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Research report

A double-blind, placebo-controlled study of edivoxetine as an adjunctive treatment for patients with major depressive disorder who are partial responders to selective serotonin reuptake inhibitor treatment

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ABSTRACT

Background: This phase 2 study examined the efficacy and tolerability of edivoxetine, a highly selective norepinephrine reuptake inhibitor, as an adjunctive treatment for patients with major depressive disorder (MDD) who have a partial response to selective serotonin reuptake inhibitor (SSRI) treatment.
Methods: Study design consisted of double-blind, 10-week therapy of adjunctive edivoxetine (6–18 mg once daily) or adjunctive placebo with SSRI. Inclusion/entry criteria included partial response to current SSRI by investigator opinion and a GRID 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) total score ≥ 16. The primary efficacy measure was the Montgomery–Asberg Depression Rating Scale (MADRS). Safety measures included treatment-emergent adverse events (TEAE) and vital signs.
Results: For the primary evaluable population ($n=63$ for adjunctive edivoxetine and $n=68$ for adjunctive placebo), the treatment groups did not differ significantly on the primary outcome of change from baseline to week 8 in the MADRS total score; the effect size of edivoxetine treatment was 0.26. Significant treatment differences, favoring adjunctive edivoxetine ($p \leq .05$), were shown for improvements in role functioning and the functional impact of fatigue. For the adjunctive edivoxetine randomized group ($N=111$), the most frequent TEAEs were hyperhidrosis (7.2%), nausea (7.2%), erectile dysfunction (6.3%) and testicular pain (6.3%). Hemodynamic changes were observed in blood pressure and pulse rate between treatment groups.
Limitations: Study was underpowered for an alpha 2-sided 0.05 significance level for the primary outcome.
Conclusions: For patients with MDD who had a partial response to SSRIs, adjunctive edivoxetine treatment was not statistically superior to adjunctive placebo on the primary outcome measure. However, pending further study, improved functioning and remission rate suggest a potential role for edivoxetine for patients with depression.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are often recommended as a first-line treatment for major depressive disorder (MDD) (NICE, 2009; Kennedy et al., 2009; Armstrong, 2011; Suehs et al., 2008) as these medications have demonstrated efficacy and good tolerability in many patients. However, not all patients achieve remission (a state of minimal or absent symptoms) in response to their initial monotherapy treatment. For example, in the study Sequenced Treatment Alternatives to Relieve Depression (STAR*D), after up to 14 weeks of treatment with citalopram, rates of remission were 28–33% with variation depending upon the instrument used to measure remission (Trivedi et al., 2006). The adverse sequelae of failing to achieve remission from MDD are becoming clear across a number of illness outcomes, including risk of relapse, rate of relapse, continued poorer psychosocial functioning, and chronicity of depression (Mauskopf et al., 2009; Kennedy and Paykel, 2004; Papakostas, 2009, Paykel et al., 1995; Judd et al., 1998).

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While some patients may experience no response to treatment, many patients will experience a partial response; that is, these patients have experienced a clinically meaningful improvement, but have not achieved remission. Switching to a different monotherapy antidepressant or adding a second agent are both viable options endorsed by treatment guidelines (NICE, 2009; Armstrong, 2011; Suehs et al., 2008) for patients who fail to remit on their initial antidepressant treatment. The optimal strategy depends on the individual patient, and a patient's preference should be incorporated when determining the next step of treatment (Montori et al., 2013). In the STAR*D study, based on their initial response and tolerability to the SSRI, patients had clear preferences as to whether they wanted to switch or add-on another medication as the second step of their treatment (Wisniewski et al., 2007). Thus, further options for both steps are needed to continue to help patients achieve remission.

Edivoxetine hydrochloride, hereafter referred to as edivoxetine, is a potent and highly selective norepinephrine reuptake inhibitor (NRI) that has shown antidepressant effects as a monotherapy in prior studies (Dubé et al., 2010 [secondary endpoints]; Pangallo et al., 2011 [primary and secondary endpoints]). Given the need for treatment options for patients who experience a partial response to SSRI, the potential efficacy and safety of edivoxetine as an adjunctive treatment were examined in a pilot study for patients with a partial response to an SSRI therapy.

2. Materials and methods

2.1. Overview

This phase 2 multicenter pilot study was conducted at 25 sites in the United States of America. All primary investigators were physicians with a specialty in psychiatry. The study was conducted between March 2009 and January 2010. The study protocol was reviewed by the applicable Ethical Review Boards (ERBs) for each clinical site, and the ERBs provided written approval of the study protocol and the informed consent forms. All patients provided written informed consent, and the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, Good Clinical Practice, and applicable laws and regulations.

