

ORIGINAL ARTICLE

Olanzapine and fluoxetine combination in severe or resistant depression

R.M. HARIDAS, S.R. PARKAR, RAM GHULAM, GAUTAM AMIN, K.G. THOMBRE, A. SRIVASTAVA, N. BHUVANESHWARI, S. TELANG, MONIKA OBRAH, NANDKISHORE TORASKAR, R.K. JALALI, KIRAN V. MARTHAH

ABSTRACT

Objective : The purpose of this study was to investigate the efficacy and safety of Fixed Dose Combination (FDC) of olanzapine 5 mg and fluoxetine 20 mg in Indian patients with severe or treatment resistant depression.

Design : This was an open, non-comparative study of seven weeks duration with an initial placebo run in period of one week.

Method : One hundred and fifty three patients were enrolled. One hundred and forty-four patients completed the study as per protocol and 151 patients were safety evaluable. One hundred and eleven patients (77%) received one tablet of FDC of olanzapine 5 mg / fluoxetine 20 mg once daily for 6 weeks, in patients (14%), the dose was stepped up at the end of 2 weeks to 2 tablets of FDC of olanzapine 5 mg/ fluoxetine 20 mg once daily for a further 4 weeks and 13 patients (9%) required dose to be stepped up at the end of 4 weeks to 3 tablets of FDC of olanzapine 5 mg and fluoxetine 20 mg once daily for last 2 weeks.

Results : One hundred and thirty four patients (93%) responded to FDC of olanzapine and fluoxetine therapy (a responder was defined as a patient with 50 % reduction over baseline in HDRS total score at the end of therapy). Statistically significant ($p < 0.0001$) reductions in HDRS total score, MADRS total score and CGI severity scores were seen with olanzapine/ fluoxetine combination. One hundred and four patients (72%) were remitters (HDRS total score of < 7) after 6 weeks of therapy.

Adverse experiences were reported by thirty one patients (20.5%). Majority of them were mild in intensity. No serious adverse event was recorded with study therapy. Three patients were withdrawn from the therapy due to adverse event.

Conclusion : Treatment with FDC of olanzapine 5 mg / fluoxetine 20 mg was highly effective and well tolerated in Indian patients with severe or treatment resistant depression.

Key words: Olanzapine, Fluoxetine, Severe depression

INTRODUCTION

Current antidepressant treatments do not help every patient with depression. Up to 30 percent of patients with major depressive disorder are resistant to conventional antidepressant treatment (Roose et al, 1986; Amsterdam & Harrig-Rohan, 1996; Fawat

1994). Treatment resistant depression, commonly defined as the failure to respond to two or more treatment trials with medication from different pharmacological classes (Nirenberg & Amsterdam, 1990), is a routinely encountered disorder often associated with severe functional impairment, morbidity and delayed recovery.

Medical therapy for such resistant disorders, include combinations of antidepressants or various augmentation strategies such as combined antidepressant-antipsychotic approach. Antipsychotic agents may exhibit antidepressant activity, either alone or in combination with an antidepressant ((Robertson & Trimble 1982), particularly in depression with psychotic features (Wolfersdorf et al, 1995; Rothchild et al, 1993; Wolfersdorf et al, 1994; Spiker, 1985). However, widespread application of augmentation with typical antipsychotics has been largely precluded by the high risk of extra pyramidal symptoms and/or tardive dyskinesia (Jeste & Caligiuri, 1993; Casey, 1993). In contrast novel antipsychotic agents such as olanzapine exhibit a substantially lower risk of extrapyramidal symptoms and tardive dyskinesia (Tollefson et al, 1997; Teran et al, 1997).

The aim of this study was to assess the efficacy and tolerability of FDC of the atypical antipsychotic agent olanzapine in combination with the selective serotonin reuptake inhibitor antidepressant agent fluoxetine in Indian patients suffering from severe or resistant depression.

MATERIAL AND METHODS

Study design

This was an open, non-comparative study with a placebo run in period of 1 week, followed by active treatment period of two weeks at the end of which the dose was to be stepped up if clinically indicated. However, patients not on antidepressants for 1 week before study entry were to enter the active treatment phase without having to go through placebo run-in period.

