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Association of atypical symptoms with bipolar disorder versus major depressive disorder: A protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support was received for this study.

Review Stage at time of this submission - The review has not yet started.

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 9 July 2026 and was last updated on 9 July 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis is to evaluate whether atypical symptoms occur more frequently in bipolar disorder (BD) than in major depressive disorder (MDD).

Rationale Distinguishing BD from MDD is clinically important because these disorders differ in their course, prognosis, and treatment. However, this distinction may be challenging because both disorders are characterized by depressive episodes defined by the same DSM-5 diagnostic criteria, and many individuals with BD initially present with a depressive episode before experiencing hypomania or mania. The potential role of atypical features in distinguishing BD from MDD has been extensively investigated. Clinical studies have suggested that atypical symptoms, including mood reactivity, hypersomnia, increased appetite, weight gain, leaden paralysis, and rejection hypersensitivity, may occur more frequently in BD than in MDD. However, to our knowledge, no systematic review and meta-analysis has yet evaluated this hypothesis.

Condition being studied According to DSM-5, atypical features are a specifier of depressive episodes that can be applied to both BD and MDD. They include mood reactivity, hypersomnia, increased appetite, weight gain, leaden paralysis, and rejection hypersensitivity.

METHODS

Participant or population The target population will include individuals with BD, including BD-I, BD-II, and other specified or unspecified BD.

Intervention Not applicable.

Comparator The comparator group will consist of individuals with MDD.

Study designs to be included We will include observational studies reporting comparative data

on atypical symptoms in individuals with BD and MDD.

Eligibility criteria We will include observational studies comparing the frequency of at least one atypical symptom (mood reactivity, hypersomnia, increased appetite, weight gain, leaden paralysis, or rejection hypersensitivity) between individuals with BD and MDD. To improve comparability across studies, we will include only studies using DSM-IV, DSM-5 or equivalent ICD diagnostic criteria.
We will exclude studies that:
– do not report data on at least one specific atypical symptom;
– are restricted to specific clinical subgroups;
– do not allow extraction of raw data on atypical symptoms;
– are based on samples overlapping with those of another included study;
– include participants with a mean age 65 years;
– include fewer than 20 individuals with BD or MDD.
We will also exclude grey literature, dissertations, and conference abstracts that have not undergone peer review.

Information sources We will search PubMed, Embase, and Scopus. Search strategies will combine terms related to atypical features (mood reactivity, hypersomnia, increased appetite, weight gain, leaden paralysis, and rejection hypersensitivity) with terms related to BD and MDD. We will also screen the reference lists of relevant reviews on atypical symptoms in BD to identify additional eligible studies. An exploratory, non-systematic search of Google Scholar will be conducted to identify any further eligible studies. No language or date restrictions will be applied. EndNote will be used to manage records and remove duplicates. Corresponding authors of potentially eligible studies will be contacted when additional information is required.

Main outcome(s) The outcomes will be the frequency of each atypical symptom (mood reactivity, hypersomnia, increased appetite, weight gain, leaden paralysis, and rejection hypersensitivity) among individuals with BD compared with those with MDD.

Data management Studies will be screened independently by at least three investigators. Any disagreements regarding study eligibility will be resolved through discussion among all investigators. Following title and abstract screening, full-text articles will be retrieved and assessed for eligibility. Reasons for exclusion at the full-text stage will be recorded. Data from eligible studies will be extracted independently by at least three investigators to allow a blinded assessment of data extraction accuracy. A standardized data extraction form will be used to collect at least the following information: authors, year of publication, study design, sample characteristics, and the frequency of atypical symptoms in BD and MDD.

Quality assessment / Risk of bias analysis Risk of bias will be assessed across predefined methodological domains. First, we will evaluate the representativeness of the study population by assessing whether participants were recruited from the general population or from clinical settings that are sufficiently representative of individuals with BD and MDD. Second, we will assess the risk of selection bias by evaluating the comparability of the BD and MDD groups with respect to age and sex, considering acceptable a maximum difference of 3 years in mean age and 5% in the proportion of men. Finally, we will assess the risk of information and misclassification bias by evaluating whether atypical symptoms were assessed using adequate and comparable instruments in both BD and MDD.

Strategy of data synthesis Random-effects meta-analyses will be conducted to estimate pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association of each atypical symptom with BD versus MDD. Between-study heterogeneity will be assessed using the I^2 statistic. Heterogeneity-based sequential sensitivity analyses will be performed for atypical symptoms showing a significant association with BD and including at least 10 studies with an I^2 >50%, sequentially excluding the minimum number of studies required to reduce I^2 below 50%. Publication bias will be assessed using Egger's test and funnel plots for variables including at least 10 studies. The trim-and-fill method will be applied to evaluate the potential impact of unpublished studies on the findings. If feasible, subgroup analyses comparing BD-I and BD-II will also be performed.
For each atypical symptom showing a statistically significant association, we will critically appraise the certainty of the evidence, classifying it as very high, high, moderate, low, or very low according to predefined upgrading and downgrading criteria based on the following domains: magnitude of the effect, risk of bias, precision, consistency, and publication bias.
The magnitude of the effect will be evaluated by converting ORs into equivalent Cohen's d values (ln[OR]/1.81). We will upgrade the certainty of the evidence by one level if the equivalent Cohen's d is

>0.8 (large or very large effect) and downgrade it by one level if it is <0.3 (small effect).
The impact of risk of bias on the findings will be evaluated by assessing whether sensitivity analyses excluding studies at higher risk of bias for each evaluated domain (representativeness, age comparability, gender comparability, and adequacy of atypical symptom assessment) yield results consistent with those of the overall analysis. We will downgrade the certainty of the evidence by one level if at least one domain-based sensitivity analysis is not consistent with the overall analysis.
Precision will be evaluated according to the width of the 95% confidence interval of the equivalent Cohen's d. We will downgrade the certainty of the evidence by one level if the confidence interval width is ≥0.4.
Consistency will be evaluated according to the degree of between-study heterogeneity, assessed using the I^2 statistic. For variables including fewer than 10 studies, we will downgrade the certainty of the evidence by one level if I^2 is ≥50%. For variables including at least 10 studies, we will downgrade the certainty of the evidence by one level if I^2 is ≥50% and the heterogeneity-based sensitivity analysis yields results that are not consistent with those of the overall analysis.
Finally, publication bias will be evaluated using Egger's test for variables including at least 10 studies. We will downgrade the certainty of the evidence by one level if (1) fewer than 10 studies are available, precluding a formal assessment of publication bias, or (2) Egger's test indicates potential publication bias ($p<0.10$) and the trim-and-fill analysis yields results that are not consistent with those of the overall analysis.
All statistical analyses will be performed using STATA Statistical Software.

Subgroup analysis If sufficient data are available, subgroup analyses comparing BD-I and BD-II will be performed.

Sensitivity analysis Sensitivity analyses based on (1) risk of bias and (2) between-study heterogeneity will be performed (see "Strategy of data synthesis").

Country(ies) involved Italy.

Keywords Atypical symptoms; Bipolar disorder; Major depressive disorder; Systematic review; Meta-analysis.

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