Brief Description of Patient Problem / Setting

During my psychiatry clinical rotation, we had a 42-year-old male with a longstanding history of schizophrenia who was admitted to the inpatient psychiatric unit for worsening auditory hallucinations, paranoid delusions, and disorganized behavior. Review of his medical records revealed three psychiatric hospitalizations within the previous year, all of which occurred following discontinuation of his prescribed oral antipsychotic medication. The patient reported that he frequently stopped taking his medication after discharge because he believed he no longer needed treatment once his symptoms improved. Family members expressed frustration regarding his inconsistent medication adherence and reported progressive social withdrawal, impaired occupational functioning, and recurrent psychiatric crises resulting in emergency department visits and hospital readmissions.

Schizophrenia is a chronic psychiatric disorder associated with significant functional impairment, reduced quality of life, and increased healthcare utilization. One of the greatest challenges in the long-term management of schizophrenia is medication nonadherence, which contributes substantially to symptom relapse, psychiatric hospitalization, emergency department utilization, and overall disease burden. Long-acting injectable (LAI) antipsychotics were developed to improve medication adherence by providing sustained therapeutic drug delivery over weeks to months, reducing the need for daily oral medication administration. Compared with oral antipsychotics, LAIs may offer improved treatment continuity, earlier identification of missed doses, and reduced risk of relapse among individuals with schizophrenia. Given this patient's history of recurrent hospitalization related to medication nonadherence, this raises the clinical question of whether long-acting injectable antipsychotics are more effective than oral antipsychotics in reducing relapse rates and psychiatric hospitalizations among adults with schizophrenia.

PICO Question

In adults with Schizophrenia, do long-acting injectable antipsychotics, compared with oral antipsychotics, reduce relapse rates and psychiatric hospitalizations?

Question Type: Treatment, Prognosis

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)? Please explain your choices.

If systematic reviews and meta-analyses were unavailable, randomized controlled trials (RCTs) would provide the next highest level of evidence to evaluate the effectiveness of long-acting injectable antipsychotics compared with oral antipsychotics. RCTs are particularly useful because random assignment minimizes bias and enables direct comparisons of relapse rates, psychiatric hospitalizations, medication adherence, and symptom control between treatment groups. Because medication adherence is a major contributor to relapse in schizophrenia, RCTs can help establish a causal relationship between treatment modality and clinical outcomes.

If RCTs were unavailable or limited, prospective cohort studies would provide valuable evidence by following patients receiving LAI antipsychotics and oral antipsychotics over time to assess differences in relapse, hospitalization rates, emergency department utilization, and treatment adherence in real-world settings. Retrospective cohort studies using large healthcare databases may also be useful for evaluating long-term outcomes and healthcare utilization among patients with schizophrenia. Additionally, mirror-image studies, which compare patient outcomes before and after switching from oral antipsychotics to LAI therapy, could provide practical insight into the effectiveness of LAIs in reducing hospitalization and relapse. Although observational studies are more susceptible to confounding factors than randomized trials, they often provide valuable real-world evidence regarding treatment effectiveness and patient adherence patterns.

PICO Search Terms

Population	Intervention	Comparison	Outcome
Adult patients with schizophrenia	Long-acting injectable antipsychotics (LAIs)	Oral antipsychotics	Reduction in relapse rates
Chronic psychotic disorders	Depot antipsychotics	Oral second-generation antipsychotics	Reduction in psychiatric hospitalization
			Improved medication adherence
			Reduced emergency department utilization

Search Term Chart

Database	Search Terms Used	Number of Results	Filters Applied	Notes/Observations
PubMed	schizophrenia AND long-acting injectable antipsychotics AND oral antipsychotics AND relapse	112	Last 10 years, English, Humans, Systematic Reviews, Meta-Analyses, RCTs	Multiple high-quality systematic reviews and meta-analyses directly compared LAIs with oral antipsychotics and reported relapse and hospitalization outcomes.

Cochrane Library	schizophrenia AND long-acting injectable antipsychotics	28	Last 10 years, English, Systematic Reviews	Identified synthesized evidence evaluating effectiveness of LAIs in preventing relapse and improving treatment adherence.
CINAHL	schizophrenia AND LAI antipsychotics AND hospitalization OR relapse prevention	41	Last 10 years, English, Peer Reviewed, Systematic Reviews, Cohort Studies	Provided additional evidence related to medication adherence, healthcare utilization, and psychiatric readmission outcomes.

