

Long-Acting Injectable Antipsychotics in Serious Mental Illness with Co-Occurring Substance Use: A Retrospective Cohort Study

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SUBMISSION DETAILS

If your paper is not accepted, please elect if you would like your submission to be reviewed as a poster. Yes, I would like to be reviewed as a poster.

Summary This educational activity focuses on the real-world use of long-acting injectable (LAI) antipsychotics in patients with serious mental illness, particularly those with co-occurring substance use disorders. Using a retrospective cohort of inpatient psychiatric patients, the study evaluates post-discharge outcomes, including one-year readmission rates, while examining the relative contributions of medication choice, illness severity, and discharge characteristics. The activity is designed to help clinicians interpret real-world evidence and apply it to complex, high-risk patient populations that are often underrepresented in randomized trials.

The findings have several important implications for clinical practice. First, they support broader and more confident use of LAIs in dual-diagnosis populations. Despite greater clinical and social complexity, patients with substance use disorders experienced similar readmission outcomes compared to those without, suggesting that LAIs may help mitigate relapse risk in this group. Second, the study highlights that factors such as illness severity, medication burden, and discharge to high-intensity outpatient care are stronger predictors of rehospitalization than the specific LAI formulation used. This reinforces the need to shift focus from medication selection alone toward comprehensive discharge planning, continuity of care, and integration of psychiatric and substance use treatment.

From a research perspective, the study addresses a key gap by evaluating outcomes in a heterogeneous, real-world population that includes both psychotic and bipolar spectrum disorders and a high prevalence of substance use. It also underscores the limitations of observational data, including confounding by indication, and highlights the need for prospective studies that better account for illness severity, social determinants, and treatment decision-making processes. Future research should further examine how integrated care models and post-discharge interventions

influence outcomes in this population.

Educationally, this activity targets gaps in clinician knowledge and perception, particularly the underutilization of LAIs in patients with substance use disorders due to assumptions about poor outcomes or adherence. By demonstrating comparable outcomes, the study challenges these biases and encourages clinicians to consider LAIs earlier and more consistently. It also emphasizes the importance of recognizing markers of illness severity and using them to guide risk stratification and discharge planning.

At a systems and policy level, the findings support investment in integrated psychiatric and addiction services, as well as enhanced transitional care programs. The identification of discharge-related factors as key drivers of rehospitalization suggests that improving access to step-down care, care coordination, and community-based supports may have a greater impact on outcomes than medication changes alone. Overall, this activity promotes a more comprehensive, systems-based approach to relapse prevention in serious mental illness, aligning pharmacologic strategies with broader clinical and social interventions.

The questions following the above will ask you to breakdown your summary.

Background Serious mental illness (SMI), including schizophrenia spectrum and bipolar disorders, is associated with high rates of relapse, rehospitalization, and functional impairment. These risks are further amplified in patients with co-occurring substance use disorders (SUDs), who often present with greater clinical complexity, younger age, housing instability, and fragmented engagement with outpatient care. Despite this, treatment approaches for dual-diagnosis patients remain inconsistent, and there are persistent gaps in both clinician expectations and management strategies for this population.

Long-acting injectable (LAI) antipsychotics are designed to address medication nonadherence, one of the primary drivers of relapse. While there is strong evidence supporting their role in reducing hospitalization in schizophrenia, their use in real-world settings, particularly among patients with co-occurring SUDs or bipolar spectrum illness, remains underutilized. Many existing studies exclude patients with substance use or are conducted in controlled settings, limiting generalizability. As a result, there is a gap in knowledge regarding how LAIs perform in more clinically complex, heterogeneous populations that reflect everyday inpatient psychiatry.

This study is relevant because it evaluates real-world outcomes in a diverse inpatient cohort, with over half of patients having co-occurring SUDs. Importantly, it challenges the assumption that substance use necessarily predicts worse post-discharge outcomes. Despite greater clinical and social complexity, patients with SUDs did not experience higher one-year readmission rates or shorter time to readmission when treated with LAIs. This suggests that LAIs may help mitigate some of the risks traditionally associated with dual diagnoses and highlights a gap in clinician perception that may lead to underutilization of these treatments.

