (1). It has also become increasingly clear that GAD is an independent entity; it is characterized by specific symptoms and risk factors, it is at least as impairing as other mood and anxiety disorders, its levels of comorbidity are no higher than levels of comorbidity in depression, and this comorbidity does not predict the course of the disorder (2).

At the same time, clinicians are crucially aware of the heterogeneity of symptoms in patients with GAD. Although recent editions of the Diagnostic and Statistical Manual of Mental Disorders have increasingly emphasized psychic symptoms in GAD, particularly "excessive worry," somatic symptoms are most commonly the presenting complaint of GAD patients in primary care (3). Furthermore, given the high comorbidity of depressive symptoms in GAD, and their associated disability (4), it is important that these be effectively targeted during treatment. Indeed, one of the reasons that antidepressant agents have come to be seen as a treatment of choice in GAD is that they have a broader spectrum of efficacy than other anxiolytics, including the benzodiazepines, buspirone, and hydroxyzine (1, 5).

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The first antidepressants demonstrating efficacy in GAD were the tricyclics. However, the relatively poor tolerability and safety profile of these agents is a concern. The introduction of the selective serotonin reuptake inhibitors (SSRIs) was an important advance in the pharmacotherapy of GAD, because these agents proved effective, well tolerated and safe; escitalopram, sertraline, and paroxetine are currently approved in several countries for the treatment of GAD. In addition, the selective noradrenaline-serotonin reuptake inhibitor (SNRI), venlafaxine, has proven effective and well tolerated in GAD, and has been approved in several countries for this indication. Thus, these agents are currently considered the first-line pharmacotherapy for GAD (1, 5).

Escitalopram is an SSRI with unique allosteric effects at a low-affinity binding site on the serotonin transporter (6). Three similarly designed randomized controlled trials have demonstrated its efficacy in GAD, as measured by the Hamilton Anxiety Scale (HAMA) and the Clinical Global Impressions Improvement score (CGI-I) (7). In the current pooled analysis, we focused on whether escitalopram is effective on different measures of anxiety and depressive symptoms, and on whether escitalopram is equally effective in GAD patients with above-median severity of depression (in the present dataset, the median HAMD-17 score was 12). A medication that decreases both anxious and depressive symptoms of GAD, and that is also effective in more severely depressed GAD patients, will be regarded by clinicians as having broad-spectrum efficacy and so as a clinically useful option in the treatment of this disorder.

METHODS

Clinical Studies

Studies of escitalopram in GAD have previously been described in detail (7). Three multicentre, randomized, 8-week, double-blind, placebo-controlled studies of nearly identical design were undertaken in specialist settings in the United States. The design of the trials differed only in the method by which dose titration was blinded.

Subjects were aged 18–80, met DSM-IV criteria for GAD, and had HAMA (8) baseline scores $\geq$18, with a minimum score of 2 on the tension and anxiety items (items 1 and 2). Exclusion criteria included a principal diagnosis of any Axis I disorder other than GAD, a score $\geq$17 on the Hamilton Depression Rating Scale 17 item scale (HAMD-17) (9), or a lower score on the Covi Anxiety Scale (10) than on the Raskin Depression Scale (11).

Each trial was initiated with a one-week single-blind placebo lead-in. Patients were then randomized double blind to escitalopram 10mg/day or placebo. Investigators had the option of increasing medication dose to escitalopram 20mg/day at week 4 and 6. Patients unable to tolerate 20mg/day of escitalopram could be returned to the starting dose for the remainder of the study.

Efficacy assessments were performed at 1, 2, 4, 6, and 8 weeks. The primary efficacy measure was the HAMA. Secondary efficacy measures included the HAMA psychic anxiety subscale [items 1–6, 14], Covi anxiety scale, Hospital anxiety and depression scale (HAD, divided into anxiety and depression subscales) (12), HAMD-17 (total, depression [items 1, 2, 7, 8, 10, 13] and anxiety [items 10, 11, 12, 13, 15, 17] subscales), Raskin depression scale, and QoL (Quality of Life, Enjoyment, and Satisfaction Questionnaire) (13).