2.2. Patient selection

The study included male and female outpatients, 18 to 65 years of age, who met criteria for MDD without psychotic features, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision® (DSM-IV-TR) (APA, 2000) and determined by clinical assessment and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Other inclusion criteria for the patients were the following: at least 1 other MDD episode before the current episode within the past 5 years, partial response (i.e. the patients had attained at least minimal clinically meaningful improvement from their current SSRI treatment, as determined by the investigator's opinion) to the current SSRI therapy, a GRID-Hamilton 17-item Rating Scale for Depression (GRID-$HAMD_{17}$,) (Williams et al., 2008) total score ≥ 16 at visits 1 and 2, SSRI treatment for ≥ 6 weeks before visit 2 and at a stable dose for at least 2 weeks before visit 2, and patient preference for adjunctive treatment rather than switching to a different antidepressant.

Patients with bipolar disorder, psychotic disorders or treatment-resistant depression (defined as failure to respond to 2 or more adequate courses of antidepressant in the current episode) were excluded, as were those with serious or unstable medical illness, women who were pregnant or breastfeeding, and patients with a known medical condition that could have been worsened by a noradrenergic medication. Concomitant medications with primarily central nervous system activity were not allowed, other than the SSRI treatment and episodic hypnotics (for short-term treatment of insomnia, and for no more than 3 days in a week or a total of 15 cumulative days).

2.3. Study design

The design was a 10-week acute, randomized study that included a 2-week double-blind placebo lead-in and an 8-week flexible-dose acute treatment phase. Patients who completed the study or who discontinued early from the study for any reason entered a 2-week taper phase. The study compared adjunctive treatment with edivoxetine 6–18 mg once daily (QD) to adjunctive placebo. All patients were receiving SSRI treatment for at least 6 weeks before study entry by history and had to maintain their SSRI and dose throughout the study. The study design consisted of 3 phases: screening, acute therapy, and taper phase. The screening phase (-3–30 days) was designed to assess the patient for possible inclusion in the study and to provide an adequate washout period for any excluded concomitant medication. At visit 2, patients who met entry criteria were enrolled into the placebo lead-in phase and received placebo QD over the 2-week interval between visits 2 and 3 to allow identification of patients who had significant improvement due to nondrug therapeutic effects and/or continued SSRI monotherapy. At visit 3, all patients were randomized in a 1:1 ratio to receive edivoxetine or placebo as adjunctive treatment during an 8-week acute treatment period (Study Period II). Patients who responded in the lead-in period by $\geq 25\%$ improvement in the 16-item Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) were randomized to treatment but *a priori* excluded from the primary efficacy analyses. Randomization was stratified by site and also by whether patients had a $<25\%$ improvement or $\geq 25\%$ improvement in $QIDS\text{-}SR_{16}$ total score from visit 2 to visit 3.

Patients randomly assigned to receive edivoxetine were started with 6 mg administered QD on the day after visit 3, and the dose was increased to 9 mg after 1 week. Patients assigned to adjunctive edivoxetine could subsequently have been titrated up a dose level, at scheduled visits only, up to a maximum of 18 mg QD, and the dose could have been decreased at scheduled or unscheduled visits to a minimum of 6 mg QD. Dose adjustments were made based on the investigator's judgment of safety and tolerability and response to treatment, indicated by a Clinical Global Impressions-Severity (CGI-S) score <3 (normal, not at all ill, or borderline ill). Based on the titration schedule, the maximum duration of treatment of adjunctive edivoxetine 18 mg would be 4 weeks. The edivoxetine treatment doses were 6 mg, 9 mg, 12 mg, or 18 mg. During the taper phase (Study Period III), patients receiving edivoxetine were tapered to 6 mg/day over a 1- to 2-week period (i.e. SSRI+edivoxetine 12 mg for 1 week followed by SSRI+edivoxetine 6 mg QD for 1 week or SSRI+edivoxetine 6 mg QD for 2 weeks).

2.4. Outcome measures

The primary efficacy measure was the clinician-rated Montgomery–Asberg Depression Rating Scale (MADRS Montgomery and Asberg, 1979) total score. The MADRS was administered independently by blinded clinicians from a centralized rating organization via telephone and was not administered by the investigators. Each item of the MADRS was assessed remotely, including the observation item, which was evaluated based on the