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Review

Long-acting injectable antipsychotics for the treatment of bipolar disorder: evidence from mirror-image studies

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***Abstract*:** Clinical trials and real-world data have shown that long-acting injectable antipsychotics (LAIs) might be an effective therapeutic option also for people with bipolar disorder (BD). However, complementing evidence from mirror-image studies investigating LAIs in BD is scattered and has not been systematically evaluated so far. We thus performed a review of observational mirror-image studies testing the effectiveness of LAI treatment on clinical outcomes in people with BD. Embase, MEDLINE, and PsycInfo electronic databases were systematically searched (via Ovid) up to November 2022. We included six mirror-image studies that compared relevant clinical outcomes between the 12-months after (post-treatment period) and the 12-months before (pre-treatment period) the initiation of a LAI treatment in adults with BD. We found that LAI treatment is associated with a significant reduction in days spent in hospital and number of hospitalizations. Moreover, LAI treatment seems to be associated with a significant decrease in the proportion of individuals with at least one hospital admission, even though data on this outcome were reported by just two studies. In addition, studies consistently estimated a significant reduction of hypo-/manic relapses after LAI treatment initiation, while the effect of LAIs for depressive episodes is less clear. Finally, LAI treatment initiation was associated with a lower number of emergency department visits in the year after LAI initiation. The findings of this review seem to suggest that the use of LAIs is an effective strategy to improve major clinical outcomes in people with BD. Nonetheless, additional research, based on standardized assessments of prevalent polarity and relapses, is needed to identify the clinical characteristics of individuals with BD who are most likely to benefit from a LAI treatment.

Keywords: antipsychotics, bipolar disorder, hospitalization, long-acting injectables, mirror-image, relapse, review

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Introduction

Bipolar disorder (BD), a chronic clinical condition characterized by recurrent mood oscillations and instability,[1,2] affects about 1–2% of the general population.[3] It is associated with poor quality of life,[4] co-occurring addictive behaviors[5] and physical comorbidities,[6] and high mortality rates.[7] Depressive and manic relapses of BD increase the need for mental health outpatient and inpatient services utilization[8,9] and are often explained by poor treatment adherence.[10,11] For this reason, long-acting injectable antipsychotics (LAIs), approved by both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for schizophrenia maintenance treatment,[12] have been proposed as a therapeutic option for improving adherence also in BD.[13–15] Although LAIs represent a widely used off-label therapeutic option for BD, no LAI has been recommended by the EMA, while only

risperidone microspheres (RM) and aripiprazole monohydrate (AM) are approved by the FDA for BD maintenance treatment.[16]

Indeed, evidence from clinical trials has shown that LAIs might be an effective and well-tolerated pharmacological option for people with BD, especially those with a predominant manic polarity and psychotic features.[15] In addition, real-world data estimated that LAIs are the most effective antipsychotics formulation for BD, being associated with a significant decrease of re-hospitalizations, as compared with their equivalent oral counterparts.[17,18] In particular, mirror-image studies, comparing outcomes in equal periods of time before and after LAI treatment,[19,20] seem to be particularly appropriate to assess the effectiveness of LAIs in people with BD. Indeed, even though based on a lower quality than randomized controlled trials, mirror-image studies have several major strengths particularly for mental health research since they do not need to account for possible differences between index and control groups. In addition, they generally include representative samples, testing objective outcome variables, such as the number of hospital admissions or emergency department visits.[19,21,22] However, evidence from mirror-image studies investigating LAIs in BD is scattered and has not been systematically evaluated so far. This would be helpful to clarify the possible role of LAIs for the maintenance treatment of BD from the relevant body of evidence accumulated in the last few years.[23,24] We thus performed a review of observational studies, based on a mirror-image design and evaluating the effectiveness of LAI treatment on clinical outcomes in people with BD.