Statistical Analyses

Efficacy analyses were based on a modified intent-to-treat (ITT) population, comprising all patients who received at least one dose of study medication and had at least one valid post-baseline efficacy assessment for the HAMA. All efficacy analyses used the last-observation-carried-forward (LOCF) approach. Data were examined using analysis of covariance (ANCOVA) with the model containing the factors treatment, study, and study center, the covariate baseline HAMA score, and included interactions between treatment and age, sex, age at onset, chronicity, weight, and comorbid depressive symptoms. Interaction tests were performed at the 0.05 significance level. Effect sizes were calculated as estimated difference divided by the standard deviation of the parameter in question.

RESULTS

The pooled ITT population comprised 427 placebo treated subjects (M:F = 195:232, mean age±SD = 39.6±13.2) and 429 escitalopram treated subjects (M:F = 182:247, mean age±SD = 38.6±12.6). All interaction tests on HAMA total score regarding age, sex, age at onset, chronicity, weight, and comorbid depressive symptoms were insignificant at the 5% significance level, indicating that escitalopram was equally effective across these different subgroups. The effects of escitalopram on the HAMA have been previously described in detail (7). Escitalopram also demonstrated a clinically relevant [i.e., effect size >0.3; (Cohen, 1988)] and significant ($p<0.001$) difference versus placebo in all anxiety and depression scales as well as in QoL (Figure 1a). In patients with above-median depression (baseline HAMD-17>12), escitalopram demonstrated a clinically relevant and significant ($p<0.01$-0.001) difference versus placebo in all scales (Figure 1b).

Escitalopram was also significantly superior to placebo for almost all the individual items of these scales (Figures 2–5).

DISCUSSION

A previous analysis of pooled data demonstrated that escitalopram was effective in the treatment of GAD, as measured by the HAMA and CGI-I scales. These results extend these

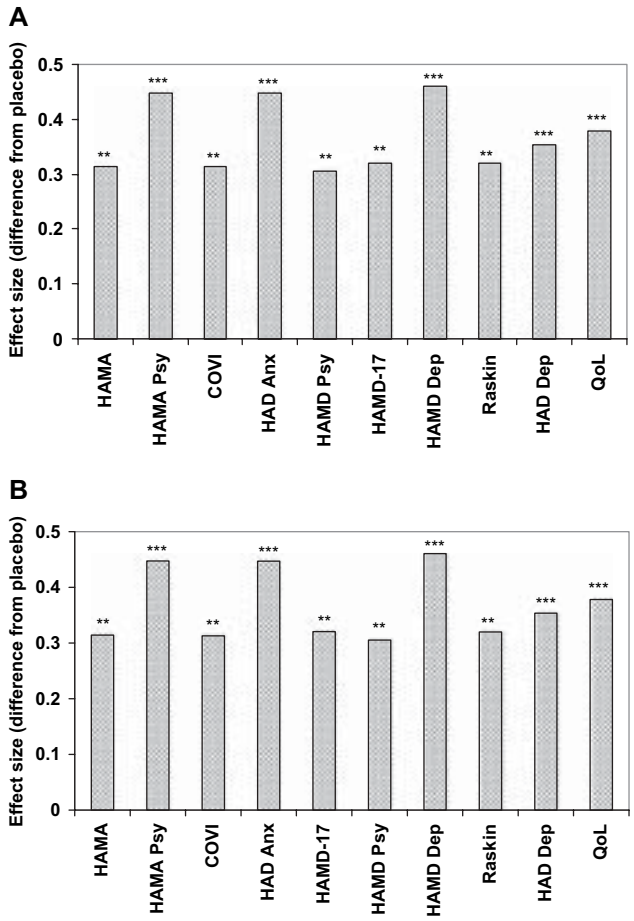

Figure 1 Effects of escitalopram on measures of anxiety, depression, and quality of life at Week 8, LOCF in A) all patients and B) in patients with above-median depression (HAMD-17>12). Significant difference versus placebo: **p≤0.01; ***p≤0.001. Significant difference versus placebo at Week 8, LOCF. ***p≤0.001. HAMA=Hamilton anxiety scale; HAMA Psy=psychic anxiety subscale of the HAMA; COVI=Covi anxiety scale; HAD Anx=anxiety subscale of the Hospital anxiety and depression scale; HAMD Psy=anxiety subscale of the HAMD-17; HAMD-17=17-item Hamilton depression scale; HAMD Dep=depression subscale of the HAMD-17; Raskin=Raskin depression scale; HAD Dep=depression subscale of the Hospital anxiety and depression scale; QoL=Quality of Life, Enjoyment, and Satisfaction Questionnaire.

findings by demonstrating that escitalopram is efficacious for anxiety as well as associated depressive symptoms and impaired quality of life. In addition, escitalopram is effective in different demographically and clinically defined subgroups of GAD subjects, including those with above-median levels of depression. These data are clinically relevant, given that GAD patients frequently present with both anxious and depressive symptoms. Indeed, anxiety symptoms continue to be more commonly disregarded than depressive symptoms by clinicians, particularly in primary care (14, 1).

