CNS Drugs (2026) 40:921–948
https://doi.org/10.1007/s40263-026-01294-9

REVIEW ARTICLE

# The Role of Long-Acting Injectable Antipsychotics in the Early Treatment of Schizophrenia

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Received: 4 August 2025 / Accepted: 31 March 2026 / Published online: 27 May 2026


## Abstract

Early and effective treatment of schizophrenia, within approximately the first 5 years after diagnosis, can help maximize responses and minimize functional decline and worsening of clinical outcomes. Suboptimal treatment selection in this early phase may increase the risk of relapse and negatively impact treatment adherence. Compared with daily oral antipsychotics (OAPs), long-acting injectable (LAI) antipsychotics, with dosing intervals of every 2 weeks or longer, provide consistent steady-state levels of medication and are useful for improving antipsychotic treatment adherence. Initiating LAI treatment as early as the first episode and within the first 5 years of illness has been associated with better treatment outcomes. Despite their well-known benefits, many clinicians reserve the initiation of LAIs for patients who have experienced relapse, often due to demonstrated non-adherence to OAPs, instead of using LAIs earlier after a schizophrenia diagnosis and before multiple relapses occur. This review highlights the advantages of initiating an LAI treatment earlier after a schizophrenia diagnosis, including LAI potential to reduce relapse rates, improve overall functioning, and reduce healthcare resource utilization and associated costs. The perceived barriers to early adoption of LAIs, strategies to reduce these barriers, and increase physician and patient confidence in LAIs are discussed. Additionally, we examine the current treatment guidelines for recommendations on early use of LAIs. Taken together, early use of LAIs is associated with improved patient outcomes, reduced relapse risk, and lower overall healthcare costs. Encouraging the adoption of LAIs as first-line treatment in clinical practice could help optimize long-term outcomes for patients with early phase schizophrenia. This review also highlights the evidence gaps and practical implications for clinical decision making.

**Key Points**

Using long-acting injectable (LAI) formulations of antipsychotics in the early phase of schizophrenia (typically the first 5 years) improves symptom severity and reduces all-cause mortality and the risk of relapse. However, they are often reserved for later in the treatment paradigm for patients with a history of non-adherence and multiple relapses.

Persistent barriers to early adoption include negative perceptions of LAIs from both clinicians and patients/family members, a lack of education, and absence of strong support for early use of LAIs in the schizophrenia treatment guidelines.

Addressing patient- and physician-specific barriers to the early adoption of LAIs could include developing educational initiatives and updating schizophrenia treatment guidelines to focus on the benefits of early introduction of LAIs for patient outcomes and quality of life.

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## 1 Introduction

Schizophrenia is often a debilitating, chronic, and relapsing mental disorder with a multifactorial etiology [1–3]. Schizophrenia affects an estimated minimum of 24 million people globally, which is equivalent to 1 in 300 individuals (0.32%), with a rate of 1 in 222 adults (0.45%) [4, 5]. According to the Global Burden of Disease report in 2019, schizophrenia was identified as the third cause of burden among 12 mental disorders in people aged 25–64 years and had a worldwide age-standardized prevalence of 287.4 per 100,000 people [6]. Yet, premature mortality, estimated at 15.22 years of life lost for patients with schizophrenia [7], may lead to an underestimation of the true lifetime morbid risk to developing schizophrenia [8]. While schizophrenia typically has an onset in early adulthood, with ~ 8% of cases beginning before the age of 18 years and a peak onset at 20.5 years [9], and requires lifelong management, early intervention is critical as it can significantly impact the course of the disease and improve overall outcomes [10, 11]. The lifetime risk of suicide in patients with schizophrenia is approximately 5% [12, 13], with the highest risk during the early stages of the illness [14].

The first 3–5 years of illness in patients with schizophrenia has been referred to as the 'critical period' for shaping the course of the disease [10, 11, 15, 16]. During this period, there is a higher potential for modification of long-term disease outcomes as biological, psychological, and social factors are still developing and exhibit greater plasticity [10, 11]. Moreover, patients recently diagnosed with schizophrenia have had limited exposure to treatment and may exhibit better response to treatment than those with long-term schizophrenia [17]. Early intervention in patients with schizophrenia is associated with improvement in clinical outcomes [18], lower long-term suicide rates [19], and moderate increases in employment rates [20] than intervention at a later stage. Antipsychotics have been the cornerstone of pharmacologic therapy for schizophrenia to help control acute psychotic episodes [5] and reduce risk of relapse [21–23], while maintenance therapy is used for long-term management after patients are stabilized on an antipsychotic regimen [1, 24, 25]. The long-term mortality rate in patients who took antipsychotics was found to be lower than that of those who did not [26]. Although the benefits of pharmacological intervention are well established, a comprehensive approach including both pharmacological and psychosocial aspects are essential for achieving the highest possible degree of functional recovery in patients with schizophrenia.

Poor treatment adherence can have significant detrimental consequences to patient outcomes, including increased risk of relapses, psychotic symptoms, hospitalization or emergency room (ER) admissions, suicide attempts, and reduced quality of life (QoL) [27–29]. Poor adherence, specifically to oral antipsychotic medications (OAPs), followed by cessation of treatment without medical guidance, is often prominently observed during the first few years of schizophrenia [28–32].

The clinical course of schizophrenia is characterized by recurring relapses, most of which occur early in the disease course, possibly due to treatment non-adherence [33, 34]. The rates of relapse are markedly higher in the early phase (first 5 years) of schizophrenia ranging from 30% to 60% during the first 2 years [35–37] and up to 80% during the first 5 years of treatment after the onset of schizophrenia [16, 34, 38]. Prevention of relapse should be an essential treatment goal intended to reduce (or offset) the impact of accumulated long-term negative outcomes accrued during the early phase of schizophrenia [39]. Relapses in the early phase of the disease can have multifactorial consequences influencing not only the clinical course of the disease but also the social, economic, and biological wellbeing of patients (Table 1).