Methods

We performed a review of evidence available from mirror-image studies exploring the effectiveness of LAI treatment in BD. We followed standard methods to report non-quantitative syntheses of the literature.[25] Embase, MEDLINE, and PsycInfo electronic databases were systematically searched (via Ovid) for articles published up to November 2022. The following search phrase was used: «('bipolar' OR 'mania' OR 'manic') AND ('antipsychotic*' OR 'neuroleptic*') AND ('depot' OR 'long-acting' OR 'decanoate' OR 'enanthate' OR 'microsphere' OR 'pamoate' OR 'palmitate' OR 'monohydrate')» as multiple purpose search in title, abstract, heading words, and keywords. No language or publication date restrictions were applied. We included mirror-image studies that compared relevant clinical outcomes between the 12-months after (post treatment period) and the 12-months before (pre-treatment period) the initiation of a treatment with a LAI in adults with BD. Only clinical outcomes with data available from at least two studies were considered. To improve the comparability of data, we excluded mirror-image studies considering different time periods, as well as gray literature, conference abstracts, dissertations, and all publications not having undergone a peer-review process. After a preliminary screening based on titles and abstracts, full texts were retrieved to evaluate their eligibility. Studies were independently screened and read in full text by three authors (P.G., C.N., and D.P.). Any disagreement was resolved by discussion with the other authors. Finally, four authors (D.C., P.G., C.N., and D.P.) independently extracted key data from eligible studies, including author(s) and year of publication, country, data source, main characteristics of the selected groups, tested LAIs, and clinical outcomes investigated with related effect sizes.

Results

Our search generated 1250 records (733 from Embase, 308 from MEDLINE, and 209 from PsycInfo) and, after removing duplicates, 883 articles were screened. Through screening by titles and abstracts 37 potentially eligible studies were retrieved for full-text assessment. Among them, 31 studies did not meet eligibility criteria and were excluded. The remaining six observational studies were included in this review.[23,24,26–29] The flowchart of the study selection process is reported in Figure 1.

Studies were conducted in Italy,[23,26] Taiwan,[28,29] and Turkey.[24,27] The sample size ranged between 17[24] and 287.[29] Two studies selected individuals with bipolar type I disorder,[27,28] while the bipolar type was not specified in the remaining studies.[23,24,26,29] The two studies from Italy were based on two completely independent, not overlapping, cohorts, that is, the Northern Milan Area Cohort (NOMIAC) study[23] ($N = 68$) and the multicenter 'Servizi Territoriali Associati per la Ricerca' (STAR–Community Services Associated for Research) Network Depot Study[26] ($N = 71$). The two studies conducted in Taiwan selected study participants from the E-Da Hospital in

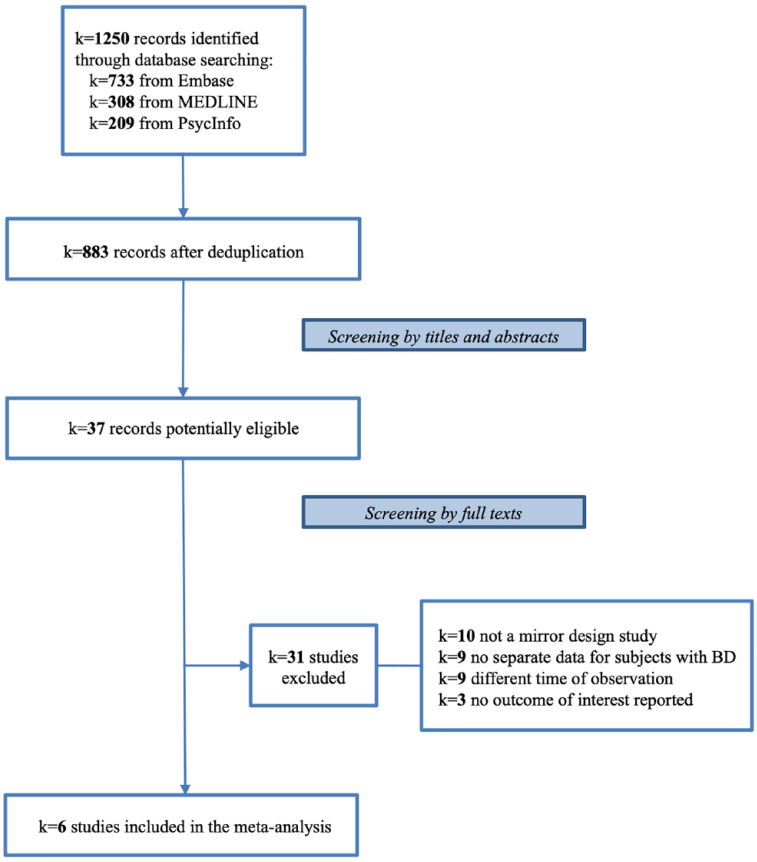

Figure 1. Flow diagram of the study selection process.

