A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ALLOPURINOL AS ADJUNCTIVE TREATMENT FOR ACUTE MANIA IN HOSPITALIZED BIPOLAR PATIENTS

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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 behavioural 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 [1]. It has been reported that the abnormalities observed during mania seem to be associated with some pathophysiological changes in the purinergic system. Recently, allopurinol, a hypouricaemic agent, has been shown to present therapeutic effects in mania associated with hyperuricaemia [2]. The objective of this double-blind, placebo controlled augmentation study was to investigate the efficacy and tolerability of allopurinol as an adjunct to lithium and haloperidol for the treatment of acute mania in hospitalized bipolar patients.

Eligible participations were 82 inpatients, age between 18–49 years and who met DSM-IV criteria for a current manic episode, on the basis of a clinical interview by an academic psychiatrist. 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. Patients were randomly allocated, 41 to lithium (1–1.2 mEq l^{-1};) + haloperidol (10 mg day^{-1}) + allopurinol (300 mg day^{-1}) (Group A) or lithium (1–1.2 mEq l^{-1}) + haloperidol (10 mg day^{-1}) + placebo (Group B) 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. 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. A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the four measurements during treatment as the within-subjects factor (time) were considered. In addition, a one-way repeated measures analysis of variance with a two-tailed *post-hoc* Tukey mean comparison test was performed in the change from baseline in each group. To compare the two groups at baseline and the outcome of the two groups at the end of the trial, an unpaired Student's *t*-test with a two-sided *P* value was used. To compare the baseline data and frequency of side effects between the protocols, Fisher's exact test was performed.

The scores of the Young Mania Rating Scale improved with allopurinol. 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 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 which occurred more often in the placebo group.

The efficacy of allopurinol to obtain a better improvement in patients with mania seems to support the purinergic dysfunction in mania.

1. Regier DA, *et al*. *Arch Gen Psychiat* 1984; **41**: 934.
2. Machado-Vieira R, *et al*. *Medical Hypotheses* 2002; **58**: 297.