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Dose-Response Efficacy and Safety of Lumateperone in Bipolar Depression: A Living Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - National Science and Technology Council (Taiwan): 112-2314-B-182-070-MY3.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202510048

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 January 2025 and was last updated on 1 July 2025.

INTRODUCTION

Review question / Objective PICOS framework: (1) Population: individuals with bipolar disorder currently experiencing a major depressive episode; (2) Intervention: lumateperone; (3) Comparator: placebo; (4) Outcomes: changes in depression severity and dropout rates as primary interests; and (5) Study Design: randomized controlled trial (RCT).

Condition being studied Our goal was to locate RCTs evaluating the efficacy and safety of lumateperone for bipolar depression.

METHODS

Search strategy (lumateperone OR ITI-007 OR ITI-722) AND (depress* OR bipolar OR affective OR mood).

Participant or population Participants with bipolar disorder currently experiencing a major depressive episode.

Intervention Lumateperone.

Comparator Placebo.

Study designs to be included Randomized controlled trial.

Eligibility criteria The inclusion criteria were: (1) RCTs that compared placebo with lumateperone (administered alone or in combination). We assumed placebo to be a zero dose of lumateperone; therefore, studies comparing lumateperone with other active agents would not yield dose-response data. (2) Participants had a bipolar depression diagnosis established by standard criteria (e.g., the Diagnostic and Statistical Manual of Mental Disorders). (3) RCTs reporting pre- and post-treatment depression

severity using a validated scale (e.g., the Montgomery-Asperger Depression Rating Scale [MADRS]) to evaluate lumateperone. We excluded studies if (1) they compared lumateperone only with other active treatments, omitting a placebo arm; (2) they enrolled patients with diagnoses other than bipolar disorder (e.g., schizophrenia); (3) they did not measure depressive symptoms as an outcome; or (4) they duplicated data from the same research protocol. In cases of multiple articles originating from the same dataset, only the one with the largest sample size and most comprehensive information was included.

Information sources We performed a thorough search of PubMed, EMBASE, Cochrane CENTRAL, ClinicalTrials.gov, and gray literature from each database's inception through July 1, 2025. We also manually searched the references in the literature.

Main outcome(s) We focused on efficacy and safety outcomes. For efficacy, the primary variable of interest was the change in depression severity, assessed using the MADRS. The primary safety metric was the dropout rate, calculated by dividing the number of participants who discontinued the trial (for any reason) by the total randomized sample.

Additional outcome(s) Secondary efficacy outcomes included: (1) global illness severity, such as the change in Clinical Global Impression-Bipolar-Severity (CGI-BP-S) overall bipolar illness and depression scores; (2) quality of life, such as scores on the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF); (3) responder rate (MADRS total score ≥ 50% decrease from baseline); and (4) remitter rate (MADRS total score ≤12). Secondary safety outcomes included (1) discontinuations due to adverse events (AEs), (2) any treatment-emergent adverse events (TEAEs), (3) mania or hypomania AEs, (4) suicidal ideation or behavior AEs, and (5) extrapyramidal symptom (EPS). These events were defined as any AEs reported over the course of the study. In addition, we were interested in metabolic effects—including body weight and laboratory values for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting glucose—which were treated as supplementary safety outcomes. If the information was not found in the published article, we contacted the corresponding author for clarification.

Quality assessment / Risk of bias analysis Risk of bias (ROB) in each included trial was assessed by the Cochrane Handbook methodology.

Strategy of data synthesis For continuous variables, we computed pre- to post-treatment changes and expressed them as standardized mean differences (SMDs) with 95% confidence intervals (CIs). For categorical variables, we calculated event counts and converted these to risk ratios (RRs) with 95% CIs. We explored whether lumateperone, compared with placebo, exhibited a dose-dependent relationship for both primary and secondary outcomes by using a one-stage random-effects DRMA. Dose-response curves were modeled with restricted cubic splines (three knots) at fixed percentiles (10%, 50%, and 90%). We evaluated model fit using goodness-of-fit statistics; the coefficient of determination (R-squared) reflected the proportion of effect-size variability that could be explained by dose.

Subgroup analysis Because we were interested in whether dose and efficacy patterns were similar for bipolar I disorder and bipolar II disorder, we did a subgroup analysis stratified by bipolar subtype.

Sensitivity analysis We performed a leave-one-out analysis to evaluate whether excluding each study individually impacted the overall findings.

Language restriction No.

Country(ies) involved Taiwan.

Keywords lumateperone, bipolar, depression, efficacy, safety.

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