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# Comparison of long-acting injectable antipsychotics with oral antipsychotics and hospital readmission rates in pediatric patients

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## Abstract

**Introduction:** Studies indicate that long-acting injectable antipsychotics (LAIAs) reduce the risk of relapse and hospitalization compared with oral antipsychotics (APs) in adults. Oral formulations of APs are well-studied in the pediatric population, but little is known regarding the off-label use of LAIAs in this population.

**Methods:** This retrospective chart review evaluated readmission rates for pediatric patients admitted to a psychiatric ward in a large academic hospital between January 1, 2015, and December 1, 2022, requiring AP therapy. The experimental group included patients initiated on LAIA therapy, and the control group included patients initiated on a new oral AP. Patients were matched by several clinical factors.

**Results:** Each group consisted of 38 patients. For the primary outcome, hospital readmission rates at 3 months, the LAIA group had a 13.2% readmission rate compared with 26.3% in the comparator group ($p = .153$). In months 4 through 6, there was a 5.3% versus 15.8% readmission rate, respectively ($p = .139$). In months 7 through 12, it was 7.9% versus 18.4% ($p = .179$). There were significantly fewer cumulative readmissions at the 1-year mark in the LAIA group ($N = 9$, 23.7%) compared with the oral AP group ($N = 18$, 47.4%) ($p = .031$). No statistically significant differences were seen in hospital length of stay although results numerically favored LAIA.

**Discussion:** In a pediatric population, the administration of an LAIA when compared with the oral equivalent resulted in numerically fewer hospital readmissions, decreased length of stay, and fewer adverse effects, but these effects were not statistically significant except for cumulative readmissions at 1 year.

**Keywords:** antipsychotics, injectable therapy, schizophrenia, bipolar disorder

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## Introduction

In pediatric populations, oral formulations of second generation antipsychotics (APs) are used in various psychiatric

conditions, including schizophrenia, bipolar disorder, and irritability associated with autism-spectrum disorder.[1] Long-acting injectable antipsychotics (LAIAs) demonstrate improved outcomes in adult patients with schizophrenia or bipolar disorder, a population that may particularly struggle with medication adherence.[2–4] The mechanism of LAIAs allows for the release of steady serum concentrations over a longer period of time when compared with oral APs.[5] In a 16-year, population-based, self-controlled case series study of 70 396 adult patients with schizophrenia, there were 48% fewer psychiatric hospitalizations, 47% fewer hospitalizations for schizophrenia, 44% fewer suicide attempts, and 37% fewer all-cause hospitalizations during periods of treatment with LAIAs compared with periods of treatment with oral APs.[2] When comparing schizophrenia spectrum disorders (SSD) in pediatric and adult patients, pediatric patients are reported to have worse outcomes linked to severe cognitive deficits, social impairment, relapses, and hospitalizations.[6] Whereas limited studies conclude that there may be improved clinical outcomes and adherence with using LAIAs when compared with oral counterparts, the lack of data supporting LAIA use in this population may lead to lower use of these formulations.[1] A meta-analysis of studies involving pediatric patients with SSD found clinical improvement of patients using LAIA formulations in up to 12 months of follow-up.[6] A retrospective database analysis concluded that, although there is limited clinical data supporting the safety and efficacy of LAIAs in adolescents, their use in patients with documented nonadherence would be appropriate.[7]

Dosing guidance for LAIAs in pediatric patients is based on data from adult populations, and LAIA use in pediatric patients lacks long-term efficacy and safety data regarding extrapyramidal symptoms (EPS) and metabolic adverse effects. Due to a lack of data, LAIA therapy tends to be used only in patients with schizophrenia or documented chronic psychotic symptoms with a history of poor medication adherence. However, there may be more benefit in using LAIA therapy earlier in pediatric patients to prevent poor prognoses in regard to relapse rates and hospitalizations.[6] Studies of LAIA formulations in adult populations often evaluate hospital readmission rates, but there are fewer studies in pediatric populations.[2,6] The objective of this study was to determine if the use of LAIA therapy in pediatric patients leads to a lower readmission rate when compared with oral AP therapy. This study may provide additional insight as there is limited evidence published on the beneficial use of LAIA therapy in pediatric patients.