SSRIs and SNRIs are now regarded as the first-line pharmacotherapy of choice in GAD partly because they decrease both anxious and depressive symptoms, whereas agents such as

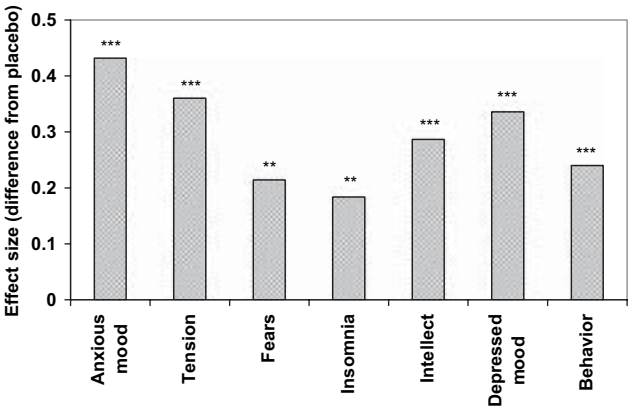

Figure 2 Effects of escitalopram on individual items of Hamilton Anxiety Scale (HAMA) psychic anxiety subscale. Significant difference versus placebo at Week 8, LOCF: **p≤0.01; ***p≤0.001.

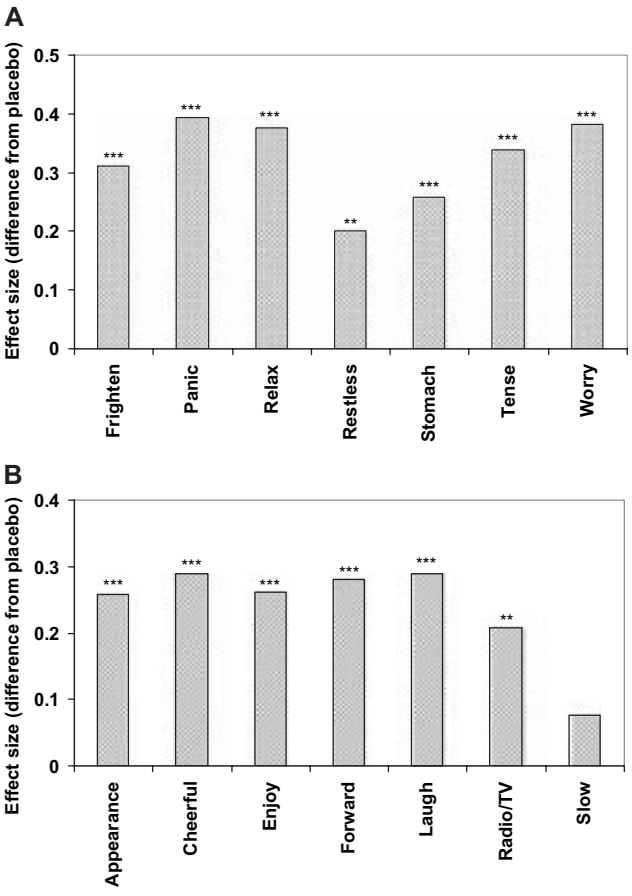

Figure 3 Effects of escitalopram on individual items of Hospital anxiety and depression scale; A) the anxiety subscale; HAD-A and B) the depression subscale; HAD-D. Significant difference versus placebo at Week 8, LOCF: **p≤0.01; ***p≤0.001.

benzodiazepines, buspirone, and hydroxyzine are effective only for anxiety symptoms (1, 5). The broad spectrum activity of escitalopram is particularly important given that GAD

