Allopurinol as adjunctive treatment for acute mania in hospitalized bipolar patients

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Objective: Mania is frequently associated with behavioral disturbances that can have serious consequences for patients and those in contact with them. Rapid control is important, even though many patients may be uncooperative. For many, the effectiveness of current treatments for acute bipolar mania is suboptimal. It has been reported that the abnormalities observed during mania seem to be associated with some pathophysiologic changes in the purinergic system. Recently, allopurinol, a hypouricemic agent, has been shown to present therapeutic effects in mania associated with hyperuricemia. The objective of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of allopurinol as an adjunct to lithium and haloperidol for treatment of acute mania in hospitalized bipolar patients. **Methods**: A total of 82 patients between the ages of 8 to 49 years and who met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for a current manic episode, on the basis of a clinical interview by an academician psychiatrist were eligible for the trial. In addition, a score of at least 20 points on the Young Mania Rating Scale was required representing at least a moderate-to-severe mania. A total of 41 patients were randomly allocated to lithium in two groups where Group A: (1–1.2mEq/l) + haloperidol (10 mg/day) + allopurinol (300 mg/day) or Group B: lithium (1–1.2 mEq/l) + haloperidol (10 mg/day) + placebo for a 6-week, double-blind, placebo-controlled study. Patients were assessed by a third year resident of psychiatry at baseline and at 7, 14, 28 and 42 days after the medication started. 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. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale. Side effects were systematically recorded throughout the study and assessed using a checklist. **Results:** Young Mania Rating Scale scores improved with allopurinol. The difference between the two protocols was significant as indicated by the effect of the group, the between-subjects factor ($F = 5.22$; d.f. = 1; $p = 0.02$), thus implying that the mean Extrapyramidal Symptoms Rating Scale scores for the placebo group were higher than the allopurinol group. However, the differences were not significant over the trial. The difference between the two groups in the frequency of side effects was not significant except for agitation that was more often in the placebo group. **Conclusions**: The efficacy of allopurinol to obtain a greater improvement in patients with mania seems to support a purinergic dysfunction in the disorder.

Keywords: adenosine, allopurinol, mania

Bipolar disorder is an episodic illness treated in phases, with each phase presenting its own set of challenges to the treating physician. Mania is frequently associated with behavioral disturbances that can have serious consequences for patients and those around them [1]. Rapid control is important, even though many patients are uncooperative. For many patients, the effectiveness of current treatments for acute bipolar mania is suboptimal [1]. Although lithium, divalproex and olanzepine (US Food and Drug Administration [FDA]-approved treatments for acute mania) show similar efficacy, clinical trials report nonresponder rates of up to 50% with these agents [2–4]. As rapid control of acute mania is desired, adjunctive agents, including a combination of two mood stabilizers or of a mood stabilizer with an antipsychotic agent, are widely used [1]. It has been reported that the abnormalities observed during mania seem to be associated with some pathophysiologic changes in the purinergic system [5]. Indeed, adenosine analogues in rats induce sedation and sleep; whereas a number of adenosine receptor antagonists in the hippocampus, such as caffeine, present behavioral and neuronal stimulant effects. These mania-like stimulant effects of xanthines include changes on motor activity, alertness, performance and

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sleep [6–8]. The purinergic system usually relates to the adenine nucleotides ATP, ADP and AMP and nucleoside adenosine, which have several biologic roles apart from those in energy metabolism [9–12]. Recently, allopurinol, a hypouricemic agent, has been shown to present therapeutic effects in mania associated with hyperuricemia [13]. The neuropsychiatric effects of allopurinol in refractory epilepsy and aggressive behavior have been suggested to be secondary to the inhibitory effect of purine degradation, enhancing adenosinergic activity [5,14].

With these considerations in mind, the aim of this double-blind, placebo-controlled study was to investigate the efficacy and tolerability of allopurinol as an adjunct to lithium and haloperidol for treatment of acute mania in hospitalized bipolar patients. To our knowledge, this study is the first clinical trial assessing the adjunctive role of allopurinol in the management of mania.

