A 6-week, multicentre, randomized controlled clinical trial to evaluate the safety and efficacy of placeboxetine hydrochloride in the treatment of major depressive disorder in an Indian setting

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ABSTRACT

Introduction: This paper describes a fictitious study of a fictitious drug. A companion paper in this issue of the Indian J Psychiatry critically examines this paper and provides author, reader, reviewer, and researcher perspectives on problems related to the design and conduct of a clinical trial; on issues related to the analysis of data; on how to write a research paper; and on how to critically read or review a journal article. Readers are invited to appraise this paper and then compare their assessment with that presented in the companion paper.

Background: This study sought to compare the safety and efficacy of placeboxetine (PB) hydrochloride extended release capsules with sertraline hydrochloride in patients diagnosed with major depressive disorder in 15 general hospitals in south India.

Materials and Methods: In a prospective, open-label, 15-center, randomized controlled clinical trial, consecutive outpatients diagnosed with major depressive disorder of at least moderate severity were randomized 1:1 to receive flexible doses of either PB or sertraline once each morning. Patients were evaluated every two weeks, until the study endpoint, using the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Rating Scale (MADRS). Safety was determined through assessments of vital signs, adverse events, study discontinuation rates, hematological parameters, metabolic parameters, electrocardiography, and other measures.

Results: Ten patients dropped out of the study from each treatment arm. There was a significant, marked improvement in HAM-D and MADRS scores in each group by the treatment endpoint. There was no significant difference between PB and sertraline groups on either HAM-D or MADRS at any visit. The response rate was 90% with PB and 92% with sertraline. The remission rate was 70% with PB and 75% with sertraline. All laboratory parameters were within normal limits in all patients. There were no serious adverse events.

Conclusions: Placeboxetine is as safe and effective as sertraline in Indian patients with major depressive disorder.

Key words: India, major depressive disorder, placeboxetine, randomized controlled trial, sertraline

INTRODUCTION

Depression is a common disorder with an estimated incidence of 15-20%. Depression is associated with considerable family and socioeconomic burden. Patients with depression often suffer medical and psychiatric comorbidity.[1,2] Although various psychological and somatic treatments are available to treat depression, response and
remission rates are low in clinical trials as well as in real world settings, and treatment-emergent adverse events are common.\textsuperscript{5,6} There is therefore a need for continued efforts in research and development to introduce newer treatments which may have a more favorable efficacy and adverse effect profile than the existing treatments.

Placeboxetine (PB) hydrochloride is one such newer treatment, recently approved by several regulatory agencies in the North American and European continents. PB belongs to the serotonin-norepinephrine (SNRI) class of antidepressant drugs. Other than its potent inhibition of the serotonin and norepinephrine transporter proteins, PB has no action at over 60 molecular targets, including receptor sites and enzymes; thereby, it can be expected to have a favorable adverse effect profile with little to no risk of pharmacokinetic drug interactions.\textsuperscript{6,7}

Four Phase III randomized, placebo-controlled trials (RCTs) conducted in 12 countries in North America and Europe found PB (75-300 mg/day) safe and effective in patient with major depressive disorder.\textsuperscript{8-11} There are no data on the safety and efficacy of PB in Indian patients. The present study therefore compared PB with sertraline, an approved antidepressant, in patients with major depressive disorder in south India.

MATERIALS AND METHODS

Study design
The present study was a 6-week, multicentre, open-label, randomized controlled trial conducted in patients recruited from the departments of psychiatry in 15 general hospitals in south India. Approval for the study was obtained from the Drug Controller General of India as well as the ethics committees at each participating site. The trial was registered at the Clinical Trials Registry of India. Informed consent for participation in the study was obtained from each patient in writing.

Sample
The sample comprised consecutive consenting male and female patients, aged 18-65 years, diagnosed with major depressive disorder that was at least 4 weeks in duration. All patients were free from psychotropic medication for at least two weeks prior to randomization, and all scored at least 18 (indicating at least moderate severity of illness) on the Hamilton Rating Scale for Depression (HAM-D). Patients were excluded if they had any other major Axis I psychiatric disorder, any medical or neurological disorder that could influence the diagnosis or treatment of depression, any condition other than depression that was not on stable treatment for at least the past one month, any condition that could pose a health risk during a clinical trial, and any clinically significant abnormality or disorder that was newly detected during the baseline assessments. Patients who were considered to be at risk of suicide were also excluded from participation in the study.

Treatment
Consenting patients who fulfilled the study selection criteria were randomized 1:1 to receive open-label treatment with either PB extended release capsules (starting dose, 75 mg/day) or sertraline tablets (starting dose, 50 mg/day). All medications were dosed in the morning. PB was obtained from Indigent Pharma, Bogasapura, India, and sertraline was purchased from commercial sources. The dose of medication was flexibly uptitrated, based on efficacy and tolerability, at the discretion of the treating clinician. Downtitration was also allowed if raised doses were not tolerated. Thus, treatment reflected real world practice. The dosing range was 75-300 mg/day for PB and 50-200 mg/day for sertraline. No other psychotropic medication was permitted during the study except for lorazepam at a maximum dose of 2 mg during a 24-h period to treat agitation or insomnia. At the end of the 6-week study, the trial medications were tapered and withdrawn.

