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Ritanserin as an adjunct to lithium and haloperidol for the treatment of medication-naive patients with acute mania: a double blind and placebo controlled trial

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Abstract

Background: Bipolar disorder is a lifelong episodic condition characterized by mood swings between mania and depression. Several lines of evidence suggest that serotonin is likely to play a pivotal role in the pathophysiology of bipolar disorder. Ritanserin, a 5-HT_2 receptor antagonist, has been reported to have antipsychotic activity. In this 6-week double blind, placebo controlled study involving moderate to severe manic patients, we assessed the effects of ritanserin plus haloperidol in combination with lithium.

Methods: 45 patients aged between 21–43 were eligible to participate as they met the DSM-IV criteria for a current manic episode, on the basis of a clinical interview by an academician psychiatrist. In addition, a score of at least 20 points on the Young Mania rating Scale was required representing moderate to severe mania. Patients were randomly allocated lithium (1–1.2 mEq/L) + haloperidol (10 mg/day)+ ritanserin (10 mg/day) (Group A) or lithium (1–1.2 mEq/L)+ haloperidol (10 mg/day) + placebo (Group B) for a 6-week, double-blind, placebo-controlled study. Patients were assessed by a third year psychiatry resident at baseline and 3, 7, 14, 21, 28 and 42 days after the medication started. All patients entered the hospital were not previously under any medication. The mean decrease in the Young Mania Rating Scale score from baseline was used as the main outcome measure of response of mania to treatment. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale. Side effects were systematically recorded throughout the study and were assessed using a checklist.

Results: Young Mania Rating Scale total scores improved with ritanserin. The difference between the two protocols was significant as indicated by the effect of group and the between-subjects factor ($F = 5.02$, d.f. = 1, $P = 0.03$). The means Extrapyramidal Symptoms Rating Scale scores for the placebo group were higher than the ritanserin group and the difference was significant in day 42. The difference between the two groups in the frequency of side effects was not significant

Conclusions: The efficacy of ritanserin to obtain a better improvement in patients with mania seems to support the 5-HT hypothesis of bipolar disorder.

Background

Bipolar disorder is a lifelong episodic condition characterized by mood swings between mania and depression. The lifetime prevalence of bipolar disorder to be 0.8. The 1 month point prevalence for bipolar disorder has been estimated as 0.4%. Acute manic episodes can have devastating consequences [1]. Management of acute mania is directed at rapidly controlling the irritability, agitation, impulsivity, aggression, and psychotic symptoms that characterize the hyperaroused state in manic and mixed episodes. It is recognized that in the clinical treatment of mania, a substantial number of patients do not respond or are partial respondents to therapy, and hence, have a poor outcome. Lithium remains the first line-choice treatment for patients with mania. However, nearly half of patients with mania fail to respond to lithium. In fact, failure rates as high as 72% to 80% have been reported for those treated with lithium [2]. Because rapid control of acute mania is desired, adjunctive agents, including combination of two mood stabilizers or of a mood stabilizer with an antipsychotic agent, are widely used [3]. Typical neuroleptics have been suggested to be superior in efficacy to lithium monotherapy. However, they do not have a large role in maintenance therapy, though, because of side effects such as extrapyramidal symptoms and tardive dyskinesia [4–6]. Atypical antipsychotics such as risperidone and olanzepine have also been used to treat bipolar disorder. Initial reports suggest that risperidone and olanzepine, when combined with mood-stabilizing agents, exhibits mood stabilizing or antimanic activity [7].

Several lines of evidence suggest that serotonin is likely to play a pivotal role in the Pathophysiology of bipolar disorder. The significant observation on which this hypothesis is base are: (1) absolute levels of the 5-HT metabolites (5-HIAA) are reduced in CSF of depressed bipolar patients and raised in mania. (2) 5-HT transport is reduced in platelets of depressed bipolar patients as well as platelets of bipolar patients in manic phase [8]. A rapidly growing body of data suggests that dysfunction in serotonergic functions may be involved in the pathophysiology of schizophrenia and bipolar disorder [8,9], and that pharmacological agents for these illnesses have their therapeutic effects mediated through serotonergic mechanisms. One of the first indications that 5-HT2 receptor antagonists may possess antipsychotic potential came from Ceulemans et al who found setoperone to be effective in reducing autistic behavior, dysphoric mood, hallucination and EPS [10]. Ritanserin a 5-HT_2 receptor antagonist has been reported to have antipsychotic activity [11].

