Journal of Affective Disorders 226 (2018) 245–250

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

# Allopurinol augmentation in acute mania: A meta-analysis of placebo-controlled trials

Alexander T. Chen*, Theodore Malmstrom, Henry A. Nasrallah

*Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, St. Louis, MO, USA*

ARTICLE INFO

*Keywords:*
Allopurinol
Bipolar disorder
Mania
Meta-Analysis
YMRS

ABSTRACT

*Background:* Allopurinol is a xanthine oxidase inhibitor commonly used in the treatment of gout. Recent studies have also shown its promise as an adjunctive treatment for manic episodes in bipolar 1 disorder, possibly through mechanisms involving the purinergic pathway. However, its efficacy across studies has been inconsistent, so we conducted a meta-analysis of the published controlled studies with the goal of determining the efficacy profile of allopurinol as an adjunctive treatment for mania in bipolar disorder.

*Methods:* An online search was conducted using PubMed for placebo-controlled, randomized, double-blind, clinical trials (RCTs) using the terms "allopurinol," "bipolar," "mania," "manic," and "YMRS" and a meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.

*Results:* Five studies met the criteria for inclusion. Three of the five studies were inpatient treatments, one study was outpatient treatment, and one study had a mixture of both. All studies used allopurinol as an adjunct in treating acute mania in bipolar disorder subjects. Four of the studies showed efficacy in the primary outcome measure between allopurinol vs. placebo groups with significantly reduced YMRS scores while one showed no significant effect size between the allopurinol and placebo groups. The overall effect size for the four studies is $d = 0.294$. No significant difference in side effects were found between groups for any of the studies.

*Conclusion:* The data suggest that allopurinol may have some efficacy as an adjunct in reducing mania symptoms during acute manic episodes in patients with bipolar disorder. Adjunctive allopurinol efficacy may be related to the mood stabilizer used. Additional controlled trials with greater sample sizes, homogenous dosing, and consistent treatment modalities are needed to determine optimal clinical application.

## 1. Introduction

Bipolar disorder (BPD) is a severe psychiatric disorder that contributes to a significant portion of mental health expenditures and functional impairment in affected individuals. Manic episodes in bipolar disorder, in particular, can be particularly challenging for the clinician as patients are often unable to assist in their own care during these states and their symptoms can result in significant risk of harm to themselves and others around them (Tohen and Grundy, 1999). Management of bipolar mania (BPM) is further complicated by the limited range of treatment options that are available and the efficacy of the mood stabilizers remain unsatisfactory. Much of the mechanisms of action in our current medications also remain unclear (Gitlin, 2006). In light of the pressures involved in finding more efficacious, more easily administered, and more economical treatment options, many studies have been conducted in recent years to find new strategies to target in BPM.

One of the more promising relationships that have surfaced in recent literature is the association of the purinergic system and BPM (Machado-Vieira et al., 2002). Studies have shown that bipolar disorder patients demonstrated elevated mean levels of uric acids during acute manic episodes compared to healthy controls (Anumonye et al., 1968; Brooks et al., 1978; Salvadore et al., 2010). This may suggest that there is increased purinergenic turnover and patients with bipolar disorder are also at increased risk of developing gout compared matched controls (Chung et al., 2010). Contemporary models of BPM have suggested that excessive dopaminergic activity contributes to the pathogenesis of mania through the activation of $PLA_2$ and GSK3 coupled receptors that lead to inflammatory and pro-apoptotic cascades (Jope and Johnson, 2004; Jope and Roh, 2006; Kim et al., 2010; Sobczak et al., 2004). Animal and human trials have indicated evidence that stimulation of adenosine $A_{2A}$ receptors decrease the affinity of dopamine $D_2$ agonist binding sites. Allopurinol is a xanthine oxidase inhibitor that reduces purine degradation and has been shown in animal models to increase

* Correspondence to: 1438 S. Grand Blvd, St. Louis, MO 63104, USA.
*E-mail address:* chena@slu.edu (A.T. Chen).

http://dx.doi.org/10.1016/j.jad.2017.09.034
Received 11 March 2017; Received in revised form 11 July 2017; Accepted 23 September 2017
Available online 30 September 2017

brain adenosine levels (Fuxe et al., 2010). Allopurinol may also have efficacy as an adjunct to antipsychotics in schizophrenia management (Akhondzade et al., 2005; Brunstein et al., 2005; Buie et al., 2006; Dickerson et al., 2009; Weiser et al., 2012). The hypothesis is that allopurinol treatment decreases dopaminergic activity through the increasing $A_{2A}$ receptor activation and lead to subsequent reduction of inflammation and apoptosis by reducing $PLA_2$ and GSK3 coupled $D_2$ receptor activation. Several human clinical trials have produced data that suggests allopurinol may have efficacy as an adjunct to mood stabilizers and antipsychotics in the treatment of BPM.

