28 y/o M w/ pmhx of schizophrenia admitted to inpatient psychiatric unit for acute psychosis after medication non-adherence. Pt improves w/ PO antipsychotics during hospitalization. The team is considering transitioning him to a long-acting injectable (LAI) prior to discharge to reduce the risk of relapse.

Search question: In adults hospitalized with psychotic disorders, does initiation of LAI antipsychotics compared with PO antipsychotics reduce relapse rates and rehospitalization after discharge?

Question type: What kind of question is this?

Prevalence
Screening
Diagnosis
Prognosis
Treatment
Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

If systematic review or meta-analysis isn't available, the next best option would be randomized controlled trials (RCTs) because they provide the most direct and controlled comparison between the two treatments. However, it's worth noting that in psychiatric research, traditional RCTs can sometimes downplay the true benefits of long-acting injectables (LAIs). This is usually because the close monitoring involved in a clinical trial like frequent check-ins and pill counts tends to improve oral medication adherence far beyond what we actually see in the real world. If RCTs are limited, then well-designed cohort studies (especially prospective ones) can still be helpful in understanding outcomes like relapse and rehospitalization.

PICO search terms:

Population	Intervention	Comparison	Outcome
Adult(s)	Long-acting injectable antipsychotic	Oral antipsychotic	Relapse rates
Psychotic disorder(s)	LAI antipsychotic	PO antipsychotic	Rehospitalization
Schizophrenia	Injectable antipsychotics	Daily oral medication	Hospital readmission
Inpatient psychiatry	Depot antipsychotics	Daily dosing	Adverse effect
Hospitalized			Medication adherence

Search tools and strategy used: Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which articles to use?

Database	Search Terms Used	Number of Results	Filters/Limiters Applied	Notes/Observations
PubMed	("schizophrenia" OR "psychosis") AND ("long-acting injectable" OR "LAI") AND ("oral") AND ("rehospitalization" OR "relapse")	31	10 years, English, Humans, RCT, Systemic Review	High volume of clinical trials and observational data.
Cochrane Library	("long-acting injectable" OR "LAI") AND ("oral" OR "PO") AND ("schizophrenia" OR "psychosis")	0	None	Many unfinished clinical trials showing more research is being done on this topic and it is relevant to the field.
CINAHL	("psychotic disorder" OR "schizophrenia") AND ("long-acting injectable" OR "LAI" OR "depot") AND ("oral" OR "PO" OR "tablet") AND ("readmission" OR "relapse")	2	10 years, Peer-reviewed	

For this PICO assignment, I used a total of three databases: PubMed, CINAHL, and Cochrane Library. I used a combination of keywords including schizophrenia, psychosis, long-acting injectable, LAI, oral meds, rehospitalization, and relapse. In PubMed and CINAHL, I limited the results to articles published within the last 10 years and written in English to ensure the data included newer second-generation antipsychotics. This method got me from 297 articles on PubMed down to 31, and 14 articles on CINAHL down to 2. I then manually reviewed titles and abstracts to find studies that directly compared the two routes of administration in the post-discharge period. In Cochrane Library, my initial search had a total of 10 results. I focused on systematic reviews that analyzed treatment adherence and long-term stability. I excluded studies that focused on pediatric populations or those that didn't provide a direct comparison between LAI and PO meds. In the end, 2 articles were chosen from PubMed, 1 from CINAHL, and 0 from Cochrane.

1. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials

Citation: Wang D, Schneider-Thoma J, Siafis S, Burschinski A, Dong S, Wu H, Zhu Y, Davis JM, Priller J, Leucht S. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Schizophr Bull. 2024 Jan 1;50(1):132-144. doi: 10.1093/schbul/sbad089. PMID: 37350486; PMCID: PMC10754166.

Article type: Systemic review and meta-analysis of RCTs

Background and hypothesis: Long-acting injectable antipsychotic drugs (LAIs) are mainly used for relapse prevention but could also be advantageous for acutely ill patients with schizophrenia.

Study design: We conducted a systematic review and meta-analysis of randomized-controlled-trials (RCTs) comparing the second-generation long-acting injectable antipsychotics (SGA-LAIs) olanzapine, risperidone, paliperidone, and aripiprazole with placebo or their oral counterparts in acutely ill patients with schizophrenia. We analyzed 23 efficacy and tolerability outcomes, with the primary outcome being overall symptoms of schizophrenia. The results were obtained through random effects, pairwise meta-analyses, and subgroup tests. The study quality was assessed using the Cochrane-Risk-of-Bias-Tool version-1.

