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Benefits and harms of low and high second-generation antipsychotics doses for bipolar depression: A meta-analysis

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ABSTRACT

The aim of this systematic review and meta-analysis was testing whether low versus high doses of second-generation antipsychotics (SGAs) are associated with different clinical benefits and harms for the acute treatment of bipolar depression. We included clinical trials comparing different doses of the same SGA monotherapy for bipolar depression. SGAs defined daily doses were used to define high and low doses. Clinical benefit outcomes included improvement, response and remission rates on Montgomery-Asberg Depression Rating Scale. Clinical harm outcomes included all-cause and adverse effect-related discontinuation rates. Data from seven clinical trials testing high and low doses of quetiapine (4 trials), cariprazine, lurasidone, and ziprasidone (1 trial each), showed no differences between lower and higher doses of selected SGAs on improvement, response and remission rates, without significant heterogeneity across studies ($I^2 = 0\%$). Subgroup analyses based on single SGAs confirmed the clinical benefit comparability between low and high doses. However, clinical harm favorable differences for low doses on all-cause ($p = 0.01$) and adverse effects-related discontinuation ($p = 0.001$) were found.

In sum, this meta-analysis showed that, although no benefits were found in terms of symptoms improvement, response and remission rates, there were clear disadvantages in prescribing higher rather than lower doses of selected SGAs. The uniform methodological strength of studies increases confidence in our findings. These data need to be integrated with individual patient characteristics (e.g., clinical urgency and adverse effect sensitivity) to optimize management of acute bipolar depression.

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1. Introduction

Bipolar Disorder (BD) is a severe, persistent mental illness, with a lifetime prevalence of about 2% in U.S. general population (Merikangas et al., 2007). It is characterized by a chronic episodic course, including common recurrence of depressive and manic/hypomanic episodes and involving varying mood, activity levels, sleep, and behavior abnormalities (APA, 2013). Nevertheless, research indicates that depression represents the predominant phase of BD (Kupka et al., 2007) and bipolar individuals spend more time with depressive versus manic/hypomanic symptoms (Miller et al., 2014). Depression, having a greater impact on patient's global psychosocial functioning (Ruggero et al., 2007), is often more pervasive and disabling than mania (Miller et al., 2014; Ketter et al., 2014). Untreated or inappropriately treated bipolar depression might significantly affect clinical outcomes and BD course (Suppes et al., 2005). Research on pharmacological management of bipolar depression has accumulated in the last decade, proposing a number of single-drug and combination treatments (Ketter, 2008; Young, 2008). Several meta-analyses, published in the last few years (Chiesa et al., 2012; Cruz et al., 2010; De Fruyt et al., 2012; Selle et al., 2014; Suttajit et al., 2014; Taylor et al., 2014), assessed efficacy and tolerability of second generation antipsychotics (SGAs) for the treatment of bipolar depression. In particular, a recent multiple-treatments meta-analysis (Taylor et al., 2014), pooling together outcome data of different doses of SGAs, highlighted that drugs such as lurasidone, olanzapine, olanzapine/fluoxetine combination, and quetiapine, might be efficacious in acute bipolar depression. Furthermore, it has been found that, at least for quetiapine (Calabrese et al., 2005; McElroy et al., 2010), higher and lower doses were comparable in terms of depressive symptom decrease, clinical response, and remission. However, it seems plausible to hypothesize that different doses of the same SGA may yield different findings in terms of overall outcomes and adverse effect-related drop-out rates (e.g. Gianfrancesco et al., 2008). Despite the amount of data on direct comparisons of SGAs at different doses already available for quetiapine (e.g. Calabrese et al., 2005; McElroy et al., 2010), a substantial body of evidence has accumulated over the last years also for other SGAs, including cariprazine (Durgam et al., 2016), lurasidone (Loebel et al., 2014a) and ziprasidone (Lombardo et al., 2012). Hence, we carried out a systematic review and meta-analysis of relevant clinical trials, aiming at assessing whether lower versus higher doses of selected SGAs for acute treatment of bipolar depression, were associated with different clinical outcomes.

2. Material and methods

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). We followed the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach for grading evidence quality as high, moderate, low, or very low, according to standard items, i.e., quality of individual studies, directness of evidence, precision and consistency of results, and publication bias (Schünemann et al., 2008).

2.1. Eligibility criteria

We included randomized, double-blind clinical trials comparing different doses of the same SGA monotherapy for the acute treatment of bipolar depression. To be considered, studies had to recruit adults with BD in a current major depressive episode, from any inpatient and/or outpatient settings. The 'low' and 'high' dose arms were defined considering mean dosages lower or equal/higher than the defined daily dose (DDD) for each SGA (WHO Collaborating Centre for Drug Statistics Methodology, 2016). We considered a dosage of 3 mg/day as the threshold to define low and high doses for cariprazine, due to the lack of relevant data available on DDD.

2.2. Outcomes

We tested different clinical outcomes, i.e., improvement, response, remission, and discontinuation. Improvement was measured by mean overall change (from baseline to endpoint) in depressive symptoms assessed with the Montgomery–Åsberg Depression Rating Scale - MADRS (Montgomery and Asberg, 1979). Response was defined as a reduction in MADRS score from baseline to endpoint of $\geq$50%. Remission was defined as an endpoint MADRS score lower than, or equal to 12 (e.g. Calabrese et al., 2005) or 10 (Durgam et al., 2016). All-cause discontinuation (acceptability) was estimated calculating the number of participants who left the study prematurely for any reason. Finally, we assessed specific discontinuation reasons (i.e., adverse effects, inefficacy).

2.3. Search strategy and data collection process

A search via Ovid for the Medline, Embase, and PsycInfo electronic databases, was performed from database inception till June 2016, with no language restrictions. We used the following search phrase: *((antipsychotic* or aripiprazole or asenapine or cariprazine or lurasidone or olanzapine or paliperidone or quetiapine or risperidone or ziprasidone) and bipolar depression and double-blind).mp.*, with 'mp' code meaning that the search included the Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields. An additional check of studies included in two relatively recent meta-analyses (Selle et al., 2014; Taylor et al., 2014) was carried out.