Kaohsiung[28] ($N = 77$) and the National Health Insurance Research database[29] ($N = 287$), respectively. Finally, medical records of individuals with bipolar disorder from the Bagcilar Meydan Community Mental Health Center[24] ($N = 17$) and from University of Health Sciences, Konya Education and Research Hospital[27] ($N = 36$) were, respectively, used by two studies conducted in Turkey. Two studies investigated mixed first (FGA) and second-generation (SGA) LAIs,[23,26] one study included only SGAs,[24] while other studies tested single agents, that is, paliperidone palmitate 1-month[27] (PP1M) and RM,[28,29] respectively. In terms of clinical outcomes reported, all studies investigated the number of days spent in hospital,[23,24,26–29] four studies the number of hospital admissions,[23,24,27,29] two studies the hospitalization rates, that is, the proportion of individuals with at least one hospital admission,[26,28] four studies acute mood (manic or depressive) relapses,[23,27–29] and other three the number of emergency department visits.[23,28,29] The characteristics of the studies included in this review are reported in Table 1. The overview of findings is summarized in Table 2.

Effect of LAIs on days spent in hospital

All included studies provided information on the number of days spent in hospital during the 1-year periods before and after initiating LAI treatment.[23,24,26–29] Caliskan *et al.*[27] reported – among 36 individuals treated with PP1M – a significant reduction in days of hospitalization from 53.9 (± 21.6) in the pre-treatment period to 13.5 (± 20.0) ($Z = -5.07$; $p < 0.001$). Similarly, Yıldızhan *et al.*[24] showed a significant reduction in days spent in hospital between pre- and post-treatment periods (15.5 ± 20.6 *versus* 2.5 ± 5.7 days; $Z = -2.22$; $p = 0.026$) among 17 subjects initiated with a SGA LAI. The NOMIAC study,[23] based on 68 participants with BD, showed an overall reduction in days of hospitalization (from 27.5 ± 27.5 to 15.1 ± 29.2 days; $Z = -3.66$; $p < 0.001$) after the initiation of LAI treatment. Interestingly, this outcome was statistically significant only among study

Table 1. Characteristics of included studies.

Study	Country	Data source	Sample size (*N*)	Mean age (years)	Male (%)	Long-acting injectable antipsychotics (*n*, %)
Bartoli *et al.*[23]	Italy	Northern Milan Area Cohort (NOMIAC)	68	45.7	48.5	AM (28, 41.2) PP1M (15, 22.0) HAL-D (15, 22.0) RM (8, 11.8) FLU-D (2, 3.0)
Bartoli *et al.*[26]	Italy	STAR (Community Services Associated for Research) Network	71	46.2	53.5	AM (30, 42.3) PP1M (16, 22.5) HAL-D (14, 19.7) RM (6, 8.5) FLU-D (3, 4.2) ZUC-D (2, 2.8)
Caliskan *et al.*[27]	Turkey	Medical records from the University of Health Sciences, Konya Education and Research Hospital	36	38.9	75.0	PP1M (36, 100)
Chan *et al.*[28]	Taiwan	Medical records from the E-Da Hospital	77	39.0	39.0	RM (77, 100)
Hsieh *et al.*[29]	Taiwan	National Health Insurance Research database (NHIRD)	287	39.8	43.2	RM (287, 100)
Yıldızhan *et al.*[24]	Turkey	Medical records from the Bagcilar Meydan Community Mental Health Center	17	41.5	47.0	AM (8, 47.0) PP1M (5, 29.4) RM (4, 23.6)