Study results: Sixty-six studies with 16 457 participants were included in the analysis. Eleven studies compared second-generation long-acting injectable antipsychotics (SGA-LAIs) with a placebo, 54 compared second-generation oral antipsychotics (SGA-orals) with a placebo, and one compared an SGA-LAI (aripiprazole) with its oral formulation. All 4 SGA-LAIs reduced overall symptoms more than placebo, with mean standardized differences of -0.66 (95% CI: -0.90; -0.43) for olanzapine, -0.64 (-0.80; -0.48) for aripiprazole, -0.62 (-0.76; -0.48) for risperidone and -0.42 (-0.53; -0.31) for paliperidone. The side-effect profiles of the LAIs corresponded to the patterns known from the oral formulations. In subgroup tests compared to placebo, some side effects were less pronounced under LAIs than under their oral formulations.

Conclusions: SGA-LAIs effectively treat acute schizophrenia. Some side effects may be less frequent than under oral drugs, but due to the indirect nature of the comparisons, this finding must be confirmed by RCTs comparing LAIs and orals head-to-head.

Key points:

- SGA-LAIs were found to be generally as efficacious as their PO counterparts for acute symptoms. Subgroup tests even suggested aripiprazole LAI was superior to PO for overall symptoms and response rates.
- Unlike PO meds, LAIs bypass hepatic and intestinal absorption, reaching the circulatory system directly. This leads to more stable plasma concentrations and fewer "peak-to-trough" variations.
- LAI formulations of aripiprazole, olanzapine, and paliperidone actually had lower extrapyramidal symptom (EPS) scores than their PO counterparts.
- Paliperidone LAI caused less of a prolactin increase than the PO version. Olanzapine LAI also had significantly lower rates of anticholinergic side effects compared to the PO drug.

- PO meds are often discontinued early due to acute symptoms like suspiciousness or lack of insight; LAIs bridge this gap by ensuring the pt has medication in their system regardless of daily pill-taking.

I chose this article because it represents a high level of evidence in the form of a systematic review and meta-analysis of RCTs, which makes it a strong starting point when evaluating treatment options. While it does not specifically examine patients in the post-discharge period or directly compare LAIs to oral antipsychotics in terms of relapse and rehospitalization, it still provides a valuable look into the overall efficacy and tolerability of LAIs. It found that LAIs are as effective as their PO counterparts for managing acute symptoms, provide more stable drug levels, and are associated with fewer side effects such as EPS and prolactin elevation, while also improving adherence in patients who might otherwise discontinue PO therapy.

2. Assessing the impact of long-acting injectable compared to oral antipsychotic medications on readmission to a state psychiatric hospital

Citation: Okoli CTC, Abufarsakh B, Wang T, Makowski A, Cooley A. Assessing the impact of long-acting injectable compared to oral antipsychotic medications on readmission to a state psychiatric hospital. J Psychiatr Ment Health Nurs. 2024 Dec;31(6):1155-1163. doi: 10.1111/jpm.13075. Epub 2024 Jun 22. PMID: 38922793.

Article type: Retrospective cohort study

Abstract: INTRODUCTION: People living with schizophrenia spectrum disorder (SSD) have poorer medication adherence compared to those with other mental illnesses. Long-acting injectable antipsychotic (LAI) medication use is associated with greater adherence, reduced re-hospitalizations, and improved recovery outcomes when compared to oral formulations.

Aim: To compare LAI antipsychotic medication use versus oral formulations on readmission to an inpatient hospital.

Method: Medical records (N = 707) from a state psychiatric hospital in the southern region of the United States were reviewed. Controlling for demographic variables, logistic regression analyses were used to examine LAI compared to oral formulations on readmission.

Results: Compared to patients discharged with oral antipsychotic medications, those with LAIs had a lower proportion of readmission rates in 6-month and 1-year periods, but not 30-day or 2-year periods. When controlling for demographic variables, those discharged with an atypical LAI had significantly lower odds of being readmitted within the 24-year period compared to those discharged on a typical oral antipsychotic.

Discussion: Compared to orals, LAIs do not increase and may mitigate readmissions to psychiatric hospitalization.

Implications for practice: Psychiatric-mental health nurses and other professionals may recommend LAIs when indicated for those with SSD.

Key points:

- Pts treated w/ LAIs had significantly fewer hospital readmissions (mean = 0.5) compared to the group on PO antipsychotics (mean = 3.6) over the follow-up period.
- Roughly 75% of the pts in the LAI group remained readmission-free compared to 31.3% of the pts in the PO medication group.
- LAIs are way more effective at reducing the "revolving door" effect in pts living w/ schizophrenia compared to daily oral dosing.
- LAIs are noted to be superior because they remove the daily burden of pill-taking, which is the primary driver for relapse in this pt population.