Each patient was to receive active treatment for six weeks at the initial (one tablet of FDC of olanzapine 5 mg and fluoxetine 20 mg once daily) or stepped up (two or three tablets of FDC of olanzapine 5 mg and fluoxetine 20 mg once daily) dose level.

Inclusion criteria

Patients of either sex, aged 18-60 years, fulfilling Diagnostic and Statistic Manual IV (DSM-IV) Diagnostic Criteria for Major

Depression and having severe depression [a total score of 20 or more on Hamilton Depression Rating Scale (HDRS)] or resistant depression [defined as failure to respond to antidepressants of two different classes (one of which is not an SSRI) after at least 4 weeks of therapy at acceptable therapeutic dose].

Exclusion criteria

Patients with a primary psychiatric disorder other than depression; patients with history of psychosis, dysthymic disorder or bipolar disorder; patients posing a serious suicide risk or severely retarded patients; patients with a baseline HDRS total score of <20; patients with a history of alcohol or drug dependence (except nicotine) in the last six months; pregnant or breast feeding women; patients with a history of hypersensitivity to olanzapine and/or fluoxetine.

Efficacy and safety variables

Hamilton Depression Rating Scale (HDRS) and Montgomery Asberg Depression Rating Scale (MADRS) were used to measure drug efficacy. The 17-items in HDRS were depressed mood, guilt feelings and self depreciation, suicidal impulses, initial insomnia, middle insomnia, late insomnia, work and interests, retardation, agitation, psychic anxiety, somatic anxiety, gastrointestinal symptoms, general somatic symptoms, sexual interests, hypochondriasis, loss of insight and weight loss. Apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, suicidal thought and pessimistic thoughts were the 10-items in MADRS.

Severity of illness and global improvement was measured on the Clinical Global Impression (CGI) scale.

Safety variables were assessed by recording adverse events as to their type, severity and causal relationship to therapy.

Statistical Analysis

The change from baseline in the total HDRS, HDRS Item No. 1 (depressed mood) score, total MADRS score and the CGI

severity score were analyzed using Wilcoxon's Signed Rank Test. Alpha was set at 0.05. Proportion of responders defined as 50% reduction over baseline in total HDRS score and proportion of remitters (total HDRS score of <7) after 6 weeks of therapy with FDC of olanzapine and fluoxetine has also been reported. Patients who had at least one post therapy evaluation were considered in intent-to-treat analysis. All patients who did not complete entire duration of study but included in intent-to-treat analysis were considered as non-responders.

RESULTS

Demographic Data

The demographic profile of patients entering the study is illustrated in Table 1. One hundred and fifty three patients (54% male and 46% female) enrolled in this study had a mean age of 35.8 years and mean body weight 56.6 kgs.

At the end of study 144 patients were evaluated for efficacy by per protocol analysis and 151 patients for intent-to-treat and safety analysis.

TABLE 1 : Summary of patient demographics

Total Number of Patients	153
Sex M/F (% of patients)	54/46
Age (years)	
Mean + SD	35.8 ± 9.3
Range	18 - 56
Weight (kg.)	
Mean + SD	56.6 ± 10.7
Range	34 - 85

TABLE 4 : Cumulative Response to FDC of Olanzapine and Fluoxetine as per last dose sequence (Per protocol population) (n=144)

Treatment	No.(%) of responders (≥50% reduction in total HDRS score)
FDC of Olanzapine 5 mg and Fluoxetine 20 mg	
Response to one tablet o.d.	109/144 (76%)
Cumulative response to two tablets o.d.	127/144 (88%)
Cumulative response to 3 tablets o.d	134/144 (93%)

Dosage and Duration of treatment

One hundred and eleven patients (77%) received one tablet of FDC of olanzapine 5 mg / fluoxetine 20 mg once daily for 6 weeks, in 20 patients (14%), the dose was stepped up at the end of 2 weeks to 2 tablets of FDC of olanzapine 5 mg/ fluoxetine 20 mg once daily for a further 4 weeks and 13 patients (9%) required dose to be stepped up at the end of 4 weeks to 3 tablets of FDC of olanzapine 5 mg and fluoxetine 20 mg once daily for last 2 weeks (Table 2).