## Methods

This was a retrospective, single-center, institutional review board–approved cohort research study assessing patients admitted to a child and adolescent psychiatric unit between January 1, 2015, and December 1, 2022. Patients were included in the experimental arm if they were newly initiated on a LAIA (aripiprazole monohydrate [AM], paliperidone palmitate 1-month [PP1M], or risperidone microspheres) during the index hospitalization. Patients were eligible for inclusion in the control arm if they were initiated on a new corresponding oral AP (aripiprazole, paliperidone, or risperidone) during the admission. Exclusion criteria included any patient discharged on 2 or more antipsychotic medications and any patient already receiving an LAIA prior to admission. As some LAIA medications require oral overlap, those discharged on the corresponding oral compound were included in the LAIA group. For both groups, the baseline characteristics collected consisted of age, weight, gender, and race. Additional data collected included concurrent psychiatric medications, primary diagnosis, chlorpromazine equivalence, psychiatric comorbidities, number of previous APs, and number of previous hospitalizations.

Propensity score matching (PSM) was used to compare the effect of an LAIA with an oral AP on rehospitalization after discharge from the index admission. Once identifying a patient initiated on a new LAIA, the PSM was used to match that patient with a patient on a newly initiated oral AP. The parameters used to match patients together included age, gender, previous hospitalizations, previous AP use, current AP compound, psychiatric diagnoses, concurrent medication use, and chlorpromazine equivalence. Descriptive statistics were used, and statistical analysis was conducted using GraphPad's unpaired *T* test calculator and GraphPad's chi-square test calculator. Statistical significance was determined by a two-tailed *p*-value set to $<.05$.

A single author completed chart reviews of all patients screened for the study. Patients were matched using the baseline characteristics and additional data points as closely as possible. For cases in which there was not an exact match, a patient with the most comparable data points was utilized. Previous hospitalization records for many of the patients were available at the study site or collected through physician notes as well as postadmission records found through the electronic health record. For any patients with records not available, the corresponding information was at default set to "not available."

The primary outcome of the study evaluated hospital readmission rates up to 3 full months after the discharge date for patients of both groups. Secondary outcomes included the comparison of hospital readmission rates at 4 through 6 and 7 through 12 months, the comparison of length of stay (LOS) during admissions up to 1 year prior to the index admission, and up to 1 year post index admission, proper initiation of LAIAs, and any incidence of side effects. Overall cumulative readmissions were also collected, evaluating patients experiencing at least 1 readmission within 1 year post index admission. Proper initiation was defined by reviewing each LAIA product's package insert and assessing if the correct oral overlap or loading dose was administered or prescribed for the respective patients.[8–10]

## Results

For the LAIA group, 48 patients were screened with 38 included in the study. Ten patients were excluded due to the use of 2 or more different APs at discharge ($N=4$), previous use of LAIA therapy ($N=4$), and inability to find a relatively close match in

**TABLE 1: Baseline characteristics**

| | LAIA Group (*N* = 38) | Oral AP Group (*N* = 38) |
|---|---|---|
| **Mean Age (range)** | 16.4 years (14 to 17) | 16.3 years (14 to 17) |
| **Mean Weight (range)** | 75.8 kilograms (41 to 139.1) | 83.6 kilograms (47.6 to 132.6) |
| **Gender, %** | | |
| Male | 39.5 | 42.1 |
| Female | 57.9 | 57.9 |
| Transgender | 2.6 | 0 |
| **Race, %** | | |
| Caucasian | 57.9 | 68.4 |
| Black | 23.7 | 15.8 |
| Hispanic | 13.1 | 13.2 |
| Other | 5.3 | 2.6 |
| **Concurrent Medications, %** | | |
| Mood Stabilizers | 28.9 | 55.6 |
| Antidepressants or Anti-anxiety | 18.4 | 26.3 |
| Sleep Agents | 13.2 | 10.5 |
| Stimulants | 2.6 | 7.9 |
| **Primary Diagnosis, %** | | |
| Bipolar Disorder | 71.1 | 71.1 |
| Schizophrenia, Schizoaffective, or Other Psychotic-Like Disorders | 26.3 | 26.3 |
| Disruptive Mood Dysregulation Disorder | 2.6 | 2.6 |
| **Psychiatric Comorbidities, %** | | |
| Attention-Deficit Hyperactivity Disorder | 26.3 | 26.3 |
| Substance Use Disorder | 15.8 | 2.6 |
| Post-Traumatic Stress Disorder | 10.5 | 2.6 |
| Autism-Spectrum Disorder | 7.9 | 5.3 |
| Borderline Personality Disorder | 0 | 5.3 |
| **Previous Hospitalizations, %** | | |
| 3 or more | 10.5 | 2.6 |
| 2 | 5.3 | 15.8 |
| 1 | 34.2 | 31.6 |
| 0 | 50 | 50 |
| **Number of Previous APs, %** | | |
| 3 or more | 13.1 | 5.3 |
| 2 | 18.4 | 5.3 |
| 1 | 44.7 | 31.6 |
| 0 | 23.7 | 57.9 |
| **Mean Chlorpromazine Equivalence Dose (mg)** | 180.9 | 183.6 |