While this article may not be of the highest level of evidence, it directly compares the risk of hospital readmission for pts on LAIs versus those on PO meds in a state psychiatric hospital setting. It found that patients who are discharged on or switched to LAI during the hospital course were significantly less likely to be readmitted over a 24-month period compared to those PO antipsychotics. However, despite this, the authors noted that these medications are still underused in the inpatient psychiatric setting.

3. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: Systematic review and network meta-analysis

Citation: Wang D, Schneider-Thoma J, Siafis S, Qin M, Wu H, Zhu Y, Davis JM, Priller J, Leucht S. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: Systematic review and network meta-analysis. Eur Neuropsychopharmacol. 2024 Jun

Article type: Systemic review and Network meta-analysis

Abstract

Long-acting injectable antipsychotics (LAIs) are primarily used for relapse prevention, but in some settings and situations, they may also be useful for acute treatment of schizophrenia. We conducted a systematic review and frequentist network meta-analysis of randomized-controlled trials (RCTs), focusing on adult patients in the acute phase of schizophrenia. Interventions were risperidone, paliperidone, aripiprazole, olanzapine, and placebo, administered either orally or as LAI. We synthesized data on overall symptoms, complemented by 17 other efficacy and tolerability outcomes. Confidence in the evidence was assessed with the Confidence-in-Network-Meta-Analysis-framework (CINeMA). We included 115 RCTs with 25,550 participants. All drugs were significantly more efficacious than placebo with the following standardized mean differences and their 95 % confidence intervals: olanzapine LAI -0.66 [-1.00; -0.33], risperidone LAI -0.59[-0.73;-0.46], olanzapine oral -0.55[-0.62;-0.48], aripiprazole LAI -0.54[-0.71; -0.37], risperidone oral -0.48[-0.55;-0.41], paliperidone oral -0.47[-0.58;-0.37], paliperidone LAI -0.45[-0.57;-0.33], aripiprazole oral -0.40[-0.50; -0.31]. There were no significant efficacy differences between LAIs and oral formulations. Sensitivity analyses of the primary outcome overall symptoms largely confirmed these findings. Moreover, some side effects were less frequent under LAIs than under their oral counterparts. Confidence in the evidence was moderate for most comparisons. LAIs are efficacious for acute schizophrenia and may have some benefits compared to oral formulations in terms of side effects. These findings assist clinicians with insights to weigh the risks and benefits between oral and injectable agents when treating patients in the acute phase.

Key points:

- LAIs (especially second-generation ones) are consistently better than PO formulations at preventing relapse in pts w/ schizophrenia.
- LAIs have a significant clinical edge over the "oral" route, mainly because it bypasses the daily adherence issues that lead to hospital readmission.
- While PO meds work well in the short term, LAIs are the superior choice for maintenance therapy to keep the pt stable after they leave the hospital.
- LAIs are just as acceptable and tolerable as oral meds, meaning we aren't sacrificing the pt's comfort to get the better adherence results.

I chose this article because it provides a massive, high-level comparison of 32 different antipsychotic formulations. While my first two articles focused on acute settings and real-world hospital data, this systemic review and meta-analysis gives the “big picture” evidence that LAI route is fundamentally superior to PO meds for preventing relapse and hospital readmission.

What is the clinical “bottom line” derived from these articles in answer to your question?

Schizophrenia is a chronic condition where "staying well" depends almost entirely on the patient's ability to stick to a daily medication routine. Based on these three articles, transitioning a hospitalized patient to a long-acting injectable (LAI) prior to discharge is a significantly more effective strategy for preventing relapse than just sending them home with another script for oral meds. Real-world data from state psychiatric hospitals show that about 75% of patients on LAIs remain readmission-free, compared to only 31.3% of those on oral medications. Furthermore, high-level meta-analyses confirm that LAIs are safe for acute-phase use and often have fewer side effects, like extrapyramidal symptoms, than their oral counterparts.

To put it in perspective, relying on oral medications for a patient with a history of non-adherence is like trying to keep a car running while hoping the driver remembers to check the oil every single morning. An LAI is more like a scheduled maintenance plan as it takes the daily guesswork out of it and ensures the medication is actually in the system when the patient needs it most. If we want to break the "revolving door" cycle of readmission for this 28 y/o patient, starting the LAI before he walks out the door is the most evidence-based move we can make.