

## Clinical Potential of Allopurinol in the Treatment of Bipolar Disorder

Sir,

The involvement of purines and uric acid in mania was proposed long ago by Kraepelin who first described the association between manic symptoms, uric acid excretion, hyperuricemia, and gout.<sup>[1,2]</sup> It was noted that remission from manic episodes temporarily

coincided with an increased excretion of uric acid.<sup>[3]</sup> Similarly, an enhanced purinergic turnover was shown and proposed as a putative causative factor in the pathophysiology of mania.<sup>[2,4,5]</sup> In addition to that, genetic data have suggested a potential role for purinergic dysfunction in the pathophysiology of bipolar disorder and recurrent major depression.<sup>[6,7]</sup> More recently, the

accumulating evidences regarding efficacy of allopurinol have further led to increased interest in studying role of purinergic system in bipolar mood disorder.

Purines play a vital role in energy metabolism both intracellularly with ATP as the energetic currency and in the extracellular space with adenosine and ATP as key regulators of neurotransmission.<sup>[8]</sup> Uric acid is the end product of purine catabolism and is produced by the enzyme xanthine oxidoreductase from xanthine or hypoxanthine; increased uric acid plasma levels may indicate increased purinergic turnover and reduced adenosinergic transmission.<sup>[2,7]</sup> Adenosine (a purine nucleoside) is a widespread neuromodulator that acts mostly through Adenosine-1 and -2A receptors, and caffeine has its stimulating effects by blocking these receptors. The experience has revealed that caffeine should be restricted or stopped in bipolar patients because of its stimulating effects.<sup>[9]</sup> Animal studies have shown that adenosine agonists exert sedative, anti-convulsant, anti-aggressive, and anti-psychotic-like effects.<sup>[10]</sup>

Allopurinol and its active metabolite oxypurinol are inhibitors of xanthine oxidase and have been proposed to present therapeutic effects in many pathological states by decreasing the production of uric acid, superoxide, and hydrogen peroxide.<sup>[11]</sup> The presence of mitochondrial dysfunction and oxidative stress in bipolar disorder in some reports are the alternate explanation for the utility of allopurinol in bipolar disorder.<sup>[12]</sup> Allopurinol has been found effective as an add-on to different anti-psychotic drugs in refractory schizophrenia, mania, and aggressive behavior.<sup>[11,13]</sup>

Machado-Vieira *et al.*<sup>[5]</sup> report two cases of refractory mania who had hyperuricemia, and their manic symptoms were treated till remission with the use of allopurinol. They suggested a possible relation between purine metabolism dysfunction and refractoriness of manic episodes; measuring serum uric acid levels in refractory cases may lead to potentially useful treatment consideration.

Akhonzadeh *et al.*'s<sup>[14]</sup> 8-week, double-blind, placebo-controlled study had 82 participants with DSM-IV criteria for a current manic episode. Patients were allotted randomly to allopurinol or placebo in addition to standard dose of lithium and haloperidol combination. The Young Mania Rating Scale scores showed statistically significant difference ( $F = 5.22$ ,  $df = 1$ ,  $P = 0.008$ ) between the two groups at the end of 8 weeks. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS), and the mean ESRS scores for the placebo group were higher than the allopurinol group. This study again supports the hypothesis of purinergic dysfunction in patients with bipolar disorder.

Machado-Vieira *et al.*<sup>[15]</sup> studied the efficacy of purinergic drugs allopurinol and dipyridamole combined with lithium in bipolar manic episode in their randomized, placebo-controlled, double-blind study; 180 adult inpatients with a DSM-IV-TR diagnosis of bipolar disorder, current episode manic with or without psychotic features were given fixed oral doses of either allopurinol 600 mg/day, dipyridamole 200 mg/day, or placebo in addition to lithium for 4 weeks. Allopurinol when combined with lithium resulted in greater mean reductions in YMRS scores from baseline to day 21 ( $P < .001$ ) and day 28 ( $P = .003$ ) compared with placebo using a linear model analysis ( $d = 0.32$ , 95% C.I. = 0.07 to 0.57). Remission rates were significantly higher for allopurinol compared to dipyridamole and placebo ( $P = 0.008$ ). Decrease in plasma uric acid levels showed a significant positive association with anti-manic effects in the allopurinol group ( $P < 0.001$ ).

Fan *et al.*<sup>[16]</sup> published a small outpatient pilot study, a double-blind, placebo-controlled trial involving 27 subjects who met DSM-IV criteria for bipolar disorder. The patients were randomized to either allopurinol or placebo as an augmentation to standard treatments of mood stabilizers or anti-psychotics. The effect of allopurinol augmentation in decreasing mean YMRS scores was modest, with an overall effect size of  $-0.25$  (Cohen's  $d$ ). Allopurinol-treated individuals who abstained from caffeine had a greater decrease in YMRS scores ( $-15.3 \pm 1.8$ ) than subjects using caffeine ( $-9.6 \pm 3.4$ ,  $P = 0.219$ ), with an effect size of  $-0.86$ .

The allopurinol augmentation did not show a statistically significant improvement over placebo in attenuating manic symptoms. Subjects with restricted caffeine use showed a greater effect size compared to caffeine users. This finding may be interpreted as corroborating the hypothesized mechanism of action of allopurinol's anti-manic effect in previous studies.

The study by Fan *et al.*<sup>[16]</sup> had several limitations including small sample size and heterogenous study population. Despite that, their findings point the need for further, larger studies to clarify the effect of allopurinol on adenosine neurotransmission. Future neuropsychiatric clinical studies on allopurinol or adenosinergic agents will need to consider the effect of caffeine intake as a confounding factor.

To summarize the discussion, all the studies so far have used allopurinol as an augmentation agent to mood stabilizers or anti-psychotics. Small sample size, heterogenous sample, study designs, and lack of multicentric data limits their application. Efficacy of add-on allopurinol in two studies<sup>[14,15]</sup> demands large and well designed study to estimate the utility of purinergic system modulators in

mood disorders. The most recent study by Fan *et al.*<sup>[16]</sup> had negative outcomes, but the fact that the caffeine users and non-users had differential response to allopurinol corroborates the hypothesis. Recent evidence of increased uric acid levels in drug-naïve subjects with bipolar disorder during first manic episode further warrants the attention of researchers to this novel mechanism in pathophysiology of bipolar mood disorder.<sup>[17]</sup>

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