In several double-blind, placebo-controlled studies, the efficacy of ritanserin and cyproheptadine were evaluated in the treatment of schizophrenia [11,12]. In add-on protocol, ritanserin and cyproheptadine were effective in concurrent treatment of negative symptoms and reduction of EPS. Beneficial effects of Ritanserin have also been demonstrated in antipsychotic-induced akathisia or when compared with anticholinergic agents. The efficacy of Ritanserin with its pharmacological profile as a 5-HT_2 antagonist is line with 5-HT hypothesis of schizophrenia [13–18].

Therefore, in this 6-week double blind, placebo controlled study involving moderate to severe manic patients, we assessed the effects of ritanserin plus haloperidol in combination with lithium. To our knowledge, this study is the first clinical trial assessing the adjunctive role of ritanserin in the management of mania

Methods

Trial organization

This was a 6 week, parallel group, placebo controlled trial undertaken in Roozbeh Psychiatric Hospital, Tehran, Iran during January 2002-January 2003.

Participants

Eligible participations were 45 in patient, age between 21–43 years old and met DSM-IV criteria for a current manic episode, on the basis of a clinical interview by an academician psychiatrist. In addition, a score of at least 20 points on the Young Mania rating Scale [19] was required representing at least a moderate to severe mania. Mental retardation, neurological or other medical impairment, the need for ongoing treatment with other psychoactive medications, and/or current substance dependence, seizure disorder requiring medication, participation in an investigational drug trial within 30 days before the start of the trial, known sensitivity to haloperidol, lithium or ritanserin, use of clozapine within 1 month before study entry; use of depot neuroleptics within one cycle before study entry, laboratory values outside the normal range, women of childbearing potential who were without adequate contraception were exclusionary criteria. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences. Written informed consents were obtained before entering into the study.

Study design

All patients entered the hospital untreated with any medications. Patients were randomly allocated 23 to lithium + haloperidol+ ritanserin (Group A) or lithium + haloperidol + placebo (Group B) for a 6-week, double-blind, placebo-controlled study. Two patients from group A and one from group B dropped out from the study leaving 42 patients who met the DSM-IV criteria for manic episode. Rapid titration of lithium to therapeutic level 1–1.2 mEq/L was facilitated by the use of the pharmacokinetic method of predicting a therapeutic dose. Weekly lithium levels were obtained for compliance monitoring. Adjunctive antipsychotic medication that was haloperidol and was started simultaneously with lithium. The dose of haloperidol was titrated up to 10 mg/day. A fixed dose of ritanserin 10 mg/day was used throughout the study. Concomitant lorazepam use was restricted to a maximum dose of 2 mg/day for the first 4 days of treatment and thereafter by up to 1 mg/day for the next 6 days. Lorazepam was not permitted beyond the initial 10 days and was not allowed within 8 hours of the administration of mania rating scale. Biperiden was permitted to treat extrapyramidal symptoms up to a maximum of 6 mg/day throughout the course of the study. Biperiden was not allowed as prophylaxis for extrapyramidal symptoms. Patients were assessed by a third year resident of psychiatry at baseline and after 3, 7, 14, 21, 28 and 42 days after the medication started. Patients were hospitalized throughout the study.

Outcome

The principal measure of the outcome was the Young Mania Rating Scale. The rater used standardized instructions in the use of Young Mania Rating Scale. The mean decrease in Young Mania Rating Scale score from baseline was used as the main outcome measure of response of mania to treatment. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) [20]. Patients were randomized to receive ritanserin or placebo in a 1: 1 ratio using a computer generated code. The assignments were kept in sealed, opaque envelopes until the point of allocation.

Side effects

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on day 3, 7, 14, 21, 28 and 42 (Table 3).

Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the seven measurements during treatment as the within-subjects factor (time) were considered. This was done for Young Mania Rating Scale scores. In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison tests were performed on the change Mania Rating Scale scores from baseline. To compare the reduction of score of Young Mania Rating Scale at week 6 compared to baseline and ESRS score in different days an unpaired two-sided Student's t-test was used. Results are presented as mean ± SD differences and were considered significant with $P = 0.05$. To compare the baseline data and frequency of side effects between the protocols, Fisher's exact test was performed. A traditional "observed cases" (OC, the patients who completed the trial) analysis in 42 days was the primary efficacy analysis. In addition, intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure was also performed. All results discussed are based on OC analysis unless otherwise stated.

Results

65 patients were screened for the study. Twenty patients were excluded before or during run in due to exclusion criteria and 45 were randomized to trial medication. No significant differences were identified between patients randomly assigned to the group A or B condition with regard to basic demographic data including age and gender (Table 1). In addition, there were no significant differences in terms of duration of illness and number of hospitalization in the both groups. 42 patients completed the trial. In the group A and B the number of dropouts were 2, and 1, respectively (Figure 1).

Ritanserin vs placebo

The mean ± SD scores of two groups of patients are shown in Figure 2. There were no significant differences between the two groups in day 0 (baseline) on the Young Mania rating Scale ($t = 0.81$, d.f. = 43, $P = 0.81$). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor ($F = 5.02$, d.f. = 1, $P = 0.03$; $F = 5.11$, d.f. = 1, $P = 0.029$ for OC and LOCF respectively). The behavior of the two treatments was homogeneous across the time (groups-by-time interaction, Greenhouse-Geisser correction; $F = 1.71$, d.f. = 2.85, $P = 0.17$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the Young Mania rating Scale ($P < 0.0001$). In both groups post-hoc comparisons showed a significant change from day 3 on the Young Mania rating Scale. The difference between the two protocols was significant at the endpoint (day 42) ($t = 3.56$, d.f. = 40, $P < 0.001$). The changes at the endpoint compared to baseline were: -22 ± 4.47 (mean ± SD) (the baseline score was 25.38 ± 3.17) and -19.33 ± 5.06 (the baseline score was 26 ± 3.58) for group A and B respectively. A significant difference was observed on the change of scores of the Young Mania

