INPLASY PROTOCOL

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Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Efficacy and Safety of Antidiabetic Agents for Major Depressive Disorder and Bipolar Depression: A meta-analysis of randomized, double-blind, placebo-controlled trials

Zhang, J[1]; Yang, X[2]; Sun, R[3]; Cai, Y[4]; Gao, K[5].

Review question / Objective: **To systematically evaluate the efficacy and safety of hypoglycemic agents for the treatment of a depressive episode of major depressive or bipolar disorder.**
Condition being studied: **Major depressive disorder and bipolar depression are highly prevalent with high recurrent rates. Both disorders are the leading causes of years lost to disability (YLD) and cause heavy burden to patients, their families, and society. However, a significant number of patients with major depressive disorder or bipolar depression do not respond or cannot tolerate current pharmacological treatments. With the exception of ketamine, most medications for major depression are monoaminergic agents. For bipolar depression, lithium, anticonvulsants, and antipsychotics are the treatment options. Agents with different antidepressant mechanism have attracted researches. Antidiabetics are among medications explored for depression. Their efficacy and safety are important to guide clinical practice and future research. However, there is still no large study to provide a firm conclusion. Therefore, a meta-analysis of currently published studies is essential to provide data for future studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 September 2020 and was last updated on 13 September 2020 (registration number INPLASY202090058).

INTRODUCTION

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METHODS

Search strategy: Three electronic databases PubMed, Embase, the Cochrane library and three clinical trials register websites clinicaltrials.gov, ISRCTN register, and ICTRP register will be searched. The search terms should include but not limited to "depression", "bipolar disorder", "hypoglycemic agents", "antidiabetic", the generic names of antidiabetic agents, and "randomized controlled trial". A manual search of references in relevant articles will be conducted as a supplemental approach.

Participant or population: All subjects who were diagnosed with an acute depressive episode of major depressive disorder or bipolar depression according to standard diagnosis criteria.

Intervention: Antidiabetic medication monotherapy or adjunct to psychotropic agents.

Comparator: Placebo alone or adjunct to psychotropic agents.

Study designs to be included: Randomized, double-blinded, placebo-controlled trials.

Eligibility criteria: Inclusion criteria: 1) The study included subjects who had major depressive disorder or bipolar disorder diagnosed with a standard diagnostic instrument; 2) The study was randomized, double-blind of an antidiabetic medication versus placebo in the treatment for an acute depressive episode; 3) Depressive severity was measured with at least one standard depressive symptom rating scale. Exclusion criteria: 1) Studies were non-randomized and double-blind, or randomized, double-blinded studies in patients who were not in an acute depressive episode; 2) Studies did not have the data for primary or secondary outcome measures; 3) Studies were open-label, case reports, case series reports, or studies on animals.

Information sources: Information will be acquired from published articles from major citation databases, and protocols and results from clinical trial registries. Authors of the original publication(s) will be contacted for missing data.

Main outcome(s): The primary outcome is the difference of changes in depression rating scale scores from baseline to endpoint between placebo and active treatment. Differences in response and remission rates are secondary outcome measures.

Additional outcome(s): Differences between placebo and active treatment in safety and tolerability are additional outcome measures. Premature discontinuation and reported adverse events such as digestive side effects, headache, dizziness, insomnia, hypoglycemia will be compared.

Data management: Two reviewers will independently extract data with a pre-designed excel sheet. Variables include but not limit to: location, publish year, type of design, setting, age, gender, medications used, adding-on medications, baseline score, change score, number of responders, number of remitters, and safety. Any disagreement on a variable will be resolved by consensus of the two reviewer or a third reviewer.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess and score the risk of bias for each study according to the Cochrane tool (RoB 2.0). Each bias will be ranked as high, low or unclear. The biases being assessed include but not limit to: selection bias, performance bias, detection bias, attrition bias, reporting bias and publication bias. Any disagreement on a bias assessment will be resolved by discussion or a third reviewer.

Strategy of data synthesis: Statistical analysis will be conducted using RevMan 5.3 and Stata 16.0. Data will be summarized using mean difference (MD) and standardized mean difference (SMD) with 95% confidence intervals (CI) for continuous variables, and risk ratio (RR) with 95% confidence intervals (CI) for dichotomous variables. Heterogeneity will be examined using Q statistics or I2 values. A fixed-effect model will be used if heterogeneity is low, whereas a random-effect model will be used if heterogeneity is significant. Subgroup analysis, meta regression and sensibility analysis will be used to detect the potential sources of heterogeneity.

Subgroup analysis: If necessary and having enough data, subgroup analysis will be carried out to detect the potential sources of heterogeneity. The factors could include but not limit to: study region, diagnosis, types of intervention, and outcome measurements. The specific subgroups analyses may also be undertaken by the final result of qualitative synthesis.

Sensibility analysis: We will carry out sensibility test for each pooled result with heterogeneity by performing step-by-step elimination analysis with removing one study a time to address possible resource of heterogeneity.

Country(ies) involved: United States & China.

Other relevant information: Jian Zhang and Xi Yang are co-first authors.

Keywords: Depression, hypoglycemic agents, meta-analysis.

Conflicts of interest: Dr. Gao was on an advisory board of Sunovion and Otsuka, was a member of a speaker's bureau of AstraZeneca, Pfizer and Sunovion, and received grant support from AstraZeneca, the Cleveland Foundation and the Brain and the Behavioral Research Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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