Search Strategy

A comprehensive literature search was conducted using PubMed, the Cochrane Library, and CINAHL to identify high-quality evidence evaluating the effectiveness of long-acting injectable antipsychotics (LAIs) compared with oral antipsychotics in adults with schizophrenia. Search terms included combinations of "schizophrenia," "long-acting injectable antipsychotics," "LAI antipsychotics," "oral antipsychotics," "relapse prevention," "psychiatric hospitalization," and "medication adherence." Boolean operators (AND/OR) were used to combine intervention, comparison, and outcome terms to maximize the retrieval of relevant studies.

Filters were applied to include English-language studies involving human subjects published within the last 10 years. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, and large cohort studies. Studies were included if they directly compared LAI antipsychotics with oral antipsychotics and reported outcomes related to relapse, hospitalization, medication adherence, emergency department utilization, or treatment persistence. Studies were excluded if they focused exclusively on first-episode psychosis without maintenance treatment outcomes, did not include a comparison group, or failed to report clinically relevant outcomes related to relapse or hospitalization. This search yielded multiple high-quality systematic reviews and meta-analyses supporting the effectiveness of LAI antipsychotics in reducing relapse and psychiatric hospitalization among adults with schizophrenia.

1. Kishimoto, T., Hagi, K., Kurokawa, S., Kane, J. M., Correll, C. U., & colleagues. (2021).

Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: A systematic review and comparative meta-analysis of randomized, cohort, and pre-post studies. The Lancet Psychiatry, 8(5), 387–404. https://pubmed.ncbi.nlm.nih.gov/33862018

Abstract

Background: Evidence of comparative benefits of long-acting injectable antipsychotics (LAIs) versus oral antipsychotics for schizophrenia has been inconsistent across study designs. The aim of this study was to evaluate the comparative benefits of LAIs versus oral antipsychotics in three study designs to inform clinical decision making.

Methods: We did a comprehensive systematic review and meta-analysis comparing LAIs versus oral antipsychotics for schizophrenia covering three study designs: randomised controlled trials (RCTs), cohort studies, and pre-post studies. Our literature search was without language restrictions, in MEDLINE and PubMed, the Cochrane Library, Scopus, and Embase, for studies published from database inception up to a last search on March 13, 2020. We also searched for unpublished studies and ClinicalTrials.gov. We included studies lasting at least 6 months that targeted adults with schizophrenia and related disorders (>80% of participants). Studies on penfluridol (neither an LAI or daily oral antipsychotic), case reports, and case series with fewer than 20 patients were excluded. Two investigators independently extracted study-level data and resolved disagreement by consensus, or via a third investigator. Study authors were contacted to obtain additional information as needed. For our primary outcome we meta-analysed the risk ratio (RR) for hospitalisation or relapse with LAIs versus oral antipsychotics by a random-effects model, with hospitalisation used preferentially over relapse. As secondary analyses, we reversed the preferential order to relapse over hospitalisation, and assessed hospitalisation risk and relapse risk individually. Other secondary outcomes included all meta-analysable data, classed by relevance to effectiveness, efficacy, safety, quality of life, cognitive function, and other outcomes, and analysed by study design. Dichotomous outcomes were expressed as pooled RR and continuous outcomes as standardised mean difference (SMD). The protocol is registered with PROSPERO (CRD42019142094).

Findings: We identified 14 687 records, of which 137 studies (397 319 patients) met the inclusion criteria (32 RCTs [23·4%; 8577 patients], 65 cohort studies [47·4%; 377 447 patients], and 40 pre-post studies [29·2%; 11 295 patients]) and were analysed. The quality of studies in terms of risk of bias varied across study designs and within each study design from low to high. LAIs were associated with a lower risk of hospitalisation or relapse than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7833 patients, RR 0·88 [95% CI 0·79-0·99], p=0·033; cohort studies: 44 studies, 106 136 patients, RR 0·92 [0·88-0·98], p=0·0044; pre-post studies: 28 studies, 17 876 patients, RR 0·44 [0·39-0·51], p<0·0001). This association was maintained across the study designs when we reversed the preferential order to risk of relapse over hospitalisation, and in individual analysis of hospitalisation risk. The association was maintained only in pre-post studies for relapse risk alone. In all other outcomes related to

effectiveness, efficacy, safety, quality of life, cognitive function, and other outcomes, LAIs were more beneficial than oral antipsychotics in 60 (18·3%) of 328 comparisons, not different in 252 (76·8%) comparisons, and less beneficial in 16 (4·9%) comparisons when analysed by study design. Significant heterogeneity was observed across all three study designs. Publication biases were apparent in cohort and pre-post studies, but effect sizes were similar after trim-and-fill analyses.

Interpretation: Although study designs have strengths and weaknesses, including potential low quality of observational studies, we consistently identified significant benefit with LAIs versus oral antipsychotics in preventing hospitalisation or relapse, in settings ranging from restricted research (RCTs) to real-word application (cohort and pre-post studies). Our findings suggest that increased clinical use of LAIs could improve outcomes in schizophrenia.

Why I Selected This Article

Why I Selected This Article

I selected this article because it is a high-quality systematic review and meta-analysis that directly aligns with my PICO question by comparing long-acting injectable (LAI) antipsychotics with oral antipsychotics in adults with schizophrenia. It focuses on clinically meaningful outcomes such as relapse prevention and psychiatric hospitalization, which are critical indicators of long-term disease stability, treatment adherence, and overall patient functioning. This study is particularly valuable because it synthesizes evidence from multiple study designs, including randomized controlled trials, cohort studies, and pre-post studies. This allows for a broader evaluation of both controlled clinical efficacy and real-world effectiveness. The inclusion of a very large sample size, approaching 400,000 patients, strengthens the statistical power and enhances the generalizability of the findings across diverse patient populations and healthcare settings. In addition, the consistency of findings across study designs provides stronger confidence in the results, despite known variability in study quality and potential bias in observational data. The article also evaluates additional outcomes, including safety, quality of life, and cognitive effects, offering a more comprehensive understanding of LAI compared with oral antipsychotic therapy. Overall, this makes the article highly relevant and useful for supporting evidence-based clinical decision-making in the management of schizophrenia.

2. Lin, D., Thompson-Leduc, P., Ghelerter, I., Nguyen, H., Lafeuille, M. H., Benson, C., Duh, M. S., & Lefebvre, P. (2021). Real-world evidence of the clinical and economic impact of long-acting injectable versus oral antipsychotics among patients with schizophrenia in the United States: A systematic review and meta-analysis. *CNS Drugs, 35*(5), 469–481.https://link.springer.com/article/10.1007/s40263-021-00815-y

Background

Long-acting injectable (LAI) antipsychotics, compared with oral antipsychotics (OA), have been found to significantly improve patient outcomes, including reduced hospitalizations and emergency room (ER)

admissions and increased medication adherence among adult patients with schizophrenia. In turn, the clinical benefits achieved may translate into lower economic burden. Real-world evidence of the comparative effectiveness of LAI is needed to understand the potential benefits of LAI outside of the context of clinical trials. This study aimed to provide a comprehensive synthesis of recent published real-world studies comparing healthcare utilization, costs, and adherence between patients with schizophrenia treated with LAI versus OA in the United States.

Methods

In this systematic literature review, MEDLINE® was searched for peer-reviewed, real-world studies (i.e., retrospective or pragmatic designs) published in English between January 1, 2010 and February 10, 2020. Comparative studies reporting hospitalizations, ER admissions, healthcare costs, or medication adherence (measured by proportion of days covered [PDC]) in adults with schizophrenia treated with LAI versus OA (or pre- vs post-LAI initiation) in the United States were retained. Random effects meta-analyses were conducted among eligible studies to evaluate the association of LAI versus OA use on hospitalizations, ER admissions, healthcare costs, and treatment adherence. A sensitivity analysis among the subset of studies that compared OA with paliperidone palmitate once monthly (PP1M), specifically, was conducted.

Results

A total of 1083 articles were identified by the electronic literature search, and two publications were manually added subsequently. Among the 57 publications meeting the inclusion criteria, 25 provided sufficient information for inclusion in the meta-analyses. Compared with patients treated with OA, patients initiated on LAI had lower odds of hospitalization (odds ratio [OR] 0.62, 95% confidence interval [CI] 0.54–0.71, *n* = 7), fewer hospitalizations (incidence rate ratio [IRR] [95% CI] 0.75 [0.65–0.88], *n* = 9), and fewer ER admissions (IRR [95% CI] 0.86 [0.77–0.97], *n* = 6). The initiation of LAI was associated with higher per-patient-per-year (PPPY) pharmacy costs (mean difference [MD] [95% CI] $5603 [3799–7407], *n* = 6), which was offset by lower PPPY medical costs (MD [95% CI] − $5404 [− 7745 to − 3064], *n* = 6), resulting in no significant net difference in PPPY total all-cause healthcare costs between patients treated with LAI and those treated with OA (MD [95% CI] $327 [− 1565 to 2219], *n* = 7). Patients initiated on LAI also had higher odds of being adherent to their medication (PDC ≥ 80%; OR [95% CI] 1.89 [1.52–2.35], *n* = 9). A sensitivity analysis on a subset of publications evaluating PP1M found results similar to those of the main analysis conducted at the LAI class level.