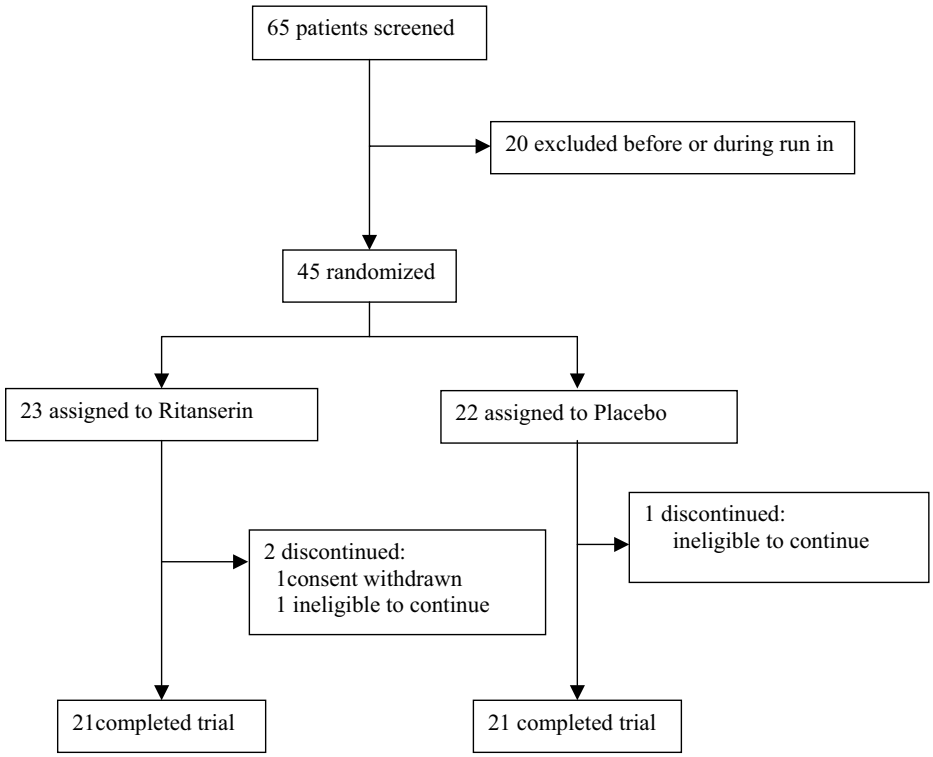

Figure 1 Trial profile

Figure 1
Trial profile

Table 1: Baseline data

	Lithium+Haloperidol+Ritanserin	Lithium+Haloperidol+Placebo	P
Age (mean ± SD)	29.69 ± 6.03	28.22 ± 6.10	0.42
Gender	Male: 14, Female: 9	Male: 15, Female: 7	0.75

Table 2: Extrapyramidal symptoms based on Extrapyramidal Symptoms Rating Scale

	Mean ± SEM Lithium + Haloperidol+ Ritanserin	Mean ± SEM Lithium + Haloperidol+ Placebo	P
Day 0	1.70 ± 0.17	1.80 ± 0.44	0.83
Day 3	2.30 ± 0.44	2.35 ± 0.42	0.93
Day 7	2.30 ± 0.20	2.80 ± 0.33	0.21
Day 14	2.65 ± 0.28	3.05 ± 0.40	0.42
Day 21	2.00 ± 0.24	2.85 ± 0.37	0.18
Day 28	1.95 ± 0.22	3.00 ± 0.49	0.059
Day 42	1.50 ± 0.17	3.00 ± 0.39	0.001***

Table 3: Number of patients with side effects

Side Effects	Lithium + Haloperidol + Ritanserin	Lithium + Haloperidol + Placebo	P
Asthenia	10 (47.60%)	7 (33.33%)	0.53
Agitation	8 (38.09%)	13 (61.90%)	0.21
Constipation	5 (23.80%)	6 (28.50%)	1.00
Diarrhea	1 (4.76%)	2 (9.52%)	1.00
Dizziness	9 (42.85%)	6 (28.57%)	0.52
Dry Mouth	12 (57.14%)	15 (71.42%)	0.52
Dyspepsia	6 (28.57%)	5 (23.80%)	1.00
Headache	5 (23.80%)	4 (19.04%)	1.00
Increased Appetite	18 (85.71%)	16 (76.19%)	0.69
Nervousness	8 (38.09%)	12 (57.14%)	0.35
Pain	5 (23.80%)	3 (14.28%)	0.69
Sleep Disorder	6 (28.57%)	4 (19.04%)	0.71
Somnolence	14 (66.66%)	17 (80.95%)	0.48
Vomiting	1 (4.76%)	2 (9.52%)	1.00
Weight Gain	19 (90.47%)	16 (76.19%)	0.40

rating Scale in day 42 compared to baseline in the two groups in ($t = 2.09$, d.f. = 40, $P < 0.042$).

Extrapyramidal Symptoms Rating Scale

The means ESRS for the placebo group were higher than the ritanserin group and the difference was significant in day 42. (Table 2). A not quite significant difference was observed between the overall mean biperiden dosage in the two groups. (106 ± 46.89 and 143 ± 56.18 for group A and B respectively (mean ± SD) ($P = 0.06$).

Clinical complications and side effects

Seventeen side effects were observed over the trial. The difference between the two groups in the frequency of side effects was not significant (Table 3).

Discussion

The present study shows Young Mania Rating Scale total scores improved with ritanserin over this 6-week double blind and placebo controlled trial. In addition, ESRS total scores at endpoint were significantly higher in patients who received only lithium and haloperidol. Total mean antiparkinsonian medication was also higher in this group. There is enough convincing Preclinical and clinical evidence to suggest that 5-HT_{2A} receptor function is altered in patients with bipolar disorder and schizophrenia [8,9]. Serotonin modulation of dopaminergic function via 5-HT_{2A} receptors may provide a viable mechanism for enhancing medications for bipolar disorder and schizophrenia. Therefore, potent 5-HT_{2A} receptor antagonism alone may contribute action of several clinically effective antipsychotics that have a reduced extrapyramidal symptoms liability [8,9,13,14]. The efficacy of ritanserin to obtain a better improvement in patients with mania seems to support this hypothesis.

