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Review article

Maintenance therapy with second generation antipsychotics for bipolar disorder – A systematic review and meta-analysis

Leif Lindström[a,1], Eva Lindström[a,1], Mikael Nilsson[b,c], Malin Höistad[b,d,*]

[a] Department of Neuroscience, Psychiatry, Uppsala University Hospital, Sweden
[b] Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), Stockholm, Sweden
[c] Health Technology Assessment, Faculty of Odontology, Malmö University, Sweden
[d] Medical Management Centre, LIME, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Background: Second generations antipsychotics (SGA) are frequently used for maintenance treatment in bipolar disorder. We systematically reviewed the efficacy and long-term effects of treatment with SGA, regardless of treatment strategy (SGA administered either as monotherapy or as adjunctive therapy), in comparison to placebo, lithium or valproate. Primary outcomes were relapses (mood episode recurrence) and discontinuation.

Method: Clinical studies were identified through database searching in PubMed, Embase, PsychInfo and Cochrane Library and critically appraised based on the Cochrane Handbook. Full data extraction of raw data was performed and analyzed with meta-analyses, and level of evidence graded using GRADE. Only randomized controlled studies (RCT) and observational studies were included, with a minimum follow-up of 6 months. Comparators used were restricted to placebo, lithium, valproate or other anti-epileptic drugs.

Results: We identified 15 RCTs on SGA in bipolar disorder with follow-up-time of 6 months up to 2 years, and one observational study reporting long-term effects of up to 4 years. A total of 6142 patients were included in the randomized trials. No long-term RCTs beyond 2 years follow-up was identified. All RCTs except for one included patients with bipolar disorder type I only. All RCTs except for two included patients pre-stabilized on the drug under investigation prior to randomization (enrichment design).

For SGA as adjunctive therapy to lithium or valproate, meta-analyses showed that treatment with either aripiprazole (RR: 0.65, 95% CI 0.50–0.85), quetiapine (RR: 0.38, 95% CI 0.32–0.46) or ziprasidone (RR: 0.62, 95% CI 0.40–0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Adjunctive therapy with quetiapine was the only drug that reduced both manic and depressive episodes.

For SGA as monotherapy, only quetiapine was shown to be better than lithium/ valproate for both manic and depressive relapses, but only for patients stabilized on quetiapine during the acute phase. As monotherapy, olanzapine, quetiapine and risperidone were shown to be superior to placebo in reducing the overall risk of relapses.

Limitations: There were considerable limitations to the evidence base of maintenance treatment with SGA in bipolar disorder. Most studies used stabilized patients, i.e. enrichment design (selection bias), had considerable dropout levels (attrition bias), and variable degree of reporting bias. No long-term RCT data on efficacy is available beyond 2 years, and almost all studies are on bipolar disorder type I patients only. Despite these limitations, we elucidate quantitative findings from meta-analyses conducted on the randomized trials published on the topic.

1. Introduction

Bipolar disorder is characterized by episodic mood swings into mania and depression. It is subdivided into bipolar disorder type I, with at least one manic episode, and bipolar disorder type II, with at least one hypomanic episode. However, both bipolar I disorder and bipolar II disorder are characterized by more time spent depressed than with mood elevations. The condition may also entail mixed states

* Correspondence to: Malin Höistad, SBU, Box 6183, 102 33 Stockholm, Sweden.
E-mail address: malin.hoistad@sbu.se (M. Höistad).
[1] LL and EL contributed equally to this paper.

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and rapid cycling (Baldessarini et al., 2012; Kroon et al., 2013; Merikangas et al., 2011). Patients with bipolar disorder have a pronounced increased risk in morbidity and mortality. This is commonly due to suicide and suicide attempts (Nordentoft et al., 2011; Schaffer et al., 2015) and to increased cardiovascular events (Ösby et al., 2016), but also co-morbidity exists between bipolar disorder, anxiety and drug abuse. Generally, individuals with bipolar disorders require life-long medication in order to control symptoms and avoid relapse (mood episode recurrence) (Bialer, 2012; Cipriani et al., 2013).

In order to prevent further mood episodes, first-line maintenance treatment is conventionally with lithium (Rybakowski, 2014). However, a considerable number of patients do not respond to (so-called non-responders) or tolerate (so called non-tolerators) lithium treatment. For lithium non-responders and non-tolerators, some anti-epileptic agents are also frequently used in view of their stabilizing effects in manic episodes, most commonly valproate or lamotrigine (Geddes et al., 2009; Weisler et al., 2006). Second generation antipsychotic agents (SGA) have also frequently been used to manage acute episodes of mania. It is now not uncommon that maintenance treatment with SGA is continued with the same drug as used during the acute episode management, most commonly as adjunctive treatment to lithium or valproate, in particular for patients with bipolar disorder type I.

