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A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients ☆

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Abstract

This double-blind, placebo-controlled study compared venlafaxine (immediate release), the first modern serotonin-norepinephrine reuptake inhibitor, with the selective serotonin reuptake inhibitor fluoxetine. Outpatients were randomly assigned to 6 weeks of treatment with venlafaxine (75–225 mg/day; $n = 102$), fluoxetine (20–60 mg/day; $n = 104$), or placebo ($n = 102$). Efficacy was assessed using the 21-item Hamilton Depression Rating Scale (HAM-D_{21}), the Montgomery-Åsberg Depression Rating Scale (MADRS), the Clinical Global Impression-Severity of Illness (CGI-S) scale, response and remission rates, and several other measures. Intent-to-treat analyses utilized both the last observation carried forward and ETRANK methods to account for missing data. At week 6 or study endpoint, venlafaxine (mean dose: 142 mg/day) was superior to placebo on most outcomes measures, whereas the differences between fluoxetine (mean dose: 41 mg/day) and placebo were less consistent. Final remission (defined as HAM-D $\leqslant$ 7) rates were 32%, 28%, and 22% for venlafaxine, fluoxetine, and placebo, respectively. Few differences between the active treatments attained statistical significance. Both active therapies were generally well tolerated; however, attrition due to adverse events, incidence of selected side effects, and increases in pulse and blood pressure favored fluoxetine over venlafaxine. This study provides further evidence that venlafaxine is effective after 6 weeks of treatment compared with placebo. The efficacy profile of fluoxetine was somewhat less consistent. It is strongly recommended that future studies of comparative antidepressant efficacy be adequately powered to detect modest between-drug differences in efficacy.

Keywords: Major depressive disorder; Antidepressants; Fluoxetine; Venlafaxine; Norepinephrine; Serotonin reuptake inhibitors

1. Introduction

Venlafaxine hydrochloride is the first member of a newer class of antidepressants now referred to as serotonin–norepinephrine reuptake inhibitors (SNRIs) (Muth et al., 1986; Holliday and Benfield, 1995). Similar to fluoxetine, the first member of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants to be widely used, venlafaxine has little or no affinity for cholinergic, adrenergic, or histaminergic receptors, which may account for the drugs' different tolerability profiles compared to tricyclic antidepressants (Ellingrod and Perry, 1994). Moreover, there is evidence that venlafaxine may be a more effective antidepressant than fluoxetine (Thase et al., 2001; Smith et al., 2002); this difference is presumed in part to be mediated by "dual" reuptake

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inhibition (Thase et al., 2001). Not all studies have found a difference between these therapies, however, and, as only 2 published studies have included a placebo control group (Rudolph and Feiger, 1999; Silverstone and Ravindran, 1999), the assay sensitivity of the individual trials may be questioned (Thase, 2002). The current double-blind, placebo-controlled study therefore was undertaken to further assess the relative efficacy and safety of venlafaxine and fluoxetine.

2. Methods

The study was conducted in 13 centers (both university-affiliated and private research clinics) in the United States. The protocols were reviewed and approved by the institutional review boards of each study site, and the study was conducted according to the Declaration of Helsinki and its amendments. Participants signed a written informed consent at the time of their enrollment.

2.1. Patients

2.1.1. Inclusion criteria

Participants were outpatients 18 years or older and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for major depressive disorder (American Psychiatric Association, 1994). All patients had symptoms present for at least 1 month before study entry and scored at least 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D_{21}).

2.1.2. Exclusion criteria

Patients were excluded if they had a history or presence of bipolar disorder or any psychotic disorder. Patients with a history of alcohol or substance abuse within the past year were excluded from the study, as were those who had any clinically significant medical disorders or abnormalities detected during the prestudy physical screening that might compromise study participation. Additionally, patients were excluded if they were acutely suicidal to the degree that precautions against suicide were needed. Another cause for exclusion was a history of nonresponse to venlafaxine or fluoxetine. Further, any patient who had received either study drug within 6 months prior to starting the double-blind treatment period was excluded. Patients were excluded if they had received any of the following treatments before entering the trial: electroconvulsive therapy within 3 months; any investigational drug or antipsychotic drug within 30 days; astemizole, cisapride, sumatriptan, terfenadine, any monoamine oxidase inhibitor, paroxetine, or sertraline within 14 days; any other antidepressant, anxiolytic, sedative-hypnotic drug (except chloral hydrate), or any other psychotropic drug within 7 days of the start of double-blind treatment; or any other drug with psychotropic effects within 7 days of the start of the double-blind treatment period unless a stable dose of the drug had been maintained for at least 1 month (3 months for thyroid or hormonal medications) before study day 1. Pregnant or lactating women were excluded from the study, as were women capable of childbearing who were unwilling to use a medically acceptable form of contraception.

Study candidates underwent a complete evaluation, including a psychiatric history and examination, HAM-D_{21}, medical history and physical examination, laboratory assessments, and electrocardiogram (ECG). Potentially eligible patients entered a single-blind, placebo phase, which typically lasted 7 days ($\pm$3 days). At study day 0, the HAM-D_{21} was repeated and other efficacy measurements described below were performed. Eligibility for randomization required no more than a 20% decrease in HAM-D_{21} during the single-blind, placebo lead-in. Patients meeting the entry criteria at both the screening and baseline visits were then randomly assigned to double-blind therapy with venlafaxine immediate release (IR), fluoxetine, or placebo.

2.2. Study medication

Study medications were dispensed in identically appearing capsules. Double-blind therapy was initiated as follows: venlafaxine IR 37.5 mg twice each day, fluoxetine 20 mg in the morning (with one placebo capsule in the evening), or placebo twice daily. If clinically indicated, patients could receive up to 2 dose increases. The venlafaxine dosage could be increased on day 15–75 mg twice daily (150 mg/day), and again on day 29–112.5 mg twice daily (maximum permitted dose: 225 mg/day). Likewise, fluoxetine could be increased on day 15–40 mg/morning (with 2 placebo capsules in the evening) and again on day 29 to the maximum permitted dose, 60 mg/morning (with 3 placebo capsules in the evening). At the end of the study, patients receiving more than 2 capsules daily entered a medication taper period of up to 2 weeks, decreasing their dosage in steps before stopping medication to avoid discontinuation effects.

2.3. Efficacy and safety assessments

In addition to the HAM-D_{21} total score, item 1 of the HAM-D (depressed mood), the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, and the Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I) scores were considered to be primary efficacy variables in the original data analytic plan. Efficacy assessments were repeated at weeks 1, 2, 3, 4, and 6 or study endpoint. Four definitions of response were compared: (1) $\geqslant$50% decrease (from week 0) in the HAM-D_{21} score, (2) $\geqslant$50% decrease in the MADRS, (3) a final CGI-I score of 1 or