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Review article

Uric acid levels in subjects with bipolar disorder: A comparative meta-analysis

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ABSTRACT

Previous research has hypothesised increased uric acid levels, possibly because of an amplified purinergic metabolism and a reduced adenosine activity, in subjects with bipolar disorder. This systematic review and meta-analysis aimed at estimating if individuals with bipolar disorder had uric acid levels higher than both healthy controls and subjects with major depression (trait marker hypothesis). It also tested if uric acid levels could differ in different phases of bipolar disorder (state marker hypothesis). Meta-analyses were carried out generating pooled standardized mean differences (SMDs), using random-effects models. Heterogeneity between studies was estimated using the I^2 index. Relevant sensitivity and meta-regression analyses were conducted.

We searched main Electronic Databases, identifying twelve studies that met our inclusion criteria. Meta-analyses showed increased uric acid levels in individuals with bipolar disorder as compared with both healthy controls (SMD = 0.65, $p < 0.001$, $I^2 = 82.9\%$) and those with major depression (SMD = 0.46, $p < 0.001$; $I^2 = 68.7\%$). However, meta-regression analyses confirmed this association only as compared with healthy controls. Finally, though uric acid levels were higher in manic/mixed phases as compared with depressive ones (SMD = 0.34; $p = 0.04$, $I^2 = 58.8\%$), a sensitivity analysis did not confirm the association.

In sum, our meta-analysis shows that subjects with bipolar disorder have uric acid levels higher than healthy controls. The potential role of factors that might clarify the nature of this association deserves additional research.

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1. Introduction

Purines play a key role in neurotransmission and neuromodulation (Burnstock, 2007), since their effects seem mediated by several receptor subfamilies (Burnstock, 2008; Krugel, 2015). Purinergic mechanisms might be involved in various neuropsychiatric diseases (Abbracchio et al., 2009; Burnstock, 2008; Ortiz et al., 2015), influencing the activity of several neurotransmitters (Burnstock, 2008; Lindberg et al., 2015). Agonists of adenosine, a purine nucleoside, have shown sedative, anticonvulsant, antiaggressive, and antipsychotic properties (Zarate and Manji, 2008), whereas its antagonists, for example caffeine, can produce 'mania-like' stimulant effects (Machado-Vieira et al., 2002; Machado-Vieira, 2012). It has been reported that a reduced adenosine activity, mainly on A1 receptors, might influence the complex network of changes on neurotransmitter pathways involved in manic behaviours (Burnstock, 2008; Machado-Vieira et al., 2002). Uric acid is the final product of purine metabolism (Grassi et al., 2013) and accounts for up to 60% of the free radical scavenging activity in human blood (Ames et al., 1981). Peripheral and central uric acid levels have a strong positive association (Machado-Vieira, 2012), and increased serum levels of uric acid may be a sign of an amplified purinergic turnover and a reduced adenosine transmission (Machado-Vieira et al., 2001). Thus, both adenosine and uric acid could be involved in mood and sleep regulation, behavioural patterns, and affective temperaments (Kesebir et al., 2014; Lorenzi et al., 2010; Ortiz et al., 2015). Several studies have shown that individuals suffering from bipolar disorders might have a purinergic system dysfunction, associated with higher uric acid levels, as compared with both healthy subjects (Bartoli et al., 2016; Salvadore et al., 2010) and individuals with other mental disorders (Albert et al., 2015; Kesebir et al., 2014). However, similar research did not replicate these findings (e.g., Wiener et al., 2014), with the relationship between uric acid and bipolar disorder remaining uncertain. Discrepancies among the previously mentioned studies might be due to the fact that uric acid levels might be markers of different bipolar phases, rather than of bipolar disorder as such (Machado-Vieira, 2012; Muti et al., 2015). Preliminary evidence showed that especially manic phases, rather than depressive or euthymic ones, might be associated with an increase of serum uric acid (De Berardis et al., 2008; Muti et al., 2015). Finally, indirect support for a role of uric acid in pathophysiological mechanisms of bipolar disorder has been proposed by pilot clinical trials showing efficacy of purinergic modulators as add-on treatment for manic symptoms (Akhondzadeh et al., 2006; Jahangard et al., 2014), as well as a significant correlation between uric acid decrease and anti-manic effect (Machado-Vieira et al., 2008).

Nevertheless, there is a lack of systematic data analysing uric acid levels in subjects with bipolar disorder. Since a body of evidence of acceptable size has accumulated, possibly overcoming gaps of previous research, we carried out a systematic review and meta-analysis to explore this topic. We aimed at estimating if uric acid might be considered a trait marker of bipolar disorder, i.e., if there were significant differences in uric acid levels comparing subjects suffering from bipolar disorder with both healthy subjects and others affected by major depression. Moreover, we tested uric acid as a state marker, estimating if there might be differences in uric acid levels across distinct phases of bipolar disorder, comparing subjects in manic/mixed phases with those in depressive or euthymic ones. To our knowledge, this is the first quantitative synthesis of the available evidence and, as such, it will allow for the assessment of strengths and consistency of the relationship, taking into account potential effect of relevant moderators and heterogeneity.

2. Methods

The current systematic review and meta-analysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (*MOOSE*) guidelines (Stroup et al., 2000). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO – registration number: CRD42016032700).

2.1. Search strategy and selection of studies

We searched PubMed, Scopus, PsycINFO (via ProQuest), Embase (via Ovid), and WorldCat electronic databases for articles published up to April 2016. No language restriction was set. Search phrases were implemented, and adapted according to different bibliographic databases and index terms, as it follows:

- PubMed: *("Bipolar Disorder"[Mesh] or bipolar [title/abstract] or mania [title/abstract] or manic [title/abstract]) and ("Uric Acid"[Mesh] or "Hyperuricemia"[Mesh] or uric acid [title/abstract])*;
- Scopus: *TITLE-ABS-KEY (bipolar and uric acid)*;
- PsycInfo (via Proquest): *(SU.EXACT("Bipolar Disorder") or ab(bipolar)) and (SU.EXACT("Uric Acid") or ab(uric acid))*;
- Embase (via Ovid): *((bipolar or mania) and (uric acid or hyperuricemia)).af.*;
- WorldCat: 1# '*uric acid bipolar*'; 2# '*uric acid mania*'; 3# '*uric acid manic*'.

References were managed using *EndNote Web* Software.

Two authors (FB and MM) independently completed the preliminary screening based on titles and abstracts, and retrieved full texts to assess studies according to relevant inclusion criteria for final eligibility. Differences in suitability for inclusion were resolved by discussion and consensus, involving all authors.

2.2. Eligibility criteria

We included observational studies providing comparative data on uric acid levels, satisfying at least one of the following scenarios: