INPLASY PROTOCOL

To cite: Li et al. Comparative efficacy and safety of different drugs for the therapy in patients with bipolar disorder complicated with anxiety disorder: a protocol for systematic review and network meta-analysis. Inplasy protocol 202070132. doi: 10.37766/inplasy2020.7.0132

Received: 31 July 2020

Published: 31 July 2020

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Support: **2018-RC-52**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Comparative efficacy and safety of different drugs for the therapy in patients with bipolar disorder complicated with anxiety disorder: a protocol for systematic review and network meta-analysis

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Review question / Objective: **What are the efficacy and safety of different drugs for the therapy in patients with bipolar disorder complicated with anxiety disorder?**
Condition being studied: **Patients with bipolar disorder complicated with anxiety disorder.**
Information sources: **The literature search will be conducted in the Cochrane Library, PubMed, Embase and Web Of Science from inception until July 30, 2020. If not, we try to contact with the authors or trial registers.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 July 2020 and was last updated on 31 July 2020 (registration number INPLASY202070132).

INTRODUCTION

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METHODS

Search strategy: We will search the Cochrane Library, PubMed, Embase , Web of Science to identify relevant published and unpublished trials from systematic searches (The relevant systematic reviews, grey literature and guidelines will also be included). The search strategy will be adapted to each database, the search terms include "bipolar disorder" , "bipolar affective disorder", "manic depressive", "manic-depressive psychosis", "anxiety disorders", etc. There will be no restrictions on publication year.

Participant or population: Patients with bipolar disorder complicated with anxiety disorder, they had to meet the following criteria: (1) aged 18-65 ; (2) bipolar I disorder, bipolar II disorder or NOS (nonspecific bipolar disorder) diagnosed by DSM-IV criteria, confirmed by the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-I/P) ; (3) anxiety disorders diagnosed by DSM-V criteria (it includes separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder, agoraphobia, GAD and panic attack specifier).

Intervention: Any pharmacological treatments.

Comparator: Placebo or any active drugs.

Study designs to be included: Only randomized controlled trial will be included.

Eligibility criteria: Eligibility criteria for the review are based on the PICOS framework. We will include studies that meet the following criteria: (1) Patients diagnosed with bipolar disorder complicated with anxiety disorder; (2) The intervention group includes any pharmacological treatments; (3) The controlled group is a placebo or any active drugs that being used in clinical practice; (4) Only randomized controlled trial will be included (RCTs).

Information sources: The literature search will be conducted in the Cochrane Library, PubMed, Embase and Web Of Science from inception until July 30, 2020. If not, we try to contact with the authors or trial registers.

Main outcome(s): The main outcome measure is the efficacy, measured by the overall mean change scores on anxiety symptom scales (rated by qualified evaluators) between baseline and week 8 (range 4 - 12 weeks), for example, Hamilton Depression Rating Scale (HAMD), The Clinician Global Improvement Scale for Anxiety (CGI-21 Anxiety) and Sheehan Panic Disorder Scale (SPS).

Additional outcome(s): The additional outcome measure is the safety, we mainly evaluate the adverse reactions or side effects of drug therapy, measured by the rating scale of adverse drug reactions in psychiatric department commonly used in clinical practice, it includes the following scales : Rating Scale for Extrapyramidal Side Effects (RSESE), Udvalg for Kliniske Undersogelser (UKU).

Data management: The date will be extracted independently by two reviewers using standardized data extraction forms. Any disagreements will be resolved through discussion between the two parties or decided by a more qualified third party.

Quality assessment / Risk of bias analysis: The methodological quality of the included RCTs will be independently evaluated by two reviewers, any disagreements will be resolved through discussion between the two parties or decided by the third reviewer.Consistent with the Cochrane Handbook for Systematic Reviews of Interventions, we will use the Cochrane bias risk assessment tool to evaluate the risk of bias, The following items will be evaluated: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other source of biases.

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Strategy of data synthesis: First of all, we will use the random effect model of StataV.15.0 to conduct paired meta-analysis of direct evidence. As for continuous variable data, we will use the SMD of 95% confidence interval to calculate and estimate, odds ratio (OR) or relative risk (RR) will be used as the outcome measure of dichotomous variable data.The statistical heterogeneity will be examined using the I2 statistic, if the P value >0.1 and I2<50%, it suggests that there is no statistical heterogeneity, the Mantel Haenszel fixed effect model will be use, if not, we will explore sources of heterogeneity by subgroup analysis and meta-regression. If applicable, Begg's and Egger's funnel plot method will be used to evaluate the potential publication bias. Consistency will be assessed using the Wald test. Secondly, we will use Markov chain Monte Carlo method in WinBUGS V.1.4.3 (MRC Biostatistics Unit, Cambridge, UK) to perform random effect network element analysis in Bayesian framework, if certain conditions are satisfied, we will use the node splitting method to examine the inconsistency between direct and indirect Comparisons. Besides, we used the surface under the cumulative ranking curve for the treatment of patients with bipolar disorder complicated with anxiety, the ranking probability of the efficacy and safety of different drugs will be estimated. The results of the rankograms, ranking probabilities plots and evidence network graph will also be presented graphically.

Subgroup analysis: Where possible, we will conduct the network meta-regression meta-analyses of data on primary outcomes for the: (1) age of participants; (2) sex ratio; (3) the severity of bipolar disorder symptoms at baseline; (4) the severity of anxiety symptoms at baseline; (5)the treatment duration. If possible, we will do some extra subgroup analyses according to the results of heterogeneity and inconsistency.

Sensibility analysis: Where possible, we will conduct a series of sensitivity analyses, trials where missing data have been imputed will be excluded, trials where high risk of bias rating have been assessed, and trials where only included patients comorbidity with other psychiatric disorders will be excluded. We will also investigate the sources of heterogeneity to determine the robustness and reliability of the consolidated results.

Language: English.

Country(ies) involved: China.

Keywords: bipolar disorder; anxiety disorder; efficacy; placebo.

Contributions of each author:
Author 1 - Yang Li - Provided methodological advice, polished and revised the manuscript.
Author 2 - Yan Meili - Study design, data extraction and drafted the manuscript.
Author 3 - Du Li - In charge of extracting data and verification, and provided expertise on treatments, outcomes and related knowledge.
Author 4 - Zhang Zhigang - Was the corresponding author and approved the final version of the manuscript.
Author 5 - Hu Shasha - Was the corresponding author, responsible for all work of the review.

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