



## Review

# Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review



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## ABSTRACT

**Background:** Bipolar Disorder (BD) long-term treatment is aimed to prevent relapses associated with worsening cognitive impairment and chronicity. Available mood stabilizers, including lithium, fail to prevent relapses in about 40% of bipolar patients. Purpose of the present paper is to review the available data about the efficacy and tolerability of mood stabilizer plus antipsychotic combined treatments.

**Method:** A research in the main database sources has been conducted to obtain an overview about the efficacy and tolerability of the combination of a mood stabilizer plus an antipsychotic in the long-term treatment of BD. Papers with different methodologies but having relapse prevention as main outcome have been included.

**Results:** Despite the heterogeneity of studies in terms of methodology, almost all papers reported a major efficacy of combined treatments respect to mood stabilizer mono-therapies but lower tolerability. The antipsychotic that presents more evidence of efficacy in combination with mood stabilizers is quetiapine.

**Discussion:** Combined treatments can be a valid option to improve relapse prevention in BD. However, the higher risk for side effects has to be taken into account and specific combinations should be preferred according to patients' medical comorbidity.

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## 1. Introduction

Bipolar Disorder (BD) is a disabling condition affecting about 1% of European population (Pini et al., 2005) and Bipolar Spectrum Disorders can show a prevalence till 8% in general population (Judd and Akiskal, 2003). Despite BD enormous social burden, the diagnosis of this condition is often delayed with obvious implications for outcome (Altamura et al., 2010). Objectives of BD treatment include not only the resolution of acute episodes, but also the prevention of relapses (maintenance treatment) (Fountoulakis et al., 2012). The importance of maintenance treatment has been remarked in last years in light of

- negative impact of number of episodes on cognition (Bellivier, 2012),
- association between relapses and brain changes (Strakowski et al., 2002), and
- poor quality of life in patients with numerous mood episodes (Scott and Colom, 2005).

Mood stabilizers, with most of the data about lithium, have totally changed long-term prognosis of bipolar patients (Malhi et al., 2012). These molecules (with obvious differences among them) showed their superiority respect to placebo both in acute episodes and in relapse prevention (Licht, 2012). On the other hand the coming of atypical antipsychotics helped the clinicians to have a rapid resolution of manic symptoms with a limited depressive switch and to ameliorate psychotic symptoms that are poorly controlled by traditional mood stabilizers (Bourin and Thibaut, 2013).

However, despite the available treatment options, unmet needs still remain. First, some patients experience full-blown relapses despite long-term mono-therapies with mood stabilizers. For example in a long-term study a mean relapse rate of 40% was reported for bipolar patients treated with lithium (Geddes et al., 2004). A relapse rate of 67.15% was reported for valproate mono-therapy in a 4-year follow-up study (Altamura et al., 2008). Second, sub-threshold episodes are unsatisfactorily prevented by mood stabilizer mono-therapies and complicate BD outcome (Homish et al., 2013). Finally some clinical dimensions such as psychotic and cognitive ones are poorly improved by long-term by mood stabilizer mono-therapies (Mora et al., 2012). Combined treatments with a mood stabilizer plus an atypical antipsychotic might be a valid option to satisfy the described unmet needs. In light of these considerations purpose of the present paper is a critical review of the available data about combination of antipsychotics plus mood stabilizers in long-term treatment of BD.

## 2. Methods

A careful search of articles on MEDLINE, PsycINFO, Isi Web of Knowledge, Medscape was performed in order to obtain a comprehensive review about the combination of an antipsychotic plus a mood stabilizer in the maintenance treatment of BD. Papers with relapse prevention as main endpoint were selected, being euthymia maintenance the most frequent outcome measure among

long-term studies. In particular, the word “Bipolar Disorder” has been associated with “maintenance treatment”, “relapse prevention”, “antipsychotic”, and “mood stabilizers”. No restriction criteria were established in relation to study design, but efficacy studies had to be longer than 12 weeks. All types of publications, including letter to the editors, were considered. Papers from 1980 to 2013, mostly in English, have been included. For the preparation of this paper the indications of PRISMA statement have been taken into account (Liberati et al., 2009; Moher et al., 2009).

According to the criteria described above, 1086 papers were initially identified. 520 out of 1086 related to the pharmacological treatment and 186 out of 520 had prevention of relapse as main outcome. Nineteen studies were finally considered as they evaluated the effectiveness of the combination of a mood stabilizer plus an antipsychotic.

Finally, evidence rating was attributed according to the number of double-blind placebo-controlled trials and the presence of an adequate total sample size (> 200)

Level A: at least three double-blind placebo-controlled trials with a total sample size > 200.

Level B: at least two double-blind placebo-controlled trials with a total sample size > 200.

Level C: at least one double-blind placebo-controlled trials with a total sample size > 200.

Level D: at least two open-label studies with a total sample size > 200 or one double blind-placebo controlled trial with a sample size < 200.

Level E: case reports.

Level F: no studies.

These rating criteria are a modified version of PORT criteria (Lehman and Steinwachs, 1998).

## 3. Mood stabilizer plus first generation antipsychotic

Few studies have investigated the efficacy of combined treatments with a mood stabilizer and a neuroleptic in light of the depressogenic effects of first generation antipsychotics and poor effects of neuroleptic mono-therapies in preventing relapses of bipolars (Bourin et al., 2005).

### 3.1. Haloperidol

Haloperidol decanoate injections (100–400 mg monthly for more than 3 years) were given to 12 patients treated with lithium, showing beneficial effects on hypomanic relapse prevention (Lowe and Batchelor, 1986) (Level E).

### 3.2. Flupenthixol

A 2-year double-blind placebo-controlled study compared bipolars treated with lithium versus patients treated with a combination of lithium and flupenthixol injections every 4 weeks. No differences were found between groups in terms of days of

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