INPLASY

The effect of long-acting injectable antipsychotics on hospital admissions and emergency department visits in persons with bipolar disorder: Protocol for a systematic review and meta-analysis of mirror-image studies

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ADMINISTRATIVE INFORMATION

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Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - Francesco Bartoli has received direct or indirect consultant and/or speaker fees from Angelini, Idorsia, Italfarmaco, Johnson & Johnson, Laboratorios Farmacéuticos Rovi, Lundbeck, Neuraxpharm, Otsuka, and Viatris, and honoraria for editorial activities from Elsevier and IMR Press.
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The other authors declare no conflicts of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 November 2026 and was last updated on 9 November 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis of mirror-image studies is to evaluate whether, in persons with bipolar disorder (BD), the initiation of long-acting injectable antipsychotics (LAIs) is associated with reduced hospital admissions for psychiatric reasons and emergency department visits, compared with the period before LAI initiation.

Rationale Poor adherence is frequent in BD and may impair clinical outcomes, increasing the risk of

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mood relapses and hospitalizations. For this reason, LAIs are considered a useful option for improving adherence and outcomes not only in schizophrenia spectrum disorders, but also in BD. In recent years, systematic reviews have investigated whether LAIs may improve outcomes in BD, with increasing evidence available from mirror-image studies comparing outcomes over equal periods before and after LAI initiation. Although the mirror-image design provides a lower level of evidence than randomized controlled trials, it is particularly appropriate to assess the effectiveness of LAIs in persons with BD, benefiting from within-subject comparisons. Moreover, it provides the opportunity to evaluate real-world objective outcomes that are burdensome for patients and health care systems, including hospital admissions and emergency department visits. A comprehensive synthesis of evidence is needed given the increasing number of published mirror-image studies.

Condition being studied According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), BD is a mental disorder characterized by the occurrence of manic/hypomanic episodes, which may alternate with depressive episodes.

METHODS

Participant or population Individuals with BD, including BD-I, BD-II, and other specified or unspecified BD.

Intervention Any first- or second-generation LAI.

Comparator Pre-LAI period within the same individuals, with any oral treatment or no treatment.

Study designs to be included Mirror-image studies.

Eligibility criteria We will include retrospective or prospective mirror-image (pre-post) studies comparing hospital admissions and/or emergency department visits over equal periods before and after LAI initiation within the same individuals. To improve comparability across studies, we will include only studies published from 2000 onwards.
We will exclude studies:
- using within-individual designs with time-varying exposure, not anchored to LAI initiation;
- including mixed diagnostic samples without separate data for individuals with BD;
- based on samples with a mean age below 18 years or above 65 years;
- not allowing the estimation of the effect size on selected outcomes;
- based on participants and outcomes overlapping with those of another study with more complete data.
We will also exclude grey literature, dissertations, and conference abstracts that have not undergone peer review.

Information sources We will search PubMed, Embase, APA PsycInfo, and Scopus databases. Search strategies will combine terms related to BD with terms related to LAIs. We will also screen the reference lists of relevant reviews in this field to identify additional eligible studies. An exploratory, non-systematic search of Google Scholar will be conducted to identify any further eligible studies. No language restrictions will be applied. EndNote will be used to manage records and remove duplicates. Corresponding authors of potentially eligible studies will be contacted if additional information is required.

Main outcome(s) The primary outcome will be the number of hospital admissions over the observation periods. If feasible, it will also be stratified by episode polarity (i.e., number of admissions due to manic, mixed, or depressive episodes). Secondary outcomes, according to their availability, will include the total number of days spent in hospital, the number of individuals with at least one hospital admission, the number of emergency department visits, and the number of individuals with at least one emergency department visit.

Data management Studies will be screened independently by at least two 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 two investigators and cross-checked for accuracy. A standardized data extraction form will be used to collect at least the following information: authors, year of publication, country, setting, data source, diagnostic criteria and BD subtypes, sample characteristics, length of observation periods, LAI agents, treatment during the pre-LAI period, concomitant treatments, handling of the index hospitalization and LAI discontinuation, and outcome data. Disagreements at any stage will be resolved through discussion with a third investigator.

Quality assessment / Risk of bias analysis The quality and risk of bias of included studies will be

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assessed independently by two investigators using the applicable items from the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group. Disagreements will be resolved through discussion with a third investigator. Each study will be rated as good, fair, or poor, with the overall judgement driven by the following items: the clarity of the study question (item 1); a clear description of the study population and eligibility criteria (item 2); the sample representativeness (item 3); the effective enrollment of all eligible subjects (item 4); a sufficient sample size, defined as at least 34 participants, allowing the detection of a standardized mean difference of 0.5 with 80% power at $\alpha = 0.05$ in a paired t-test, assuming a pre-post correlation of 0.5 (item 5); a clear description of the LAI intervention, including information on concomitant oral treatments (item 6); the use of clearly defined and reliably assessed outcomes (item 7); the handling of attrition, including the retention of LAI discontinuers in the analyses (item 9); and the adequacy of statistical methods (item 10). Items 8 (blinding of assessment), 11 (interrupted time-series design), and 12 (group-level intervention) will be considered not applicable, given the objective nature of the outcomes, the mirror-image design, and the individual-level intervention, respectively.

Strategy of data synthesis Random-effects meta-analyses, using the restricted maximum likelihood estimator (REML), will be conducted. Ratios of means (RoMs) and risk ratios (RRs), with corresponding 95% confidence intervals (CIs), will be used for continuous and dichotomous outcomes, respectively. Equivalent standardized mean differences (SMDs) will be used to estimate the magnitude of the effect according to standard cut-offs (small: 0.2; medium: 0.5; large: 0.8). To account for the paired nature of mirror-image data, a conventional pre-post correlation of $r = 0.5$ will be imputed. Additional sensitivity analyses will be based on empirical mean r values estimated from available individual participant data. Between-study heterogeneity will be assessed using the I^2 statistic. In addition, 95% prediction intervals (PIs) will be calculated. Heterogeneity-based sequential sensitivity analyses will be performed for outcomes 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 outcomes including at least 10 studies, and the trim-and-fill method will be applied to evaluate the potential impact of unpublished studies. Statistical analyses will be performed using R, with the metafor package.

Subgroup analysis Subgroup analyses, if sufficient data are available, will be performed to account for: i) length of observation periods (12 months vs. other); ii) study design (prospective vs. retrospective); iii) inclusion of individuals discontinuing LAI treatment (yes vs. no).

Sensitivity analysis Sensitivity analyses will be performed excluding studies rated as poor quality (see "Quality assessment / Risk of bias analysis") and accounting for different pre-post correlation values and between-study heterogeneity (see "Strategy of data synthesis"). Moreover, if sufficient data are available, analyses will be repeated for LAI generation (first- vs. second-generation) and for each LAI agent, including agent-specific data from studies with mixed samples. Additional analyses of hospitalization outcomes will be performed using data excluding the index hospitalization leading to LAI initiation from the pre-LAI period, when reported or obtainable.

Country(ies) involved Italy; Canada; USA.

Keywords Long-acting injectable antipsychotics; Bipolar disorder; Systematic review; Meta-analysis; Hospitalizations; Emergency department visits.

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