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Research paper

Efficacy and safety of long-term antidepressant treatment for bipolar disorders – A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Efficacy and safety of long-term use of antidepressants (AD) in bipolar disorder (BD) patients remains highly controversial. Here we performed a meta-analysis of randomized controlled trials (RCTs) exploring the efficacy and safety of long-term AD use in BD patients.

Methods: English-written literature published in peer-reviewed journal was systematically searched from Pubmed, EMBASE, CENTRAL, PsycINFO and Clinicaltrials.gov. Each database was searched from its first available time to August 31, 2016. Additional papers were searched from recent guidelines, expert consensus and systematic reviews by hand. RCTs exploring the efficacy and safety of long-term (≥ 4 m) antidepressant treatment for patients with bipolar disorder were eligible. Two authors (HF, JL) independently extracted the data. Risk ratio (RR), number needed to treat (NNT) and/or number needed to harm (NNH) for new depressive episodes and new manic/hypomanic episodes were calculated. Subgroup analyses were performed based on treatment regimen (AD monotherapy or combined with MS), types of antidepressants, funding source, bipolar subtypes and treatment duration.

Results: Eleven trials with 692 bipolar disorder patients were included in the meta-analysis. The risk of bias assessment demonstrated moderate bias risk. Antidepressants were superior to placebo in reducing new depressive episodes in bipolar disorders without increasing risk of new manic/hypomanic episodes either used as monotherapy or in combination with MS. Subgroup analyses revealed that greater benefit and lower risk may be achieved in BD II than in BD I. However, compared with MS monotherapy, AD monotherapy significantly increased the risk of affective switch with no improvement in prophylaxis of new depressive episodes.

Conclusions: Reduced new depressive episodes may be achieved by long-term AD treatment with no significantly increased risk of new manic/hypomanic episodes in BD, particularly in BD II. The elevated risk of affective switch of AD monotherapy compared with MS monotherapy may be contributed to the protective effect of MS in diminishing manic/hypomanic episodes. Further studies are needed to verify our findings.

1. Introduction

Depressive episodes in bipolar disorder (BD) usually exhibit higher prevalence, longer duration, more serious harm on social function and higher burden than manic/hypomanic episodes (Bopp et al., 2010; Judd et al., 2002; Miller et al., 2014; Michalak et al., 2008; Solomon et al., 2010), while the treatment of bipolar depression, especially long-term treatment, is much less studied and far less optimized in clinical practice than mania/hypomania (Grunze et al., 2013). Practice guidelines and expert consensus (Grunze et al., 2013; Goodwin, 2009; Yatham et al., 2013; Malhi et al., 2015; Pacchiarotti et al., 2013) recommend avoiding use of antidepressants (AD) for BD patients, only if the depressive episode is very severe and shows poor response to mood stabilizers (MS) or atypical antipsychotics (AP) monotherapy. And, even in the case of indispensable use of AD for acute treatment of bipolar depression, the use of AD is recommended to be limited in 6–8 weeks after full remission of depression (Yatham et al., 2013), much shorter than the recommended continuation and maintenance treatment duration in unipolar major depressive disorder (MDD)(Davidson, 2010). Nevertheless, these recommendations have never been backed up by explicit evidence.

Although discouraged from guidelines, the long-term AD use in BD

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patients is commonly seen in clinical practice, with as high as 40% of patients taking AD in the maintenance phase (Grande et al., 2013). This may be due to the inadequate effectiveness or poor tolerability of recommended treatment regimens, namely, the MSs and APs. However, the use of antidepressant in bipolar disorder (BD) treatment, especially long-term treatment, is highly contentious since two of most commonly concerned questions about this topic, namely, the effectiveness of long-term AD treatment for prophylaxis of new depressive episodes and the risk of new manic/hypomanic episodes inducement are exceedingly inconclusive due to the limited and inconsistent evidence from clinical trials (Pacchiarotti et al., 2013; Gitlin, 2012; Ghaemi, 2012).

A previous meta-analysis exploring the benefits and risk of long-term AD treatment for BD patients demonstrated that long-term adjunctive AD treatment had little protection for depression relapse while significantly increased risk of affective switch (Ghaemi et al., 2008). However, the results of this meta-analysis may be biased by repeated using of data for more than one time in multiple-arm trials. Besides, the authors didn't differentiate comparisons between AD and placebo from comparisons between AD and MS, which may result in confounding results since MS and placebo is considered explicitly to have different effects on depression relapse prevention and affective switch inducement. Moreover, several new studies with different findings have been published since the publication of the meta-analysis. Therefore, we conducted this updated meta-analysis of randomized controlled trials (RCTs) to address the efficacy and affective switch risk of long-term AD use in BD patients.