AM, aripiprazole monohydrate; FLU-D, fluphenazine decanoate; HAL-D, haloperidol decanoate; PP1M, paliperidone palmitate 1-month; RM, risperidone microspheres; ZUC-D, zuclopenthixol decanoate.

participants with a full adherence to LAI treatment (i.e. those treated for the whole 12-month period) and those treated with SGA LAIs. Consistently, the multicenter STAR Network Depot Study[26] showed an overall reduction in the number of days spent in hospital (from 16.3 ± 23.5 to 5.9 ± 13.4 days; $Z = 4.25$; $p < 0.001$), though not among individuals that early discontinued LAIs. No differences between SGA and FGA LAIs were estimated. In addition, data from the Taiwan National Health Insurance Research database[29] reported a significant decrease in the number of days of hospitalization among those with ($n = 36$) and without ($n = 251$) a rapid cycling course (-15.0 ± 6.0 days and -10.3 ± 2.2 days, respectively). However, no statistically significant differences were reported by Chan *et al.*[28] in terms of days spent in hospital during both the pre-treatment and the post-treatment periods, among 77 individuals with BD treated with LAIs.

Effect of LAIs on number of hospital admissions

A significant decrease in the number of hospital admissions in the year after LAI initiation, as compared with the previous year, was estimated in all four studies providing this information.[23,24,27,29] Caliskan *et al.*[27] reported a reduction in hospital admissions from 1.47 ± 0.50 during the pre-treatment period to 0.33 ± 0.53 during the post-treatment period ($Z = -5.07$; $p < 0.001$). A similar trend was confirmed by the NOMIAC study,[23] showing a significant decrease in hospital admissions after LAI treatment ($p = 0.001$). Yıldızhan *et al.*[24] highlighted that admissions per year were reduced from 0.9 ± 1.24 to 0.1 ± 0.39 after treatment ($Z = -2.48$; $p = 0.013$). Finally, data from the Taiwan National Health Insurance Research database showed that the number of hospital admissions after LAI treatment significantly dropped ($p < 0.001$) in people with BD both with and without a rapid cycling course.[29]

Table 2. Effect of long-acting injectable antipsychotics on clinical outcomes: overview of findings of included studies.

Study	Days spent in hospital	Number of hospital admissions	Hospitalization rates[a]	Mood relapses	Emergency department visits
Bartoli *et al.*[23]	↓	↓	N/R	↓ hypo/manic episodes ↔ depressive episodes	↓
Bartoli *et al.*[26]	↓	N/R	↓	N/R	N/R
Caliskan *et al.*[27]	↓	↓	N/R	↓ manic and mixed episodes ↔ depressive episodes	N/R
Chan *et al.*[28]	↔	N/R	↓	↓	↓
Hsieh *et al.*[29]	↓	↓	N/R	↓ in rapid cycling sample ↑ in non-rapid cycling sample	↓
Yıldızhan *et al.*[24]	↓	↓	N/R	N/R	N/R

↓, reduction after LAI treatment; ↑, increase after LAI treatment; ↔, no significant variations after LAI treatment; N/R, not reported.
[a]Proportion of subjects with at least one hospital admission.

Effects of LAIs on hospitalization rates

Two studies provided data on hospitalization rates, that is, the proportion of individuals with at least one hospital admission.[26,28] Chan *et al.*[28] reported that, in 44 patients who had continuously received RM, rehospitalization rates during the 1-year follow-up were significantly lower than before enrollment (18.2% *versus* 45.5%; $p < 0.001$). Nonetheless, no pre–post treatment differences were estimated among 33 subjects who had not regularly received RM ($p = 0.13$). More recently, the STAR Network Deport Study[26] estimated a statistically significant decrease of hospitalization rates in 71 people with BD initiating LAI (from 62.0% to 22.5%; $p < 0.001$). Consistently, this reduction was confirmed among LAI continuers ($p < 0.001$), though not among those who early discontinued LAI treatment ($p = 0.13$).