TABLE 2 : Dosage and Duration of Treatment (Per protocol population) [n=144]

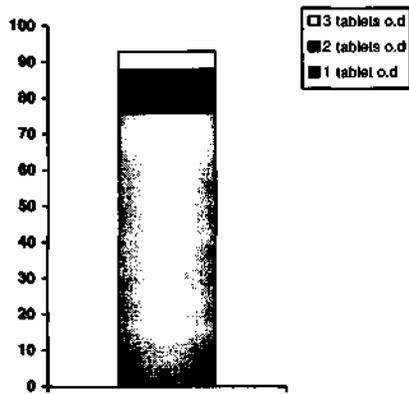
Treatment	No. (%)of patients
FDC of Olanzapine 5 mg and Fluoxetine 20 mg	
One tablet o.d. for 6 weeks	111 (77%)
One tablet o.d. for 2 weeks followed by 2 tablets o.d. for 4 weeks	20 (14%)
One tablet o.d. for 2 weeks, 2 tablets o.d. for next 2 weeks followed by 3 tablets o.d. for last 2 weeks	13 (9%)

TABLE 3 : Clinical Response to FDC of Olanzapine and Fluoxetine (>50% reduction over baseline in HDRS total score)

Population	Percent of responders
Intent-to-treat (n=151)	89%
Per protocol (n=144)	93%

TABLE 5 : Proportion of Remitters (HDRS total score < 7)

Population	Percent of remitters
Per-protocol (n=144)	72%



(Fig. 1)

Cumulative Response *Rate to FDC of Olanzapine 5 mg and Fluoxetine 20 mg (Per-protocol population)

* 50% reduction over baseline in HDRS total score

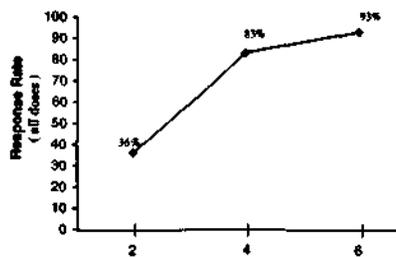


Figure 2.

Clinical Response *Rate to FDC of Olanzapine 5 mg and Fluoxetine 20 mg (Per-protocol population)

* 50% reduction over baseline in total HDRS score

Clinical Efficacy

The proportion of responders (reduction of 50% over baseline in HDRS total score) in the intent-to-treat and per protocol population is depicted in Table 3. The response rate was 89% in the intent-to-treat population and 93% in the per protocol population.

The clinical response at each dosage level of FDC of olanzapine 5 mg and fluoxetine

TABLE 6 : Summary of depression scores (mean + SD) at baseline and final visit in patients treated with FDC of Olanzapine and Fluoxetine (All doses - Per protocol population)[n=144]

Parameter	Mean +SD Scores
HDRS (total)	
Baseline	29.27 ± 5.46
Mean decrease	23.75 ± 6.86
Percentage decrease	81.36 ± 19.35
p-value*	<0.01
HDRS Item No. 1(Depressed mood)	
Baseline	3.17 ± 0.67
Mean decrease	2.42 ± 0.88
Percentage decrease	76.62 ± 24.29
p-value*	< 0.01
MADRS (total)	
Baseline	31.02 ± 6.38
Mean decrease	26.12 ± 7.49
Percentage decrease	84.55 ± 18.16
p-value*	< 0.01
CGI Severity	
Baseline	4.00 ± 0.64
Mean decrease	2.95 ± 1.11
Percentage decrease	73.53 ± 24.38
p-value*	< 0.0001
CGI Improvement**	
Final visit	0.51 ± 0.74

*p < 0.05 is statistical significant.

**Smaller positive values for this variable indicate greater improvement; the score is given only for assessment at the final visit.

