Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials

STUDY PROTCOL

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Review title

We will perform a systematic review and NMA of the efficacy, tolerability, and safety of antipsychotics and/or mood stabilizers, and conducted a risk-benefit analysis of each medication for patients with bipolar disorder (BD) in the maintenance phase.

Anticipated or actual start date

25/02/2020

Anticipated completion date

22/05/2020

Stage of review at time of this submission

The review has not yet started (25/02/2020)

Funding sources/sponsors

The Health and Labor Sciences Research Grants (H29-Seishin-Ippan-001, 19GC1012)

Conflicts of interest

None

Review question

We will investigate which antipsychotics and/or mood stabilizers are better for patients with BD in the maintenance phase.

Searches

The authors will search Embase, MEDLINE and the Cochrane Central Register of Controlled Trials for studies published prior to March 15, 2020. The search terms will include (bipolar disorder OR mania OR manic OR hypomania OR hypo-mania OR rapid cycle OR rapid-cycle OR bipolar depression OR affective) AND (randomized OR random OR randomly) AND (depot OR decanoate OR enanthate OR long acting injectable OR microsphere OR once monthly OR palmitate OR pamoate OR valproic acid OR valproate OR divalproate OR divalproex OR carbamazepine OR oxcarbazepine OR risperidone OR olanzapine OR aripiprazole OR quetiapine OR perospirone OR ziprasidone OR clozapine OR amisulpride OR asenapine OR blonanserin OR clothiapine OR iloperidone OR lurasidone OR mosapramine OR paliperidone OR remoxipride OR sertindole OR sulpiride OR tiapride OR chlorpromazine OR thioridazine OR mesoridazine OR loxapine OR molindone OR perphenazine OR thiothixene OR trifluoperazine OR haloperidol OR fluphenazine OR droperidol OR zuclopenthixol OR pimozide OR flupenthixol OR prochlorperazine OR lithium OR lamotrigine) AND (placebo). We will also search clinical trial registries such as ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/) to ensure the included set of RCTs was comprehensive, and to minimize the influence of publication bias.

Condition or domain being studied

Adult patients with BD in the maintenance phase

Participants/population

Inclusion criteria were: (1) randomized controlled trials (RCTs) of antipsychotics and/or mood stabilizers lasting at least 12 weeks, (2) studies including adult patients with any subtype BD in the maintenance phase, (3) studies including patients with any mood symptoms at recruitment, (4) open studies and those with any level of blinding, and (5) studies with/without an enrichment designs. Exclusion criteria were: (1) studies with child/ adolescent patients with BD, (2) continuation studies that randomly assigned patients with acute symptoms to treatment groups, (3) monotherapy and/or combination therapy studies of antidepressants with mood stabilizers or antipsychotics. Recent meta-analyses demonstrated that antidepressants might increase the risk of mood swings with no improvement in prophylaxis of new depressive episodes in patients with BD,10 and a previous NMA reported that lithium plus imipramine might increase relapse/recurrence of manic episodes in BD type I (BDI).7 Therefore, we excluded antidepressant studies from our meta-analysis.

Intervention(s), exposure(s)

Antipsychotics and/or mood stabilizers

Comparator(s)/control

Antipsychotics, mood stabilizers and/or placebo

Types of study to be included

We will include only randomized trials to assess the beneficial effects of the treatments.

Main outcome(s)

Recurrence/relapse rate of any mood episode

Measures of effect

Risk ratio

Additional outcome(s)

Recurrence/relapse rate of depressive episodes, recurrence/relapse rate of manic/hypomanic/mixed episodes, all-cause discontinuation, discontinuation rate due to adverse events, mortality rate, and incidence of individual adverse events

Measures of effect

Risk ratio

Data extraction

The literature search, data extraction, and data input into spreadsheets for analysis will be done simultaneously and independently by at least two authors (TK, TI, YM, KS, and MO). The authors will double-check the accuracy of data transfer and calculations in the study. We will analyze extracted data based on intention-to-treat or modified intention-to-treat principles. When data required for meta-analysis were missing in the articles, we will search for these data in published systematic review articles. We will attempt to contacted original study investigators to obtain unpublished data.

Risk of bias (quality) assessment

We will assess the methodological quality of the included trials in accordance with the Cochrane risk of bias criteria as set out in the Cochrane Handbook for Systematic Reviews of Interventions.

Strategy for data synthesis

The first will include: (1) placebo-controlled and head-to-head trials of monotherapy of antipsychotics and/or mood stabilizers, and (2) combination or augmentation studies where the two drugs used were specified. The second NMA will include studies in which second-generation antipsychotic (SGAs) combined with lithium or valproate (LIT/VAL) were compared with placebo-LIT/VAL. A Bayesian NMA based on random-effects models, was will conduct using the netmeta package. We fitted random-effects frequentist NMAs, in which we will assume a common random-effects standard deviation for all comparisons in the network. The risk ratio (RR) and 95% credible interval (95% CI) will be calculated. The heterogeneity standard deviation will be also calculated for all outcomes. The odds ratios and their 95% CIs will be calculated for mortality rate and completed suicide rate because incidences of these outcomes are very rare. We will assesse network heterogeneity using $\tau 2$ and I^2 statistics with the netmeta package. We will conduct a statistical evaluation of consistency using the design-by-treatment test (globally) and the node-splitting approach or Separate Direct from Indirect Evidence test (locally). The Bayesian analyses will also estimate rank probabilities (i.e., probability of each treatment obtaining each possible rank as shown by their relative effects). The surface under the cumulative ranking area will be calculated to rank the interventions.

Analysis of subgroups or subsets

We will perform a meta-regression analysis in the first NMA to examine whether some potentially confounding factors (e.g., publication year, duration of study, number of total patients, percent female, and mean age) will be associated with the extent of effect on primary and secondary outcomes.

In addition to analyses conducted previously, we also will perform sensitivity analyses for primary and secondary outcomes in the first NMA, in which we will give only half the weight to: (1) studies that included both BDI and other BD patients (when focusing on studies including only BDI patients), (2) studies that included rapid-cycling BD patients and those that excluded rapid-cycling BD patients (when focusing on studies excluding rapid-cycling BD patients because rapid-cycling BD is considered to be more difficult to stabilize than non-rapid-cycling BD), (3) non-double-blind studies (when focusing on double-blind studies), (4) study arms that were “enriched” (when focusing on non-enriched studies), and (5) study arms supported by industry sponsors (when focusing on non-industry sponsorship studies).

Type and method of review

Network meta-analysis

Systematic review

Mental health and bevaioural conditions

Language

English

Country

Japan

Current review status

Ongoing