Effect of LAIs on mood relapses

Four studies explored the effectiveness of LAI treatments for the prevention of mood relapses.[23,27–29] Hsieh *et al.*[29] reported a reduction in mood relapses in subjects with a rapid cycling course treated with RM, varying from 6.83 mood episodes in the pre-LAI period to 4.33 in the post-LAI period ($p < 0.001$); nonetheless, an increase in the number of episodes was observed in the non-rapid cycling subgroup ($p < 0.001$). Chan *et al.*[28] estimated a reduction in hospitalizations due to both manic ($p = 0.005$) and depressive ($p = 0.002$) episodes in individuals regularly receiving RM, but not among those who discontinued it. Consistently, Caliskan *et al.*[27] found an overall decrease in the number of relapses ($p < 0.001$) in subjects treated with PP1M. This reduction was possibly attributable to the lower incidence of manic ($p < 0.001$) and mixed episodes ($p = 0.008$), while no statistically significant differences were estimated for depressive relapses ($p = 0.32$). Similarly, the NOMIAC study cohort[23] estimated that subjects receiving either FGA LAIs or SGA LAIs had an overall decrease in hospitalization days due to hypo-/manic episodes ($p = 0.031$), but not in those related to depressive ones ($p = 0.64$).

Effect of LAIs on emergency department visits

Three studies reported data on the potential difference in emergency department visits before and after LAI initiation.[23,28,29] Data from the Taiwan National Health Insurance Research database[29] showed a statistically significant decrease ($p < 0.001$) in the number of emergency department visits among subjects with BD, regardless of the rapid cycling course. Chan *et al.*[28] found statistically significant reductions in subjects with either regular ($n = 44$) or irregular ($n = 33$) RM administrations ($p < 0.001$ and $p = 0.013$, respectively). Conversely, in the NOMIAC study cohort,[23] the reduction in the number of emergency department visits was statistically significant in subjects with full adherence to LAI regimen ($p = 0.014$), but not in those with partial or no adherence ($p = 0.06$).

Discussion

Summary of findings

In this review, we narratively synthesized the available evidence on effectiveness of LAI treatment among people with BD, summarizing relevant real-world data from 1-year mirror-image studies. As a whole, the findings of this review seem to suggest that the use of LAIs might be an effective strategy to improve major clinical outcomes in people with BD. According to the results of the included studies,[23,24,26–29] we found that the initiation of LAI treatment is associated with a significant reduction in days spent in hospital. This finding was consistent across all studies but one, which did not estimate any relevant effect of LAI treatment.[28] Similarly, consistent results emerged in terms of number of hospitalizations: a statistically significant reduction of hospital admissions in the year after LAI initiation was estimated by all eligible studies from which this information was available.[23,24,27,29] Moreover, LAI treatment seems to be associated with a significant reduction of hospitalization rates, even though data on this outcome were reported by just two studies and confirmed only among patients who regularly received LAIs.[26,28] In terms of mood relapses, mixed findings emerged from the evidence considered: LAI treatment is likely to reduce the overall number of relapses, but its effectiveness for manic and depressive recurrences is mixed. Indeed, although the included studies were consistent in estimating a significant reduction of hypo-/manic relapses after LAI treatment initiation, its effect in preventing depressive episodes is less clear. Only one study showed a reduction of depressive relapses, at least among those who were regularly treated with a LAI,[28] while other studies[23,27] did not report any effect. Finally, consistent results from three studies[23,28,29] estimated a number of emergency department visits lower than during the year before LAI initiation.

Interpretations of findings and clinical implications

The findings of this review provide some meaningful insights and relevant clinical implications. First, the effects of LAI treatment on the clinical outcomes investigated seem consistent across the different investigated agents. Indeed, this review included studies which were heterogeneous in terms of LAI drug class and/or specific agent studied. The overall benefit of LAI treatment seems to be a *pharmacological formulation* effect, likely to be due to the improvement of treatment adherence,[30] rather than a *single drug* effect related to the specific agent of choice. This is further supported by the favorable outcomes observed only in subjects regularly treated with LAIs, and not in those discontinuing this treatment regimen,[23,26,28] a finding consistent across different patient populations and diagnostic categories.[31,32]