TABLE 7 : Adverse Events (No. and % of patients) [n=151]

Adverse Events (AEs)	No. (%) of patients
Somnolence	15 (9.9%)
Dizziness	6 (4.0%)
Tremor	5 (3.3%)
Headache	4 (2.6%)
Insomnia	4 (2.6%)
Nausea	4 (2.6%)
Anorexia	3 (2.0%)
Akathisia	2 (1.3%)
Sweating, diarrhoea, hypomania, extrapyramidal syndrome, urticaria, dry mouth, asthenia, chest pain, constipation, flatulence, retrosternal burning.	1 (0.7%) each
Total AEs	54
Total No. of patients with AEs	31/151 (20.5%)

TABLE 8 : Patients withdrawn from the study due to Adverse Events

Patient Code	Description of AEs	Intensity	Relation to treatment
02020	Hypomania	Mild	Probable
	Akathisia	Moderate	Probable
07015	Chest pain	Severe	Not related
08001	Somnolence	Moderate	Possible
	Constipation	Mild	Probable
	Anorexia	Mild	Possible
	Dizziness	Mild	Unrelated

20 mg is shown in Table 4 and Fig. 1.

Clinical response (>50% reduction over baseline in total HDRS score) was seen within 2 weeks in 36% of patients, within 4 weeks in 83% patients and within 6 weeks in 93% of patients treated with FDC of olanzapine and fluoxetine (Fig. 2).

One hundred and four patients (72%) in the per protocol population had HDRS total score of <7 after 6 weeks of treatment with FDC of olanzapine and fluoxetine and were considered as remitters (Table 5).

Table 6 summarizes the results of analysis of the HDRS total score, HDRS Item No. 1 (depressed mood) score, MADRS total score, CGI severity and improvement scores in the evaluable population. All the efficacy variables showed statistically significant decrease ($p < 0.01$) at the end of treatment.

Adverse Events

One hundred and fifty one patients were safety evaluable. Adverse events were reported by 31 patients (20.5%) [Table 7]. Of these 31 patients, 18 were receiving treatment with one tablet of FDC of olanzapine 5 mg and fluoxetine 20 mg, 6 with two tablets of olanzapine 5 mg/fluoxetine 20 mg and 7 with three tablets of FDC of olanzapine 5 mg and fluoxetine 20 mg. Somnolence was the most frequent adverse event reported by 15 patients (10%). Majority of adverse events were mild in intensity. Three patients were withdrawn because of adverse events (Table 8). All adverse events resolved satisfactorily.

DISCUSSION

Major depression is one of the most common mental illnesses. The high prevalence of depressive illness and its associated morbidity, mortality and economic consequences call for more effective and better tolerated treatments. Tricyclic agents (TCAs) have been the cornerstone of antidepressant therapy for many years but despite their undoubted efficacy, they have a non-selective mechanism of action. They affect reuptake of noradrenaline and serotonin, interact with several receptor subtypes (e.g., alpha adrenoreceptors, muscarinic and histamine H_1 -receptors) and are associated with unwanted anticholinergic, central nervous system and cardiovascular effects which limit their use particularly in elderly patients and in those with cardiac disease. Similarly, monoamine oxidase inhibitors (MAOIs) are effective in the treatment of depression but have a poor tolerability profile and the older agents (e.g., phenelzine, tranylcypromine) require dietary restriction to avoid hypertensive crisis. In the past decade, options for the treatment of depression were considerably increased with the introduction of selective serotonin reuptake inhibitor's (SSRIs). The SSRIs have comparable efficacy against depression but have an improved side effect profile. In clinical trials, compared with TCAs, SSRI have been associated with fewer adverse effects, particularly cardiovascular effects and a better safety profile in overdose. However, approximately 30 to 40% of patients with depression fail to respond to

treatment with a single antidepressant agent.