Conclusions

Based on multiple studies with varying sub-types of patient populations with schizophrenia in the United States published in the last decade, this meta-analysis demonstrated that LAI antipsychotics were associated with improved medication adherence and significant clinical benefits, such as reduced hospitalizations and ER admissions, compared with OA. Lower medical costs offset higher pharmacy costs, resulting in a non-significant difference in total healthcare costs. Taken together, these findings provide strong evidence on the clinical and economic benefits of LAI compared with OA for the treatment of schizophrenia in the real world.

Why I selected this article

I selected this article because it evaluates the real-world effectiveness of long-acting injectable (LAI) antipsychotics compared with oral antipsychotics in adults with schizophrenia, a clinically significant issue given the high rates of relapse and nonadherence in this population. The study provides a comprehensive systematic review and meta-analysis of U.S.-based real-world evidence, which strengthens its relevance to everyday clinical practice beyond controlled trial settings. It examines key outcomes that are directly applicable to patient care, including hospitalization rates, emergency room utilization, medication adherence, and overall healthcare costs. This is particularly important because medication adherence is a major determinant of relapse prevention and long-term stability in schizophrenia. Additionally, the article evaluates both clinical and economic outcomes, offering a balanced perspective on whether the higher upfront medication costs of LAIs are offset by reduced healthcare utilization. Overall, I chose this article because it provides high-level evidence to support decision-making regarding the selection of antipsychotic formulations and their impact on both patient outcomes and healthcare systems.

3. Okoli, C. T. C., Kappi, A., Wang, T., Makowski, A., & Cooley, A. T. (2022). The effect of long-acting injectable antipsychotic medications compared with oral antipsychotic medications among people with schizophrenia: A systematic review and meta-analysis. *International Journal of Mental Health Nursing, 31*(3), 469–535.https://pubmed.ncbi.nlm.nih.gov/34931437/

Abstract

Long-acting injectable (LAI) antipsychotic medications may be an important modality of reducing costs, improving symptoms, and fostering quality of life outcomes for those with schizophrenia. Our objective was to systematically review and conduct a meta-analysis of the effectiveness of LAIs compared with oral antipsychotics on medication adherence, symptom remission/relapse, rehospitalization, outpatient visits, emergency department visits, healthcare costs, and social functioning. We performed a systematic search of PsycInfo, CINAHL, PubMed, and Scopus databases to examine studies meeting inclusion criteria prior to August 30th, 2020. Randomized controlled trials, retrospective studies, prospective studies among people with schizophrenia with at least 6-month follow-up data were obtained. Overall effect sizes and associated 95% confidence intervals (CI) were estimated with random-effects modeling. We found 75 articles meeting our inclusion criteria, including 341 730 individuals with schizophrenia. Systematic review results indicated that LAIs compared with orals improved medication adherence (25/29 studies), symptom remission/relapse (10/18 studies), rehospitalizations (26/49 studies), emergency department visits (9/17 studies), medical costs (11/15 studies), and social functioning (5/9 studies); however, LAIs also increased outpatient visits (7/16 studies) and pharmacy costs (10/10 studies). Meta-analytic results of studies with similar outcome measures did not find differences between LAIs and orals in respect to outcomes, except lowering emergency department visits and increasing pharmacy costs. The differences

between the results of the narrative synthesis and the meta-analyses were possibly because of the low availability of studies with similar outcomes in the pooled analyses. Our overall results suggest that LAIs are at least comparable to orals in supporting important healthcare outcomes for those with schizophrenia. These findings support clinical practice in encouraging providers to prescribe LAIs when indicated.