Patients & methods

Trial organization

This was a 6-week, parallel-group, placebo-controlled trial undertaken in Roozbeh Psychiatric Hospital, Tehran, Iran from October 2003 through September 2004.

Participants

Eligible participations were 82 inpatients, aged between 19 and 49 years old and they met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [15] 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 (YMRS) [16] was required representing at least a moderate-to-severe mania. Neurologic or other medical impairment, the need for ongoing treatment with other psychoactive medications, and/or current substance dependence, mental retardation (intelligence quotient [IQ] < 70), history of renal or liver function impairments, history of allergic reactions to allopurinol, 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 allopurinol, 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 [101] and subsequent revisions and approved by ethics committee at Tehran University of Medical Sciences. Written informed consents were obtained prior to entering into the study.

Study design

Patients were randomly allocated 41 to lithium + haloperidol + allopurinol (Group A) or lithium + haloperidol + placebo (Group B) for a 6-week, double-blind, placebo-controlled study. Rapid titration of lithium to a 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. Haloperidol was the concomitant antipsychotic in this trial and was started simultaneously with lithium. The dose of haloperidol was titrated up to 10 mg/day. A fixed dose of allopurinol 300 mg/day (three-times daily) 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 h of the administration of mania rating scale. Biperiden was permitted to treat extrapyramidal symptoms up to a maximum of 4 mg/day throughout the course of the study. Patients were assessed by a third year resident of psychiatry at baseline and at 7, 14, 28 and 42 days after the medication started. Patients were hospitalized throughout the study.

Outcome

The principal measure of the outcome was the YMRS. The rater used standardized instructions in the use of YMRS. The mean decrease in YMRS score from baseline was used as the main outcome measure of response of mania to treatment. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) [17]. Patients were randomized to receive allopurinol 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.

Safety measures

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 1**). Laboratory tests obtained included a complete blood cell count with differential, liver and renal-function tests.

Table 1. Number of patients with side effects.

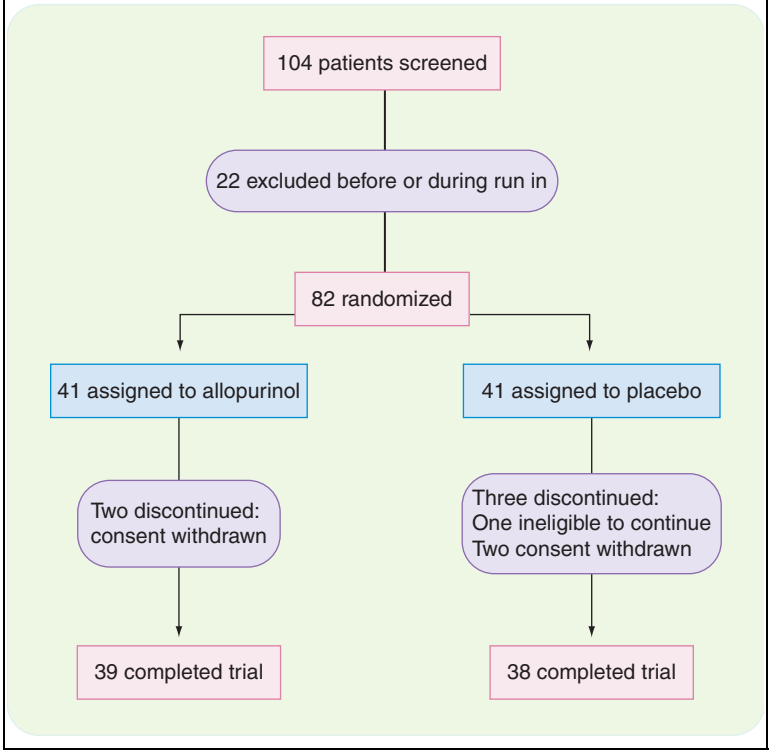
Side effects	Lithium + haloperidol + allopurinol	Lithium + haloperidol + placebo	p
Asthenia	13 (31.70%)	8 (19.51.33%)	0.31
Agitation	16 (39.02%)	26 (63.41%)	0.04*
Constipation	10 (24.39%)	12 (29.26%)	0.80
Diarrhea	2 (4.87%)	3 (7.31%)	1.00
Dizziness	14 (34.14%)	10 (24.39%)	0.46
Dry mouth	23 (56.09%)	27 (65.85%)	0.49
Dyspepsia	12 (29.26%)	10 (24.39%)	0.80
Headache	11 (26.82%)	9 (21.95%)	0.79
Increased appetite	28 (68.29%)	24 (58.53%)	0.49
Nervousness	16 (39.02%)	21 (51.21%)	0.37
Pain	10 (24.39%)	6 (14.63%)	0.40
Sleep disorder	12 (29.26%)	8 (19.51%)	0.44
Somnolence	27 (65.85%)	33 (80.48%)	0.21
Vomiting	2 (4.87%)	4 (9.75%)	0.67
Weight gain	35 (85.36%)	33 (80.48%)	0.77