This systematic review aimed to evaluate the effect and safety of maintenance treatment using second generation antipsychotics, either as monotherapy or as adjunctive therapy for at least 6 months, for individuals with bipolar disorder. The primary outcomes were relapse (mood episode recurrence) and discontinuation.

2. Methods

This systematic review was conducted at the *Swedish Agency for Health Technology Assessment and Assessment of Social Services* (SBU) and published as a HTA-report in Swedish (SBU, 2015a). The SBU uses a peer-review protocol process including pre-specified objectives and followes the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol was registered in the Euroscan database on Health Technology Assessments (www.euroscan.org).

2.1. Eligibility

The inclusion criteria was set up according to a structured so-called PICO framework, specifying the population, intervention, control and outcome, see Table 1. Excluded studies were studies on treatment of acute episodes, patients diagnosed with schizoaffective disorders or other serious psychiatric or neurological disorders, or treament comparing with other SGAs or anti-depressive medication. Studies that did not include quantitative results on relapse were also excluded. Only HTA-reports, systematic reviews, well-designed randomized control trials and well-designed observational studies formed the basis of the assessment of level of evidence. Other publications formats such as letter to the editor, conference abstracts were excluded.

Table 1
Study selection criteria according to PICO.

Population	Individuals (adults > 18y) with bipolar disorder
Intervention	Second generation antipsychotics (SGA), administered either as monotherapy or as adjunctive treatment to lithium or valproate
Control	Lithium, valproate, anti-convulsive medication or placebo
Outcomes	Discontinuation, relapses (any mood episode), manic relapse, depressive relapse, rating scale scores, adverse events

2.2. Search strategy and study selection

The electronic literature search was performed by an information specialist and included the databases PubMed, EMBASE and The Cochrane Library. Last search date was January 30, 2015. The text words and mesh terms used are available in Supplementary materials S1. All languages were accepted provided there was an abstract in English. Two reviewers (LL and EL) independently screened the titles and abstracts identified by the search strategy. The literature search yielded 2148 abstracts, of which 144 were considered potentially relevant. Full-text articles were assessed for relevance according to the predetermined inclusion/exclusion criteria. Any disagreement was resolved by discussions. Reference lists were screened for additional studies of relevance. We did not acquire data from unpublished trails.

2.3. Risk of bias assessment

Articles which met the inclusion criteria were assessed by the two independent reviewers (EL and LL) for risk of bias using standardized critical appraisal checklists from SBU (SBU, 2015b) adapted from the Cochrane Handbook for systematic reviews of interventions (http://training.cochrane.org/handbook). The critical appraisal checklists systematically identify any potential limitations in study design and execution, such as selection bias, performance bias, lack of blinding, detection bias, attrition, reporting bias or the presence of conflicts of interest. Only studies being rated as low to moderate risk of bias were included. Studies were assessed as having a high risk of bias when several limitations were present and when it was considered that the results could not provide reliable information. When there was lack of consensus about the quality of a study, the articles were appraised by the entire project group. The final overall assessment included 16 studies. Full flow chart of the literature selection process in found in Supplementary materials S2 and risk of bias assessment in Supplementary materials S3.

2.4. Data extraction

From each included study, data was extracted by either of the two independent reviewers (EL or LL), and the extracted data was audited and complimented by a third reviewer (MH). Any disagreements were resolved by discussion. The data extracted included: study type, diagnosis, index episode, intervention, dosages, follow-up time, n patients in screening phase, n patients in stabilization phase, n patients in each treatment arm, n patients completed study, n patients reported in efficacy analysis, n patients reported in safety analysis, n patients completed study in each arm, treatment discontinuation (defined as n ITT – n completers), the total number of patients with relapses (symptomatic relapse), number of patients with manic or depressive relapse, adverse events during randomized phase (weight gain, tremor, akatisia, daytime sleepiness and insomnia), and rating scale scores, mean change in total score from baseline to endpoint (for YMRS – Young Mania Rating Scale, MADRS - Montgomery-Asberg Depression Rating Scale CGI-BP – Clinical Global Impressions-Bipolar Severity overall). In case of missing data, authors were contacted.

Relapse (mood episode recurrence) was used as defined by original authors. In most studies, relapse was defined as: YMRS > 20 or MADRS > 20 at two sequential visits, or at last visit before dropout/discontinuation, or discontinuation due to a mood episode, hospitalization due to a mood episode, or initiation of other drug treatment not included in the study (anti-psychotic, anti-depressive or anxiolytic). Discontinuation was commonly defined by original authors as discontinuation of drug due to relapse or mood episode, due to lack of effect, due to adverse event, did no longer fulfill inclusion criteria, serious non-adherence, wrong randomization, loss to follow-up, consent withdrawn, or upon physicians recommendation.