2. Materials and methods

2.1. Literature search

Clinical trials were searched from Pubmed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), PsyINFO and Clinicaltrials.gov using "bipolar disorder", "manic-depressive disorder", "antidepressant or tricyclic OR tetracyclic OR serotonin reuptake inhibitor OR noradrenaline reuptake inhibitor OR monoamine oxidase inhibitor OR sertraline OR venlafaxine OR escitalopram OR citalopram OR paroxetine OR fluoxetine OR mirtazapine OR fluvoxamine OR bupropion OR wellbutrin OR duloxetine OR trazodone OR nefazodone OR reboxetine OR moclobemide OR mianserine OR amitriptyline OR chlorimipramine OR St John's wort OR hypericum OR imipramine OR doxepin OR maprotiline", "randomized controlled trials". Publication date was restricted from every database's first available time to 2016/08/31. Free text search and Mesh search were combined to improve the recall ratio. The references of included studies and guidelines were also systematically searched by hand. The detailed description of search strategies and results in each database was shown in Appendix.

2.2. Inclusion criteria

Studies included in this meta-analysis should meet the following criteria:

(1) Inclusion of patients diagnosed with Bipolar I, II or NOS type by Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IV, DSM-IV-TR, DSM-5) or Bipolar Disorder by International Classification of Diseases (ICD-9, ICD-10) or research domain criteria (RDC) criteria. When both unipolar and bipolar depressed patients were included, the data of bipolar depressed patients should be reported separately.
(2) Allocation of patients should be based on randomization.
(3) The average total duration of AD treatment should be lasted for at least 4 months (we defined the "long-term" as ≥4 m based on the criteria used in a previous meta-analysis exploring the efficacy and safety of antidepressant for acute treatment (16 weeks) of bipolar disorder (Sidor and Macqueen, 2011)).
(4) Data about the treatment-emergent of new depressive episodes or manic/hypomanic episodes during long-term antidepressant treatment for patients who achieved clinical remission or response should be reported.

2.3. Exclusion criteria

(1) Naturalistic study or observational study design.
(2) Only data about efficacy and safety of acute AD treatment for bipolar depression was reported.
(3) Study protocols or inadequate data reporting (no available data for meta-analysis).
(4) Repeated reporting.

2.4. Data extraction

Data about the demographic information (gender, age), index episode (depression, mania or not specified), inclusion criteria (diagnosis, severity, course), treatment regimen (AD monotherapy or in combination with MSs or APs), pharmacotherapy (AD name, dosage, duration) and outcome-related variables (definition of new depressive episodes (relapse or recurrence) and manic/hypomanic episodes (affective switch), time to new depressive or manic/hypomanic episode, duration of new depressive or manic/hypomanic episodes, dropout rates) were extracted from the included studies. This procedure was performed independently by two investigators (JL, HF) under the guidance of *Cochrane Handbook for Systematic Reviews of Interventions,* any discrepancy detected in the extracted data was settled by discussion among three authors of this paper (BSL, JL, HF). Key missing data or perplex information of included studies were addressed through e-mail contact with the authors.

2.5. Risk of bias assessment

Risk of bias of each included trial was assessed according to *Cochrane Handbook for Systematic Reviews of Interventions.* The assessment includes the following six items: randomization generation, allocation concealment, blindness of participants and personnel, blindness of outcome assessment, incomplete outcome data and selective reporting. Risk of bias summary figure was generated according to the above six items by Revman 5.3.

2.6. Data synthesis and analysis

Risk ratio (RR) for new depressive episodes was selected as the primary outcome. Risk ratio for new manic/hypomanic episodes, number needed to treat (NNT) and number needed to harm (NNH) derived from risk difference (RD) were selected as secondary outcomes. Due to the exceedingly inconsistent reporting about dropouts in different studies and insufficient data about time to new affective episodes, we finally abandoned meta-analysis of dropout rate, time to new affective episodes and duration of new episodes, leaving the data analysis limited to dichotomous data about new depressive or manic/hypomanic episodes. When different criteria of new depressive, manic/hypomanic episodes were presented in a trial, data about the most formal and commonly used criteria, namely, the criteria of depressive or manic/hypomanic episode based on RDC, DSM or ICD diagnostic system, was selected for meta-analyses. Pooled estimates were tested by Z statistic, and significance was achieved when a two-tailed P value was less than 0.05.

Heterogeneity between included studies was assessed by the Q statistic and the I^2 statistics. $P < 0.1$ for Q statistic or $I^2 > 35\%$ was taken as indicator of statistical significant heterogeneity (Higgins and Thompson, 2002). Mantel-Haenszel fixed -effect model (Mantel and Haenszel, 1959) was selected for meta-analyses due to low heterogeneity detected between studies. Subgroup analyses were