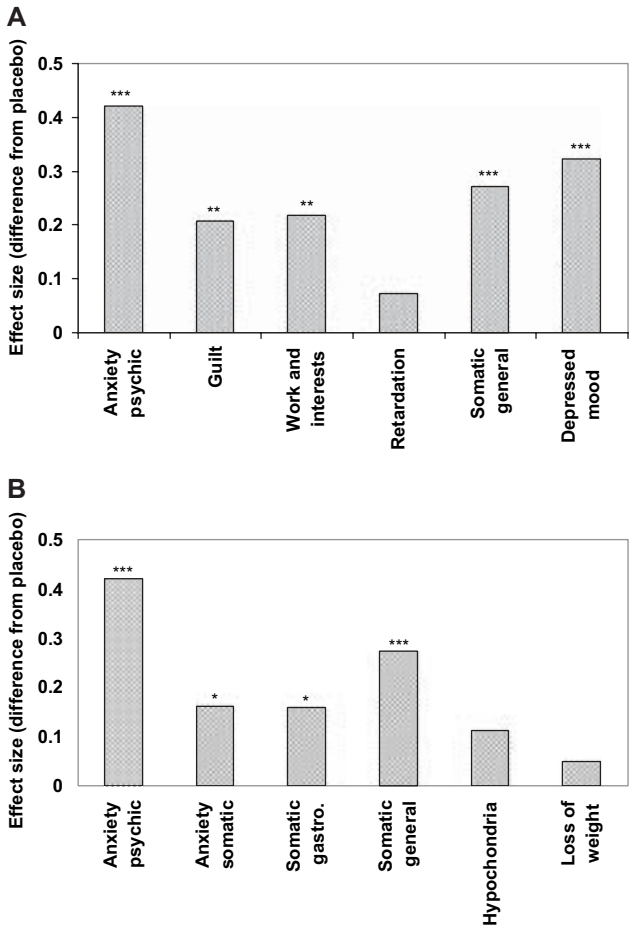

Figure 4 Effects of escitalopram on individual items of Hamilton Depression Scale (HAMD-17) A) depression subscale and B) anxiety subscale. Significant difference versus placebo at Week 8, LOCF: *p≤0.05; **p≤0.01; ***p≤0.001.

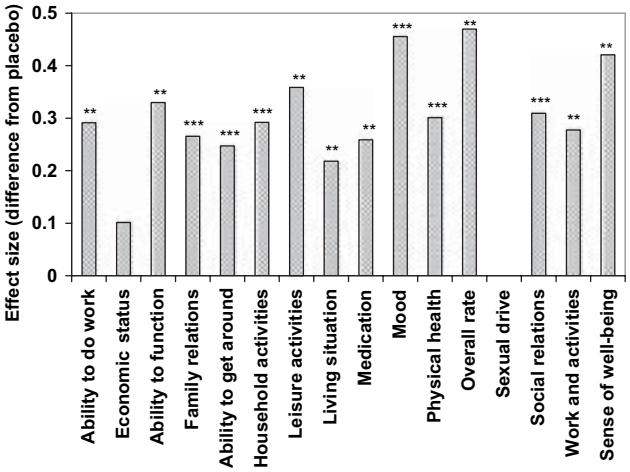

Figure 5 Effects of escitalopram on individual items of Quality of Life. Significant difference versus placebo at Week 8, LOCF: **p≤0.01; ***p≤0.001.

patients frequently go on to develop comorbid major depression, and that there is some evidence from epidemiological data that appropriate pharmacological intervention for GAD may prevent this sequela (15).

It is important to emphasize, however, that the studies included herein were designed to exclude patients with comorbid major depressive disorder or severe symptoms of depression. Patients with such comorbidity are a particularly important group, given their relatively high disability and poor prognosis, and require early and robust intervention (4, 16). To date, there have been few studies of patients with comorbid GAD and major depressive disorder, but aggressive treatment with antidepressants would arguably be the most likely pharmacological intervention to show efficacy in this context (16).

Nevertheless, the findings here indicate that escitalopram does have broad-spectrum effects on both anxiety and depressive symptoms, whether assessed by clinician-rated instruments such as the HAMA or self-rated measures such as the HAD, as well as associated disability. This is consistent with previous data demonstrating the efficacy of this medication in both major depression as well as in anxiety disorders including GAD (7), panic disorder (17), and social anxiety disorder (18).

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