AP = antipsychotic; LAIA = long-acting injectable antipsychotic.

the oral AP group ($N = 2$). For the oral AP equivalent group, 1264 total patients were admitted during the time frame and screened with 38 matched patients included in the study. Table 1 displays the baseline characteristics of both groups with some differences noted in number of previous antipsychotics used, concurrent medications, and previous hospitalizations. Table 2 outlines the nuances among the patients in the LAIA group regarding indication for LAIA use, side-effect incidence, medication dosing, and appropriateness of initiation.

The hospital readmission rates at the various studied intervals are illustrated in the Figure. For the hospital readmission rates at 0 to 3, 4 to 6, and 7 to 12 months, the results were not statistically significant, whereas the difference in cumulative readmissions at 1 year was significant. The LAIA group had 9 unique readmissions in 1 year compared with 18 in the oral AP group.

For 1 year prior to the index admission, the average cumulative LOS for the LAIA group versus the oral AP group was 7 and 8.8 days, respectively ($p = .548$). For the current (index) admission, the LOS was 9.6 days in the LAIA group and 8.8 days in the oral AP group ($p = .277$). For 1 year post index admission, the cumulative LOS for hospitalized patients was 4.6 days in the LAIA group and 7.8 days in the oral AP group ($p = .310$).

For safety outcomes, 1 patient in the LAIA group and 4 patients in the oral AP group experienced EPS requiring adjustments to

**TABLE 2: LAIA group initiation breakdown**

| | Aripiprazole (*N* = 27) | Paliperidone (*N* = 10) | Risperidone (*N* = 1) |
|---|---|---|---|
| **LAIA Indication, %** | | | |
| Bipolar Disorder | 92.6 | 0 | 100 |
| Schizophrenia, Schizoaffective, or Other Psychotic-Like Disorders | 3.7 | 90 | 0 |
| Disruptive Mood Dysregulation Disorder | 3.7 | 0 | 0 |
| Side Effects, % | 3.7 | 0 | 0 |
| **LAIA Dosing** | 100%, 300 mg<br>0%, 400 mg | 90%, 234 mg + 156 mg<br>10%, 156 mg + 156 mg | 100%, 25 mg |
| **Proper Oral Overlap or Loading Doses, %** | 85.2[a] | 80[b] | 100 |

LAIA = long-acting injectable antipsychotic.
[a]85.2% received a 14-day oral overlap aripiprazole course, 14.8% received less than 14 days of oral overlap.
[b]80% received oral paliperidone until receiving both loading doses in the 3- to 11-day window, 20% second loading dose given outside the time frame.

medication therapy. In the LAIA group, 1 patient receiving PP1M experienced muscle tightness. In the oral AP group, 2 patients on oral aripiprazole experienced akathisia, and 2 patients on oral risperidone experienced muscle tightness.

## Discussion

Whereas most outcomes were not shown to be statistically significant, there was a positive trend in the reduction of hospital readmission rates when comparing the LAIA group with the oral AP group at 0 to 3, 4 to 6, and 7 to 12 months. Only when the data was pooled for the entire 12 months of follow-up was there a significant difference with fewer readmissions in the LAIA group when compared with the oral comparator group.[6]

Analyzing the average hospital LOS for both patient groups and the nature of LAIA utilization, it seems reasonable that the LAIA therapy group would have a longer index LOS as LAIA medications have initiation protocols that may extend a patient's LOS. For example, with the utilization of loading dosing requiring a 3- to 11-day window for paliperidone palmitate, this may have led to a longer LOS for the index admission when compared with the oral AP group. Interestingly, the larger difference in LOS for up to 1 year postadmission seems promising for additional benefits of LAIA use in patients as the patients receiving LAIAs spent about half the time in the hospital when compared with the oral AP group although this difference did not reach statistical significance. The shorter hospital stays for the patients receiving LAIAs may be attributable to improved clinical psychopathology or functionality that is seen with both pediatric and adult patients on LAIA formulations.[6]