** Significant result.*

Statistical analysis

A two-way repeated measures ANalysis Of VAriance (ANOVA, time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the four measurements during treatment as the within-subject factor (time) were considered. This was carried out for YMRS scores. In addition, a one-way repeated measures ANOVA with a two-tailed *post hoc* Tukey mean comparison test was performed on the change Mania Rating Scale scores from baseline. To compare the reduction of the score of YMRS at week 6 with baseline and ESRS score in different days, an unpaired two-sided Student's t-test was carried out. Results are presented as mean ± standard deviation (SD) differences and were considered significant with $p \leq 0.05$. To compare baseline data and frequency of adverse events between the protocols, Fisher's exact test was performed. Intention-to-treat (ITT) analysis with last observation carried forward (LOCF) procedure was carried out.

Figure 1. Trial profile.



Results

Initiatlly 104 potential study candidates were identified. However, 22 patients did not meet study inclusion and exclusion criteria. Therefore, 82 bipolar patients were randomized into this study. Two patients from the allopurinol group and three from the placebo group dropped out from the study leaving 77 patients who met the DSM-IV criteria for manic episode (**Figure 1**). 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 2). In addition, there were no significant differences in terms of duration of illness and number of hospitalizations in both groups.

Allopurinol vs placebo

The mean ± standard deviation (SD) scores of two groups of patients are shown in Figure 2. There were no significant differences between the two groups at day 0 (baseline) on the YMRS (t = 0.82; d.f. = 80; p = 0.41). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor (F = 5.22; d.f. = 1; p = 0.02. The behavior of the two treatments was not homogeneous across the time (groups-by-time interaction, Greenhouse–Geisser correction; F = 3.00; d.f. = 2.18; p = 0.04). In addition, a one-way repeated measures ANOVA showed a significant effect of both protocols on the YMRS (p < 0.0001). In both groups *post hoc* comparisons showed a significant change from day 7 on the YMRS. The difference between the two protocols was significant at the end point (day 42) (t = 3.33; d.f. = 80; p < 0.001). The changes at the end point compared with baseline were: -21.14 ± 4.94 (mean ± SD) (the baseline score was 26.43 ± 3.04) and -17.75 ± 7.64 (the baseline score was 25.90 ± 2.87) for group A and B, respectively. A significant difference was observed on the change of scores of the YMRS on day 42 compared with baseline in the two groups in (t = 2.38; d.f. = 80; p < 0.01).

Extrapyramidal Symptoms Rating Scale

Although the mean ESRS for the placebo group was higher than the allopurinol group, differences were not significant over the trial (Table 3).

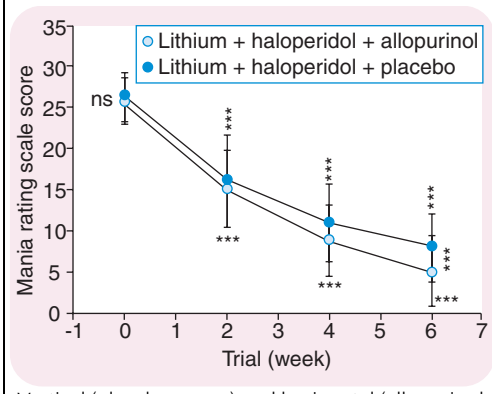
Clinical complications & side effects

In total, 15 side effects were observed over the trial. The difference between the two groups in the frequency of side effects was not significant except for agitation that was more common in the placebo group (Table 1).