Assessments
Patients were assessed at baseline and, again, at 2-weekly intervals using the HAM-D, the Montgomery-Asberg Rating Scale (MADRS), and the Clinical Global Impression Scales for Severity and Improvement (CGI-S and CGI-I). Response was defined as 50% or greater improvement in HAM-D scores, and remission as a final HAM-D score of 10 or lower.

All adverse events were recorded. Safety assessments included assessment of vital signs, hematological measures, metabolic parameters, liver function tests, renal function tests, thyroid function tests, and the electrocardiogram (EKG).

Statistical analysis
The primary outcome measure was the improvement in the HAM-D score after 6 weeks of treatment. Secondary outcomes were post-baseline changes in MADRS ratings as well as safety measures. Means were compared within groups using the paired t test and between groups using the independent sample t test. Frequencies were compared between groups using the Chi square test. Alpha for statistical significance was set at 0.05.

RESULTS
A total of 209 patients were screened. Nine patients did not meet the study selection criteria; thus, 200 patients were recruited, with 100 patients randomized to each group. Of these, 10 dropped out of each treatment arm, leaving 90 completers in each group. Reasons for drop out included adverse events (n=12), inefficacy (n=6), and withdrawal of consent (n=2). The reason for drop out could not be ascertained in one patient.
The sociodemographic and clinical description of the sample is presented in Table 1. The sample was relatively young and predominantly male. The groups were comparable at baseline on all sociodemographic and clinical variables.

At the 6-week study endpoint, the mean (standard deviation) dose of PB was 250.8 (37.4) and that of sertraline was 110.5 (26.9). The mean HAM-D scores across the course of the study are presented in Figure 1. There were no significant differences in HAM-D ratings between groups either at baseline or at any assessment point afterwards. The primary outcome, improvement in HAM-D scores between baseline and endpoint, was significant for both PB ($P<0.001$) and sertraline ($P<0.001$) groups; in fact, there was statistically significant improvement in HAM-D scores at the first (2-week) follow up, itself ($P<0.01$ for each group), indicating robust, early improvement with treatment.

Similar results were obtained with the MADRS assessments [Figure 2]. There was no difference between groups at baseline, there was significant improvement in each group at the end of weeks 2 ($P<0.01$) and 6 ($P<0.001$), and there were no significant differences between groups at any follow up visit.

The response rate was 90% with PB and 92% with sertraline. The remission rate was 70% with PB and 75% with sertraline. The two groups did not differ significantly on either measure [Table 2].

Table 3 presents adverse events that were reported by at least 2% of the patients in either group during the course of the study. Both drugs were well tolerated. Most of the adverse events occurred early during the course of the study. All adverse events recorded were transient and mild to moderate in severity. PB was associated with significantly less nausea and headache than sertraline; otherwise, adverse events did not differ significantly between the two groups.
There were no significant changes in heart rate or blood pressure at any time point. There were no abnormalities identified in the EKG or in any of the hematological and biochemical parameters studied. Metabolic parameters are presented in Table 4. There were no differences in metabolic parameters between groups at either baseline or endpoint, nor between baseline and endpoint in either group.

**DISCUSSION**

In this 15-centre, 6-week, parallel group, randomized controlled trial conducted in Indian outpatients with major depressive disorder that was at least moderate in severity, PB was as effective as sertraline in attenuating depression rating scores on the HAM-D and MADRS. Statistically significant improvement in HAM-D and MADRS scores were evident at the end of 2 weeks of treatment, itself. The response (90%) and remission (70%) rates with PB were high, and were comparable with those achieved with sertraline (92% and 75%, respectively). PB was very well tolerated and was associated with significantly less nausea and headache than sertraline; in contrast, no adverse event occurred at a greater frequency with PB relative to sertraline. PB did not adversely affect heart rate, blood pressure, hematological measures, biochemical measures, metabolic measures, and the EKG. These data confirm in Indian patients the favorable results obtained for PB in the Phase III regulatory trials conducted in the North American and European continents.\(^{[8-11]}\)

The recommended dosing range of PB is 75-300 mg/day, as identified in the Phase III clinical trials.\(^{[8-11]}\) It is noteworthy that, in this Indian study, the mean endpoint dose was 250 mg/day; that is, towards the higher end of the dosing range. Despite the administration of these higher doses, PB was tolerated as well as or better than sertraline. PB therefore appears to be a useful addition to the therapeutic armamentarium for the treatment of major depressive disorder in Indian patients.

**SUMMARY**

This is the first RCT of PB in Indian patients with major depressive disorder. PB is effective and well tolerated, and is as safe and effective as sertraline in this regard.

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**REFERENCES**

No references are cited because this paper, which describes a fictitious study of a fictitious drug, was prepared specifically for the purpose of discussion in the companion article (published in this issue of the *Indian J Psychiatry*) on how to design and conduct RCTs, and how to write, read, and review papers on RCTs in psychiatry.