INPLASY

Dose-effect trajectory of lumateperone in schizophrenia: Protocol for a meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - Taiwan Ministry of Science and Technology.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 January 2025 and was last updated on 12 January 2025.

INTRODUCTION

Review question / Objective Population: patients with an established diagnosis of schizophrenia-spectrum disorder; Intervention: lumateperone; Comparison: placebo; Outcome: changes in severity of psychiatric symptoms, response rates, dropout rates, and side effect rates; Study design: peer-reviewed randomized controlled trial (RCT).

Rationale To investigate the relationship between different doses of lumateperone and the treatment of schizophrenia, this study systematically reviewed randomized controlled trials (RCTs) for the inclusion in a dose-response meta-analysis. The study will focus on assessing the efficacy of lumateperone used to treat schizophrenia, as well as evaluating the acceptability of lumateprone treatment by analyzing dropout and side effect results.

Condition being studied Schizophrenia.

METHODS

Search strategy The keywords (Lumateperone OR ITI-007 OR ITI-722) AND (psychosis OR psychotic disorder OR schizophreni* OR schizoaffective disorder OR delusional disorder) were used to conduct a comprehensive literature search using PubMed, EMBASE, Cochrane Central, and ScienceDirect database from inception to January 20, 2025. The registration website, ClinicalTrials.gov, was also searched.

Participant or population Patients with an established diagnosis of schizophrenia-spectrum disorder.

Intervention lumateperone.

Comparator Placebo.

Study designs to be included Peer-reviewed randomized controlled trial.

Eligibility criteria Studies were included to this study based on the following criteria: (1) RCTs comparing placebo with lumateperone (with or without co-administration). In this DRMA, we assumed the placebo to be a zero dose of lumateperone, thus RCTs that compare lumateperone with other drugs were not included; (2) Participants with established diagnosis of schizophrenia-spectrum disorder based on valid criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders, or the International Classification of Diseases); (3) RCTs that assessed schizophrenia symptom severity using a validated scale, such as the Positive and Negative Syndrome Scale (PANSS), before and after a lumateperone treatment course. The exclusion criteria were as follows: (1) The study did not have a placebo group; (2) Study participants were not diagnosed with schizophrenia, such as bipolar disorder; (3) Data for schizophrenia symptom severity before and after the treatment course was not available; (4) Duplicate dataset with a larger study. For studies with overlapping datasets, we included the study with the largest sample size and most detailed data.

Information sources PubMed, EMBASE, Cochrane Central, ScienceDirect database, ClinicalTrials.gov.

Main outcome(s) This DRMA focused on the two primary outcomes of efficacy and acceptability. Efficacy was measured by the difference between the pre- and post-intervention assessments PANSS score for schizophrenia symptom severity. We also assessed treatment efficacy for the PANSS subscales, namely the positive and negative schizophrenia symptoms, as well as the efficacy for treatment responders. Response is usually defined by a >30% improvement in PANSS scores [3]. Safety was measured as the all-cause dropout rate, which was the quotient of the number of dropouts divided by the total number of participants randomized in each treatment arm. Other secondary safety outcomes that were assessed included incidences of (1) any side effects and (2) common side effects, such as headache, nausea, dizziness, etc.

Data management Endnote and Excel.

Quality assessment / Risk of bias analysis The risk of bias was evaluated by two researchers (YC Chen and CW Hsu) using the Cochrane Risk of Bias Tool version 2 (ROB2). Disagreements were resolved through consensus between the two researchers, and a third researcher (PT Tseng) was consulted as necessary.

Strategy of data synthesis We used mean dose of lumateperone for dose categories and explored the relationship between lumateperone dosage and study outcomes. We investigated a couple of effect sizes in this study. First, we calculated the change in schizophrenia symptom scores from before and after intervention, and converted them into standardized mean differences (SMDs) with 95% confidence intervals (CIs). Second, we assessed the number of responders, dropouts, and events of side effects and converted them into risk ratios (RRs) with 95% CIs. Moreover, we were interested in treatment effects over time between different dose categories, so we additionally assessed the relationship between treatment duration and improvement in psychotic symptoms. In this study, we used one-step DRMA method utilized by our team in previous similar studies [4-6]. We implemented methodologies developed by Greenland [7] and Orsini [8] to investigate potential nonlinear trends in the data. Restricted cubic splines with three knots were placed at fixed percentiles (10%, 50%, and 90%) [9], which corresponds to different lumateperone doses. We assessed for heterogeneity using the variance partition coefficient, which is an extension of the I-squared statistic, and represents the percentage variance attributable to heterogeneity [10]. We used the dosresmeta package in R software for all analyses. Statistical significance was set at $p < 0.05$.

Subgroup analysis No subgroup analyses will be conducted.

Sensitivity analysis We performed two sensitivity analyses to examine the robustness of our findings. First, while the new drug lumateperone may have data available on registration platforms like ClinicalTrials.gov, these data are often not published or peer-reviewed. Nonetheless, such data are crucial for maintaining the integrity of the evidence base [11]. Therefore, we conducted a sensitivity analysis by including such trials and reanalyzing the effect sizes for all outcomes. Second, we conducted a leave-one-out analysis to assess the influence of each study on the overall results.

Language restriction No language or region restrictions were applied in the search.

Country(ies) involved Taiwan.

Keywords lumateperone; dose-response; ITI-007; ITI-722; efficacy.

Contributions of each author

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