Table 2. Baseline data.

	Lithium + haloperidol + allopurinol	Lithium + haloperidol + placebo	p
Age (mean ± SD)	29.53 ± 6.72	28.82 ± 6.860	0.63
Gender	Male: 19, Female: 22	Male: 23, Female: 18	0.50

Figure 2. Mean ± SD of the two protocols on the Mania Rating Scale.



Vertical (placebo group) and horizontal (allopurinol 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.
***p < 0.001
ns: Non-significant; SD: Standard deviation.

Discussion

The present study shows YMRS scores improved with allopurinol over this 6-week double-blind and placebo-controlled trial. In addition, agitation was significantly higher in patients who received only lithium and haloperidol. Clinical characteristics of the patients, such as sex, age and duration of illness, did not differ between groups and cannot explain differences in the therapeutic outcome. Therapy with 300 mg/day of allopurinol was well tolerated, and no clinically important side effects were observed. It would appear that the therapeutic benefit of combined therapy has to be attributed to the effects of allopurinol. A purinergic system impairment, mostly at adenosine A1 and adenosine triphospate (ATP) receptors, may provide new insights to integrate the modulatory aspects on the altered intracellular signaling observed during mania related to kindling and secondary messenger systems [5]. Interestingly, adenosine agonists, as well as most mood stabilizers, have been shown to prevent kindling formation, a model postulated for both epilepsy and bipolar disorder [18]. Indeed, changes in the neuroprotective and neuromodulatory profile of adenosine mostly by reduced adenosinergic activity at A1 receptors may occur during mania, increasing transmembrane signaling [5]. The efficacy of allopurinol to obtain a greater improvement in patients with mania seems to support this hypothesis. To the best of our knowledge, this study is the first clinical study that suggests the

Table 3. Extrapyramidal symptoms based on Extrapyramidal Symptoms Rating Scale.

Day	Lithium + haloperidol+ allopurinol (mean ± SD)	Lithium + haloperidol + allopurinol (mean ± SEM)	p
14	4.24 ± 2.59	4.85 ± 3.46	0.36
28	3.80 ± 2.48	4.29 ± 2.92	0.41
42	2.58 ± 1.83	3.02 ± 1.62	0.25

SEM: standard error of the mean; SD: standard deviation

potential use of allopurinol as an adjunctive treatment in acute mania and therefore it is not possible to draw any comparisons with others trials. Nevertheless, it is in line with a case report that showed the beneficial effects of allopurinol in mania associated with hyperuricemia [13]. One of the advantages of combination therapy in acute mania is that dosing can often be lower and, therefore, may produce fewer side effects and in particular, extrapyramidal symptoms.

The limitations of the present study, including the short period of follow-up should be considered and so further research in this area is needed. In addition, from a scientific viewpoint, the therapeutic effects of allopurinol without an additional neuroleptic drug would be more interesting. However, since the patients in this trial were in the acute phase of mania and with severe symptoms, the ethic committee did not approve a study with allopurinol as the only drug with lithium. Finally, the results demonstrate that the combination of allopurinol 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 allopurinol with lithium and haloperidol was well tolerated in these acutely manic patients. Based on this study, we suggest that allopurinol and purine metabolism in the treatment and neurobiology of bipolar disorder should be further investigated.

Highlights

- Mania is frequently associated with behavioral disturbances that can have serious consequences for patients and those around them.
- Rapid control is important, even though many patients are uncooperative. For many patients, the effectiveness of current treatments for acute bipolar mania is suboptimal.
- It has been reported that the abnormalities observed during mania seem to be associated with some pathophysiologic changes in the purinergic system.
- Allopurinol, a hypouricemic agent, has been shown to present therapeutic effects in mania associated with hyperuricemia.
- The present study shows Young Mania Rating Scale scores improved with allopurinol over this 6-week double-blind and placebo-controlled trial. In addition, agitation was significantly higher in patients who received only lithium and haloperidol.

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