Another important issue is related to the heterogeneous effects of LAIs on the prevention of mood episodes. In this review, we reported consistent findings in terms of reduction of hypo-/manic mood recurrences after initiating LAI treatment. Conversely, this does not hold true for depressive episodes, for which mixed findings were estimated by the included studies.[23,27,28] The clinical benefit of LAIs in BD might thus be influenced by the specific polarity of mood relapses, with a prevailing antimanic – rather than antidepressant – effect of LAIs in BD,[13,15,33] suggesting their use especially for those with a predominantly manic polarity.[34] Indeed, the majority of SGA agents showing some benefit in the management of bipolar depression, such as quetiapine, lurasidone, and cariprazine,[35,36] do not have an available long-acting formulation, whereas the use of olanzapine LAI is rare for its poor tolerability.[12] In addition, since the pharmacological profile of FGA LAIs is characterized by a higher affinity for dopamine D_2 receptors, this would make them less appropriate for the long-term prophylaxis of depressive relapses in BD.[33]

Finally, it remains unclear what is the clinical profile of subjects with BD who might most benefit from LAI treatment. For instance, some research highlighted that, along with a predominantly manic course, the occurrence of psychotic features, and low adherence, LAI treatment might be appropriate especially for subjects with a rapid cycling course.[37] However, just one study included in this review stratified results according to the occurrence of a rapid cycling course.[29] In addition, although mixed features are frequent in BD and significantly influence its course,[38] only one study[27] tested the effectiveness of LAI treatment on mixed episodes. Nonetheless, other factors might be involved in LAI treatment response, including low global functioning, early stages of BD, comorbid alcohol and substance use disorders, low illness insight, lithium discontinuation, as well as a family history of bipolar disorder.[39–42] Additional research is needed to define putative

correlates of effectiveness of LAI treatment in people with BD.

Limitations

The findings of this review should be interpreted with caution considering some limitations. First, we summarized results from mirror-image studies based on real-world data that might increase the external validity of relevant results, though affecting their internal validity.[43,44] It should be considered that evidence quality from mirror-image studies is likely to be lower than from randomized controlled trials. Second, the number of studies included in this review is small with limited sample sizes and they are based on a heterogeneous reporting of clinical outcomes. Third, despite the majority of clinical outcomes considered in this review was based on objective measures such as hospitalizations and emergency department visits, less reliable information was available for mood relapses, mainly derived from medical records and not from standardized assessments. Considering the heterogeneity of mental health care delivery systems, clinical outcomes, such as the number and days of hospital admissions, might have been partly influenced by several contextual and local factors that may determine the likelihood of hospitalization.[45] Moreover, systematic data on LAI safety and tolerability, either on other important outcomes such as suicidal behaviors, were not available. In addition, we could not assess potential differences between different LAIs. This might be crucial since some LAIs, such as AM and PPM1, have shown differential effectiveness in other clinical populations.[46–48] Finally, we could not evaluate the potential influence of concomitant oral treatments on clinical outcomes. Although it is likely that low adherence to medications is a distinctive feature of subjects included in the studies, we cannot rule out at least a partial effect by concomitant treatments, such as lithium and other mood stabilizers, on the clinical improvement after LAI initiation.

Conclusions

Evidence from mirror-image studies exploring the effectiveness of LAI treatment in people with BD suggests their ability to improve core clinical outcomes such as hospitalizations and emergency department visits, as well as to prevent manic relapses. Additional research is needed to clarify the clinical profile of individuals with BD who are more likely to benefit from a LAI treatment.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Francesco Bartoli: Conceptualization; Methodology; Project administration; Writing – original draft.

Daniele Cavaleri: Conceptualization; Data curation; Investigation; Writing – original draft.

Christian Nasti: Data curation; Investigation; Writing – original draft.

Dario Palpella: Data curation; Investigation; Writing – original draft.

Pierluca Guzzi: Data curation; Investigation; Writing – original draft.

Ilaria Riboldi: Methodology; Visualization; Writing – review & editing.

Cristina Crocamo: Methodology; Validation; Writing – review & editing.

Sofia Pappa: Methodology; Supervision; Writing – review & editing.

Giuseppe Carrà: Methodology; Project administration; Supervision; Writing – review & editing.

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Competing interests

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