The study also addresses a performance gap related to treatment focus. While clinicians often

emphasize antipsychotic selection, the findings demonstrate that LAI formulation was not independently associated with readmission after adjusting for confounders. Instead, markers of illness severity, such as discharge to high-intensity outpatient care and greater medication burden at discharge, were the strongest predictors of rehospitalization. This suggests that relapse risk is more closely tied to overall illness severity and system-level factors than to the specific medication used.

Additionally, the study highlights structural and social contributors to outcomes, including homelessness and demographic disparities, which are more prevalent in patients with SUDs. These factors are often under-addressed in routine care but play a critical role in post-discharge stability. The findings reinforce the importance of integrated care models that address both psychiatric illness and substance use, as well as the need for robust discharge planning and continuity of care.

Overall, this information enhances clinical practice by supporting broader and more confident use of LAIs in complex, dual-diagnosis populations while shifting attention toward comprehensive care planning. It encourages clinicians to move beyond medication selection alone and incorporate illness severity, social determinants, and care transitions into risk assessment and management strategies aimed at reducing rehospitalization.

Educational Learning Objectives

Learning Objective 1 Understand the prevalence and clinical complexity of co-occurring substance use disorders in patients with serious mental illness, and how these factors influence inpatient course and post-discharge outcomes.

Learning Objective 2 Evaluate the real-world effectiveness of long-acting injectable antipsychotics in reducing psychiatric readmissions, including differences between patients with and without substance use disorders.

Learning Objective 3 Identify key predictors of psychiatric rehospitalization, particularly markers of illness severity such as higher medication burden and need for intensive outpatient services at discharge, and incorporate these into discharge planning and risk assessment.

Methods This retrospective cohort study examined adult psychiatric inpatients at a single urban academic center between January 2020 and October 2022 who were initiated on a long-acting injectable antipsychotic prior to discharge. The sample included 370 patients with schizophrenia spectrum or bipolar disorders, stratified by presence of co-occurring substance use disorders. Data were extracted from the electronic medical record, including demographic variables, clinical history, inpatient course, discharge characteristics, and post-discharge outcomes. The primary outcome was psychiatric readmission within one year, with secondary measures including time to readmission and emergency psychiatric visits. Statistical analyses included descriptive comparisons, chi-square and t-tests, and multivariable regression models, including negative binomial regression, to evaluate predictors of readmission and adjust for illness severity and treatment complexity.

Results Over half of the cohort (52.2%) had co-occurring substance use disorders and were younger with greater clinical complexity. Approximately one-third of patients were readmitted within one year, with no significant differences in readmission rates or time to readmission between those with and without substance use. Similarly, substance use was not associated with readmission frequency after adjustment. Among LAI formulations, first-generation agents were associated with higher readmission counts in unadjusted analyses, but these differences were no longer significant after controlling for illness severity and treatment complexity. Multivariable analyses identified discharge to high-intensity outpatient care and greater medication burden as the strongest predictors of rehospitalization. Overall, outcomes were comparable across groups, suggesting that LAIs may mitigate relapse risk even in more clinically complex, dual-diagnosis populations.

Conclusion These findings support the use of long-acting injectable antipsychotics as an effective strategy for reducing relapse risk in patients with serious mental illness, including those with co-occurring substance use disorders. Comparable readmission outcomes across groups suggest that LAIs may help mitigate the elevated risk typically associated with dual diagnoses. The results emphasize that illness severity and discharge complexity, rather than medication selection alone, are the primary drivers of rehospitalization. Clinically, this highlights the importance of comprehensive discharge planning, continuity of care, and integration of psychiatric and substance use treatment. From an education and systems perspective, the study challenges biases that may limit LAI use and supports broader, earlier implementation alongside investment in post-discharge support services and coordinated care models.

Scientific Significance This study contributes to the growing body of real-world evidence evaluating long-acting injectable antipsychotics in clinically complex populations. It is notable for including a high proportion of patients with co-occurring substance use disorders, a group often underrepresented in controlled trials. The findings demonstrate that LAIs are associated with similar readmission outcomes despite greater baseline clinical severity, suggesting a potential risk-mitigating effect. Additionally, the attenuation of formulation-specific differences after adjustment highlights the role of confounding by indication in observational research. By identifying illness severity and care transitions as key predictors of outcomes, the study advances understanding of the multifactorial drivers of relapse and underscores the need for integrated, systems-level approaches beyond pharmacologic intervention alone.

Will your paper cite external research? Yes

Please cite all references here in AMA format. Baeza FLC, da Rocha NS, Fleck MPA.

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