The limitations of the present study, including the small number of patients should be considered so further research in this area is needed. Finally the results demonstrate that the combination of ritanserin with lithium and a conventional antipsychotic was superior to lithium and conventional antipsychotic alone for the rapid reduction of manic symptoms. The combined use of ritanserin with

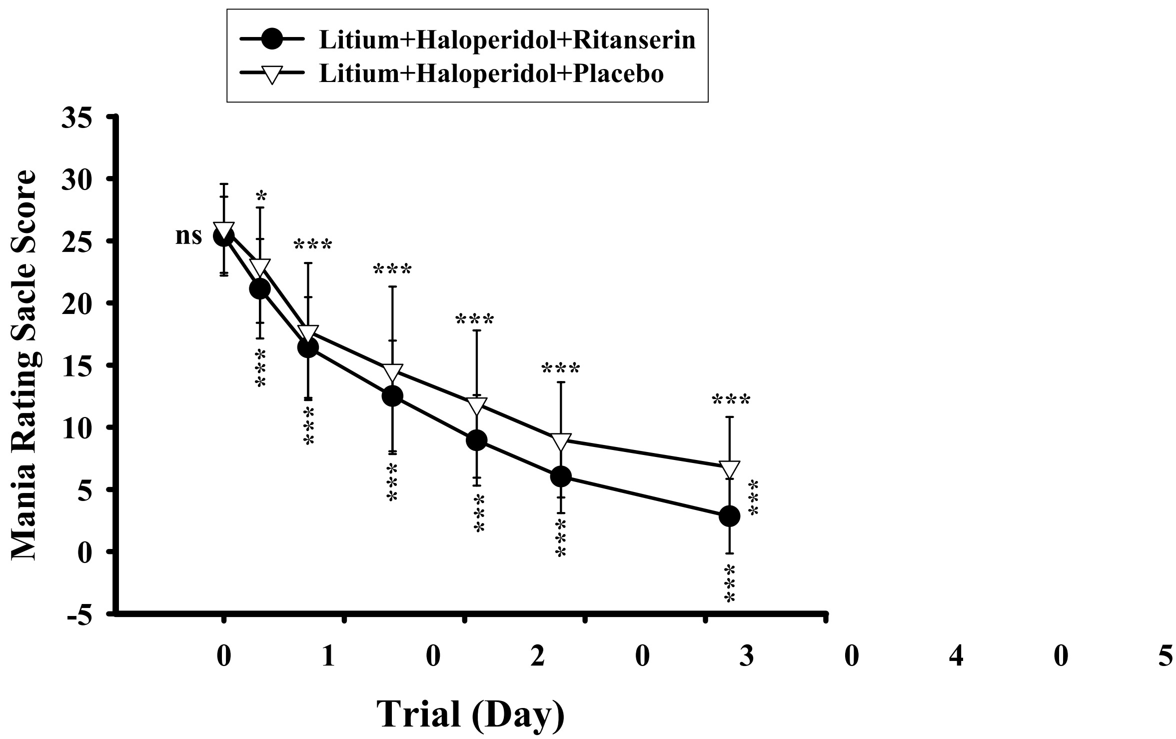

Figure 2
Mean ± SD of the two protocols on the Mania Rating Scale. ns=non-significant, *<0.05 and ***<0.001. Vertical (ritanserin group) and horizontal (placebo group) symbols were used to express statistical significance versus their respective baseline value. In addition, the vertical symbol is for between-subjects comparison at the end point.

lithium and haloperidol was well tolerated in these acutely manic patients.

Competing Interest
None declared.

Authors' contribution
Shahin Akhondzadeh (principal investigator and statistical support, clinical neuropsychopharmacologist).

Mohammad Reza Mohammadi (clinical coordinator, psychiatrist)

Hassan Mohajeri (trialist, resident of psychiatry)

Homayoun Amini (clinical coordinator, psychiatrist)

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