Given the new evidence that emerged over the last decade regarding the purinergic pathway as a viable target for BPM therapy, we decided to conduct a meta-analysis of the effectiveness of allopurinol adjunctive therapy in reducing the severity of symptoms in BPM and hypothesize that the treatment group will have significantly reduced manic symptoms compared to the placebo group in bipolar disorder subjects with acute manic episodes.

## 2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (Moher et al., 2009).

### 2.1. Search criteria

An online search was conducted using PubMed for placebo-controlled, randomized, double-blind, clinical trials (RCTs) using the terms “allopurinol,” “bipolar,” “mania,” “manic,” and “YMRS.” There were no restrictions placed upon date of publication or language. The last database search was performed in August 2016.

### 2.2. Inclusion criteria

All included studies met the following criteria:

1. Randomized, double-blind, placebo-controlled trials using allopurinol as an adjunctive treatment agent.
2. Subjects were diagnosed with bipolar disorder and were receiving treatment with mood stabilizers and/or antipsychotics in addition to allopurinol augmentation.
3. Diagnosis of bipolar disorder based on either the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR, and DSM-V) or International Classification of Diseases (ICD 9 or 10).

### 2.3. Exclusion criteria

Studies were excluded if:

1. Study did not meet all inclusion criteria.
2. Data provided in the study were unclear and/or inadequate for proper statistical analysis.
3. Study data overlapped with at least one other study containing a larger patient sample size.
4. Study did not use the YMRS as the primary outcome measure.

### 2.4. Data collection

Study data were independently verified by investigators and all study inclusions and exclusions were determined by consensus. For any studies that used a shared patient sample, only the data from the study with the largest sample was included in the meta-analysis.

### 2.5. Data items

The primary outcome in the various studies was the total score on the Young Mania Rating Scale (YMRS). The baseline data for the treatment and placebo groups were also obtained from each study. Lastly, data on study-specific outcome measures were included for discussion as well.

### 2.6. Statistical analysis

The primary outcome measured in this meta-analysis was the mean change in the YMRS score between the placebo and treatment groups of the studies. Effect sizes were calculated as Cohen's d and standardized differences were calculated independently from articles, where possible, to ensure accuracy.

## 3. Results

### 3.1. Literature search

Five studies were assessed for eligibility and all were included. The results of our search and screening process are detailed in Fig. 1. The details for the included trials are listed in Table 1 and the effect sizes are shown in Fig. 2.

### 3.2. Akhondzadeh et al. (2006)

Over an 8-week period treatment group received allopurinol 100 mg three times daily (300 mg total daily) with 1–1.2 mEq/L of lithium daily and haloperidol 10 mg daily while placebo group received placebo with 1–1.2 mEq/L of lithium daily and haloperidol 10 mg daily for 8 weeks. Subjects were allowed lorazepam up to 2 mg/day for the first 4 days and 1 mg/day for the next 6 days as needed and non after the first 10 days. Biperiden was allowed for extrapyramidal symptoms (EPS) up to a max of 4 mg/day throughout the study.

There were 75 subjects total, with 38 randomly allocated to treatment and 37 randomly allocated to placebo group. Subjects scored at least 20 points on the YMRS and were treated inpatient for active moderate to severe mania with a diagnosis of bipolar 1 disorder per DSM-IV criteria. No significant differences were found at baseline between groups. Majority of subjects in each group had mania with psychosis (38 in treatment and 37 in placebo group). Mean age was 29.58 ± 6.75 for treatment group and 28.89 ± 6.89 for placebo group. Duration of illness for treatment group was 4.81 ± 1.43 years and 4.64 ± 1.72 years for placebo group. There no significant differences in the distribution of males to females between treatment and placebo groups.

Baseline mean YMRS was 26.43 ± 3.04 for treatment group and 25.90 ± 2.87 for placebo group with no significant differences between groups. Endpoint mean YMRS was 4.63 ± 3.97 for treatment group and 8.00 ± 4.27 for placebo group with a significant between group difference at endpoint ($p = 0.008$, $d = 0.561$). No significant differences in side effects were noted between groups other than agitation, which was lower in the treatment group compared to the placebo group (16 vs. 33, $p = 0.03$).

### 3.3. Machado-Vieira et al. (2008)

In this 4 week trial, treatment group received allopurinol 600 mg daily with lithium daily to maintain a level of 0.6–1.2 mmol/L while placebo group received placebo with lithium daily to maintain a level of 0.6–1.2 mmol/L for 4 weeks. There was also a third group in the study that received dipyramidole 200 mg daily with lithium daily to maintain a level of 0.6–1.2 mmol/L. Subjects were allowed diazepam up to 20 mg/day for the as needed throughout the study except for the 12 h prior to rating scale recordings.