Subsequent medical therapy may include combinations of antidepressants or various augmentation strategies such as a combined antidepressant- antipsychotic approach. Atypical antipsychotic agents, such as olanzapine, cause fewer extrapyramidal adverse effects than conventional antipsychotics and has been shown to be an advantageous augmentation strategy for treatment-resistant depression. Olanzapine/fluoxetine combination treatment has shown a significantly higher rate of response than monotherapy with olanzapine or fluoxetine (Shelton et al, 2001). In clinical studies (World Psychiatric Congress, 2000), olanzapine/fluoxetine combination patients showed numerically greater improvement on the Hamilton Depression Scale (HDRS) and statistically greater improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) than either monotherapy. Additionally, olanzapine plus fluoxetine was associated with a statistically significant greater proportion of patients showing a >50% improvement on the MADRS. There were no significant differences between groups for extrapyramidal symptoms or significant adverse drug events. Further using MADRS for evaluation, meta-analysis of two double blind studies involving 797 subjects diagnosed with non-psychotic, unipolar, treatment-resistant depression showed that olanzapine/fluoxetine combination patients achieved significantly greater total score improvement (-7.31) at week 1 than olanzapine subjects (-5.18, $p = 0.013$) or fluoxetine subjects (-5.26, $p = 0.004$). This significant effect abided during eight weeks of treatment (endpoint: olanzapine/fluoxetine combination -11.60, olanzapine -7.55, $p < 0.01$; fluoxetine -8.73, $p < 0.01$).

The present study was conducted to test the efficacy of olanzapine and fluoxetine in treatment of Indian patients with severe or resistant depression. One hundred and eleven patients (77%) received treatment with one tablet of FDC of olanzapine 5 mg and fluoxetine 20 mg once daily for 6 weeks; in 20 patients (14%) the dose was stepped up to 2 tablets (i.e., olanzapine 10 mg/fluoxetine 40 mg) once a day and in 13 patients (9%) the dose required further to be stepped up to 3 tablets (i.e., olanzapine

15 mg/ fluoxetine 60 mg) per day. A cumulative response rate of 89% (in the intent-to-treat population) was achieved at the end of 6 weeks of therapy. The drug was well tolerated; 2% of patients had to discontinue therapy with FDC of olanzapine and fluoxetine due to adverse events.

It appears that combined administration of olanzapine and fluoxetine results in pharmacodynamic synergy and a neurochemical basis for the synergistic antidepressant effect has been suggested (Shelton et al, 2001).

CONCLUSION

FDC of olanzapine 5 mg and Fluoxetine 20 mg once daily may be an effective and safe for the treatment of patients with severe or treatment resistant depression.

Declaration of Interest : This study is sponsored by a grant from Ranbaxy Laboratory Ltd.

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R.M. HARIDAS, Prof. and Head, Dept. of Psychiatry, Sir JJ Group of Hospitals, Mumbai
 S.R. PARKAR, Prof. and Head, Dept. of Psychiatry, Seth GS Medical College and KEM Hospital, Mumbai
 RAM GHULAM, Associated Professor and Head, Dept. of Psychiatry and Superintendent, Mahatma Gandhi Medical College, Indore
 GAUTAM AMIN, Consultant Psychiatrist and Psychotherapist, Dr. Contractor's Hospital, Vadodara
 K.G. THOMBRE, Consultant Psychiatrist, Ramprasad Chambers, Nana Peth, Pune
 A. SRIVASTAVA, Asst. Prof. of Psychiatry, Deccan College of Medical Sciences and Owaisi Hospital, and Research Centre, Hyderabad
 N. BHUVANESHWARI, Prof. of Psychiatry, Gandhi Hospital, Secunderabad
 S. TELANG, Consultant Psychiatrist, Jehangir Hospital and Medical Centre, Pune
 MONIKA OBRAH, Clinical Research Associate, MACR, Ranbaxy Laboratories Ltd.
 NANDKISHORE TORASKAR, Senior Research Scientist, Clinical Data Management, Ranbaxy Laboratories Ltd.
 *R.K. JALALI, Associate Director - MACR, Ranbaxy Laboratories Ltd.
 KIRAN V.MARTHAK, Vice President - MACR, Ranbaxy Laboratories Ltd.

*Correspondence