The patients in the LAIA group also had a decreased incidence of side effects when compared with the oral AP group, which may be attributable to longer durations of action with LAIA medications and short hospital stays with less monitoring time. When investigating the side effect in the LAIA group, the patient side effect was experienced while the patient was taking oral paliperidone prior to switching to the LAIA formulation. This may have been due to the patient being prescribed 9 mg of oral paliperidone at initiation, which was then

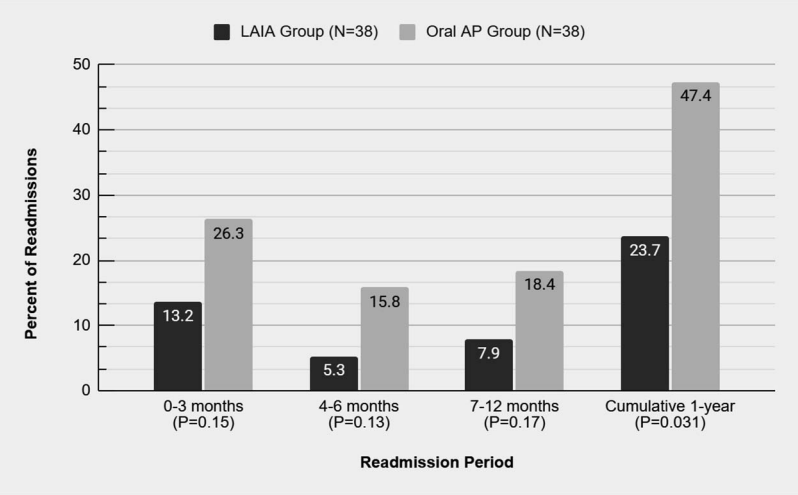


**FIGURE: Hospital readmission rates of patients on long-acting injectable antipsychotic therapy compared with oral antipsychotic therapy (LAIA = long-acting injectable antipsychotic; Oral AP = oral antipsychotic)**

decreased to 6 mg and then switched to the LAIA formulation after side effects resolved. Similarly in the oral AP group, all 4 patients who experienced EPS were not started on the lowest available dose of their respective medication. In pediatric patients, it is important to emphasize initiating oral APs at lower doses and titrating upward to assess for tolerance.

LAIA prescribing was seen most often in pediatric patients with bipolar disorder diagnoses, followed by schizophrenia, schizoaffective, or other psychotic-like disorders with 1 patient having disruptive mood dysregulation disorder. Fittingly, as aripiprazole is FDA-approved for the treatment of bipolar disorder in pediatric patients and AM is approved for this indication in adults, AM was most frequently prescribed for patients with bipolar disorder.[8] With schizophrenia or other psychotic disorders, the paliperidone LAIA was most prescribed, which may be due to oral paliperidone's labeled indications for schizophrenia and schizoaffective disorder in adults and schizophrenia in adolescents.[9] Paliperidone LAIA had the lowest rate of proper initiation when compared with the package inserts of all three LAIA compounds. This may have been due to difficulties in obtaining timely follow-up injection appointments after discharge as 2 patients were not fully loaded prior to discharge. Several patients were continued on oral paliperidone beyond the first initiation dose, but this can be considered appropriate as a possible dosing strategy seen in the adult population is to continue oral paliperidone for 4 to 7 days after the first initiation dose to accommodate the delay in achieving peak plasma levels.[11] These prescribing trends may guide prescribers in deciding which LAIA may be most beneficial for their patients who benefit from injectable therapy.

There were limitations associated with the study. The lack of statistically significant results was likely due to the small sample size. In addition, as a single-center study, patient hospitalizations and readmissions to other facilities were not captured. The study's retrospective uncontrolled design is also a limitation. Using the PSM, the patients were matched as closely to each other as possible, but not all patients were matched exactly. For example, the LAIA group had more patients with a higher number of APs used and previous hospitalizations, potentially indicating a more severely ill population. This may be why statistical significance was not seen in some outcomes. This study did not distinguish between disease states for the LAIA or evaluate the concurrent medications' potential effects on disease treatment.

In conclusion, the administration of LAIAs when compared with use of oral APs in pediatric patients may reduce hospital readmission rates, subsequent hospitalization LOS, and the incidence of side effects. These outcomes cannot be fully validated at this time due to the lack of statistical significance, but do indicate that additional studies with larger sample sizes focusing on individual disease states are warranted. Whereas long-term tolerability of oral formulations is well-studied in this population, additional research is needed for the LAIA formulations.

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