Why i selected this article

I selected this article because it directly addresses my PICO question by comparing long-acting injectable (LAI) antipsychotics with oral antipsychotics in individuals with schizophrenia and evaluating outcomes that are highly relevant to clinical practice. Specifically, the study examines medication adherence, symptom relapse, rehospitalization, emergency department visits, healthcare utilization, costs, and social functioning. These outcomes closely align with my clinical question regarding whether LAIs reduce relapse rates and psychiatric hospitalizations compared with oral antipsychotics. This article provides a high level of evidence because it is a systematic review and meta-analysis that included 75 studies and over 341,000 individuals with schizophrenia. The large sample size and inclusion of multiple study designs provide a comprehensive assessment of LAIs in both research and real-world settings. The study found that LAIs were associated with improved medication adherence and demonstrated benefits in several studies related to relapse prevention, rehospitalization, emergency department utilization, and healthcare costs. Because medication nonadherence is a major contributor to relapse and psychiatric hospitalization in schizophrenia, these findings are particularly relevant to my PICO question. I selected this article because it evaluates both clinical and healthcare utilization outcomes, providing a comprehensive perspective on the effectiveness of LAIs compared with oral antipsychotics. Overall, it offers strong evidence that supports the use of LAIs as an important treatment option for improving long-term outcomes in individuals with schizophrenia.

4. Wang, D., Schneider-Thoma, J., Siafis, S., Qin, M., Wu, H., Zhu, Y., Davis, J. M., Priller, J., & Leucht, S. (2024). Efficacy, acceptability and side-effects of oral versus long-acting injectable antipsychotics: Systematic review and network meta-analysis. *European Neuropsychopharmacology, 83*, 11–18. https://doi.org/10.1016/j.euroneuro.2024.03.003

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 using the Confidence-in-Network-Meta-Analysis (CINeMA) framework. 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 differences in efficacy 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.

Why i selected this article

This article was selected because it is a recent (2024) systematic review and network meta-analysis that synthesized evidence from 115 randomized controlled trials involving 25,550 participants with schizophrenia, making it among the largest and highest-quality bodies of evidence available on this topic. Although the primary focus of the study was the acute treatment phase of schizophrenia rather than long-term relapse prevention, it directly compared long-acting injectable (LAI) antipsychotics with their oral counterparts across multiple clinically relevant outcomes, including symptom improvement, treatment acceptability, and adverse effects.

This study was included because it provides important context for understanding the overall effectiveness of LAIs compared with oral antipsychotics. The findings demonstrated that LAIs were at least as effective as oral formulations in reducing acute schizophrenia symptoms and, in some cases, were associated with fewer side effects. These results support the use of LAIs as a viable treatment option and complement the evidence from studies focused on relapse prevention and hospitalization outcomes. Additionally, the large sample size, rigorous methodology, and inclusion of multiple antipsychotic agents strengthen the reliability and generalizability of the findings. While the study does not directly address relapse rates or psychiatric hospitalizations, it contributes valuable evidence regarding the efficacy and tolerability of LAIs, which are important factors when selecting long-term treatment strategies for patients with schizophrenia.

Clinical Bottom Line

Based on the current body of evidence, long-acting injectable (LAI) antipsychotics are an effective treatment option for adults with schizophrenia and generally demonstrate advantages over oral antipsychotics in improving medication adherence and reducing relapse-related outcomes. Across multiple systematic reviews and meta-analyses, LAIs were consistently associated with lower rates of relapse, psychiatric hospitalization, and emergency department utilization, particularly in real-world clinical settings where medication nonadherence is common. Improved adherence appears to be a primary

mechanism by which LAIs achieve these benefits, as sustained medication delivery reduces the risk of missed doses and treatment interruptions.

The evidence also suggests that LAIs achieve clinical outcomes at least comparable to those of oral antipsychotics for symptom control, while offering potential advantages in treatment continuity and, in some cases, tolerability. Real-world studies further demonstrate reductions in healthcare utilization and medical costs associated with fewer psychiatric hospitalizations and emergency department visits, although pharmacy costs may be higher. Collectively, these findings support the use of LAIs as an evidence-based maintenance treatment strategy for reducing relapse risk and promoting long-term stability in individuals with schizophrenia.

When applying this evidence to clinical practice, particularly among underserved or vulnerable populations, several implementation factors must be considered. Although LAIs may be especially beneficial for patients with a history of medication nonadherence, barriers such as transportation challenges, unstable housing, limited access to outpatient mental health services, insurance restrictions, and fragmented healthcare systems may affect treatment accessibility and continuity. Additionally, cultural beliefs, stigma associated with injectable medications, varying levels of health literacy, and mistrust of healthcare systems may influence patient acceptance and engagement with treatment.

Overall, the evidence supports the use of long-acting injectable antipsychotics as an effective strategy for reducing relapse and psychiatric hospitalization in adults with schizophrenia. However, optimal outcomes depend not only on medication selection but also on addressing social, cultural, and structural barriers to care. Integrating LAIs within comprehensive treatment plans that include patient education, care coordination, family involvement, and accessible community mental health services is likely to maximize their clinical benefit and improve long-term outcomes.