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Version 2

ADMINISTRATIVE INFORMATION

Title

Protocol of the study "Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar disorder and major depressive disorder: a systematic review with meta-analysis of randomized controlled trials"

Registration

This protocol was not registered before the commencement of the study.

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Author Contributions

KSJL, ICKW and EWC had the original idea for this study and contributed to the development of the idea and study design. KSJL wrote the first draft of the study protocol. KSJL and YH independently conducted a systematic review and reviewed the literature for relevance. KSJL and YH undertook the analysis. KSJL, YH, ICKW and EWC contributed to interpretation of the analysis. KSJL and YH wrote the first draft of the paper. KSJL, YH, ICKW and EWC critically reviewed the results and the manuscript. FMCB reviewed the data and presentation of the paper, and provided clinical input. ICKW and EWC provided oversight to all aspects of this project. KSJL and EWC are the guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Amendments

First Amendment for this study protocol was conducted in June 2016 (version 2, 20160621). A sensitivity analysis was added to investigate the effect of combination treatment by excluding RCTs with a combination treatment arms (antipsychotics and antidepressants) from the primary analysis. GRADE evaluation was conducted in this version of the protocol.

Support

This work was not supported by any funding.

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INTRODUCTION

Rationale

Cariprazine is a novel antipsychotic agent recently approved for the treatment of schizophrenia [1-3] and bipolar mania[4-7]. Significant improvement in mental disorder symptoms has been shown in published randomized controlled trials (RCT). However, sample sizes of RCTs are small and previous meta-analyses only included a small number of RCTs[8-11]. Furthermore, previous meta-analyses did not specifically investigate the tolerability/safety profile of cariprazine.

Objective

The objective of this study is to systematically review all available literature related to the tolerability and safety of cariprazine use, to investigate the risk of all reported adverse events (primary outcome) in adult patients (aged 18 years old or above) receiving cariprazine or placebo in phase II/III RCTs.

METHODS

Study design

This is a systematic review with a meta-analysis.

Types of study to be included

Studies of the following designs will be eligible for inclusion: randomized, placebo-controlled, phase II/ III clinical trials, with at least one cariprazine treatment arm.

Participants/ population

Study population are patients diagnosed with mental disorders (schizophrenia, bipolar disorder or other mental illnesses) and treated with cariprazine. Therefore, all patients assigned to cariprazine-treatment arms or placebo arms will be included.

Intervention and comparator

Intervention arm will comprise of cariprazine treatment and comparator arm will comprise of placebo.

Information sources

The literature search will be conducted using electronic databases and RCTs registers including PubMed, Embase, PsycINFO, the Cochrane library and trial registries, including the metaRegister of controlled trials (www.controlled-trials.com), the Clinical trials government (http://www.ClinicalTrials.gov) and the World Health Organisation International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/).

Search strategy

Key words used for the search will include "Vraylar OR (trans-4-(2-(4-(2,3-dichlorophenyl)piperazine-1-yl)-ethyl)-N,N-dimethylcarbamoyl-cyclohexyl-amine) OR RGH-188 OR cariprazine". No publication time or language limit will be set in literature search.

Study record

Two independent reviewers will conduct the literature search, title and abstract screening with respect to the eligibility criteria as mentioned above. Full texts of studies likely to be eligible as judged by reviewers will be downloaded from electronic databases. Full text articles will be assessed by reviewers independently for confirmation of eligibility. Any disagreement will be resolved by discussion and reassessment.

Data items

Variables for data collection will include study design information (RCT phase, inclusion and exclusion criteria, cariprazine dose, region, design of control arm, treatment duration), number of patients included (in several steps including randomization, treatment or follow-up period), number of patients with any adverse events (whether diagnosed by clinician or defined by changes in laboratory parameters), and changes in laboratory parameters.

Outcomes and prioritization

The primary outcomes of this study will include: (1) overall discontinuation of treatment due to adverse events, (2) extrapyramidal side effect (EPS) related outcomes (discontinuation due to EPS-related adverse events, number of patients with recorded EPS adverse events, mean change of EPS-related scales), (3) metabolic-related outcomes (mean change of metabolic syndrome related laboratory parameters, number of patients with potentially clinically significant change) and (4) cardiovascular risk related outcomes. The focus is placed on these four categories of outcomes as these are the adverse events that have raised major concerns toward atypical antipsychotic medications[12-18].

The secondary outcomes will be other tolerance/safety outcomes including risk of discontinuation of treatment due to other reasons, other adverse events reported, and the mean change of other laboratory parameters from baseline to the end of treatment.

Risk of bias assessment and reporting

This study will be conducted following guidance provided in the Cochrane Handbook [19] and will be reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [20].

The methodological quality of included RCTs will be assessed using the Cochrane Collaboration tool for assessing the risk of bias [21]. Domains including sequence generation, allocation concealment, blinding method, incomplete outcome data, selective outcome reporting and other sources of bias will be assessed. Based on the information assessed, each domain will be graded as "low risk of bias", "high risk of bias" or "unclear risk of bias" for each RCT. Domain assessments will be conducted by two reviewers independently. Domains with disagreement will be resolved by discussion and reassessment.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines will be applied to assess the body of evidence[22 23]. An evidence profile table (EP) and a summary of findings table (SoFs) will be generated using GRADEpro [24] for the primary outcomes. Judgement criteria will be designed for individual outcomes and grading will be done by two independent reviewers. Disagreements will be resolved by discussions to reach consensus.

Data synthesis

Only studies homogeneous in terms of study design (randomized, placebo-controlled trial), study population (patients with mental disorders), intervention (any dosage of cariprazine) and outcome reporting (discontinuation of treatment and adverse events record) will be synthesised.

Continuous outcomes (mean change of scale, mean change of body weight or other laboratory parameters) will be reported as the mean difference with 95% confidence intervals (95% CI). Standardized mean difference will be calculated to compare results from other studies. Dichotomous outcomes (discontinuation of treatment, number of patients with any adverse events) will be reported as a relative risk with 95% CI. Narrative summary will be conducted for outcomes reported in less than 2 RCTs. The Mantel-Haenszel method with random effects model will be applied.

Heterogeneity will be assessed using Cochran's Q statistical test and $P < 0.10$ will be considered significant. The I^2 statistic will also be calculated to estimate the proportion of total variation among

studies, where values of 25%, 50% and 75% will be regarded as low, moderate and high heterogeneity, respectively. Review Manager 5.3 [25] will be used to conduct all analyses.

Subgroup analysis

All primary outcomes will be analysed in subgroups. Results of subgroup analysis will be compared between subgroups. Subgroups will be stratified by dose (low dose group: <6mg/day and high dose group: ≥6mg/day) and indication (schizophrenia, manic episodes of bipolar disorder and bipolar I depression). Post-hoc sensitivity analysis will be conducted to exclude studies investigating patients with major depressive disorder from the primary analysis and results of sensitivity analysis will be compared with the primary analysis, to investigate the possible effect by adjunctive antidepressant.

Meta-bias

Funnel plots will be used to assess publication bias if more than 10 studies are included in this study.

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