In patients with early phase schizophrenia, use of long-acting injectable (LAI) antipsychotics has demonstrated improvements in symptom severity and reduction of all-cause mortality, suicidal risk, and risk of relapse [40–43]. The benefits of LAIs have been well documented in pragmatic and explanatory trial designs [42, 44–46]. Despite growing evidence to support the early adoption of LAIs during first years of disease, underutilization in clinical practice, particularly during the first 5 years following a diagnosis of schizophrenia, remains [10, 15, 47]. Many psychiatrists reserve the use of LAIs for later stages of illness, following multiple relapses and demonstrated medication non-adherence [48]. LAIs, with dosing intervals of 2 weeks to 6 months, have the potential to overcome the challenge of treatment adherence in patient subgroups who are likely to become non-adherent or discontinue treatment of daily oral regimens [49–51]. In total, 15 LAI formulations (including 7 first-generation and 8 second-generation drugs) are currently approved in various regions worldwide, including the US, Europe, and Canada [52–54]. Currently available second-generation LAIs have variable pharmacokinetic properties and administration frequencies [55]. Among these, aripiprazole monohydrate (every 4 or 8 weeks), aripiprazole lauroxil (every 4, 6, or 8 weeks), olanzapine pamoate (every 2 or 4 weeks), risperidone LAI (microspheres; RLAI) (every 2 weeks), 1-month RLAI (copolymer formulation: every 4 or 8 weeks, or in situ microparticles: every 4 weeks), as well as paliperidone palmitate 1-month (PP1M), 3-month (PP3M), and 6-month (PP6M) formulations are approved and currently marketed in the US and/or the European Union [52, 54].

Overall prescription rates of LAIs for schizophrenia ranged from 14.7% to 28.1% in Europe [56–58], 15% in the US [59, 60], and were as low as 6.5% in Canada, whereas

**Table 1** Impact of schizophrenia relapse

| | |
|---|---|
| Clinical impact | Treatment resistance [157]<br>Reduced response to antipsychotic treatment [157, 158] or development of secondary treatment resistance [159]<br>Aggravation or recurrence of symptoms [157, 160]<br>Mixed evidence on disease progression [157] |
| Social impact | Higher rates of unemployment, divorce, homelessness, incarceration, premature death (vs non-relapse cohort) [161, 162]<br>Loneliness [160]<br>Caregivers experience increased psychological burden [163] |
| Economic impact | Increased healthcare costs (healthcare resource utilization, inpatient and outpatient care, medication) [164]<br>Healthcare costs can be twice as much as those for patients who never relapsed [165]<br>Overall, high burden on caregiver and society [166] |
| Biological impact | Extended duration of relapse affects brain integrity (loss of brain tissue, decrease in total cerebral volume, specifically frontal lobe and white matter) [167, 168] |

over 62% of LAIs are prescribed as third-line treatment or later [61]. Only ~10% of patients tend to receive LAIs in the first year of their disease [62–64]. Although there are review articles on LAIs that address guidelines, reasons for and barriers to their use, including more recently with a specific focus on LAI use in the early years of schizophrenia, we are not aware of a review that has covered all of these aspects, including pharmacoeconomic data, with a focus on people with schizophrenia in the first 5 years of illness. Hence, this review discusses the need for early intervention in schizophrenia and the potential merits of positioning LAIs as a first-line treatment in schizophrenia.

## 2 Literature Search

To ensure a comprehensive understanding of LAI use in early phase schizophrenia, defined as within the first 5 years of diagnosis, we conducted a content-guided, narrative literature search across multiple electronic databases, including PubMed, Google Scholar, and Scopus, using the following search terms: ("long-acting injectable antipsychotics" OR LAI) AND ("early phase schizophrenia" OR "first episode schizophrenia" OR "early schizophrenia" OR "early illness" OR "within five years") AND ("efficacy" OR "effectiveness" OR "outcomes") AND ("pharmacoeconomics" OR "cost-effectiveness") AND ("treatment guidelines" OR "recommendations" OR "guidelines"). Our primary focus was on studies involving patient populations within the first 5 years of illness, aiming to capture early disease progression versus LAI usage during this critical period. Questions to be addressed by this review included efficacy and effectiveness of LAIs in the early phase of schizophrenia; long-term benefits of early LAI adoption; cost effectiveness of LAIs; current treatment guidelines and recommendations for schizophrenia; barriers to early adoption of LAIs; increasing physician confidence/reduced barriers (see section headers below). Given the pragmatic nature of this review, we deliberately included a wide variety of study designs, such as randomized controlled trials (RCTs), cohort studies, case-control studies, observational studies, and other pragmatic designs. This inclusive approach was intended to maximize data diversity and to reflect real-world clinical practice scenarios of early stage illness in people with schizophrenia.

## 3 Efficacy and Effectiveness of LAIs in the Early Phase of Schizophrenia

There is a growing body of evidence on the patient-centered benefits of LAI usage in patients within the first 5 years of schizophrenia diagnosis, including several RCTs, open-label studies, observational studies, and meta-analyses. Most of these studies assessed the efficacy of LAIs in terms of symptom control, relapse prevention, treatment adherence and discontinuation, and hospitalization rates (Table 2). This section summarizes the key outcomes described in these studies.

Two studies examining RLAI microspheres and PP1M showed that both LAIs and OAPs were effective in terms of symptom control, with the LAIs performing better regarding patient adherence and rate of relapse [65, 66]. Additional analyses showed that the benefit was more pronounced when the LAI was initiated within the early phase versus long-term schizophrenia [67–71].

In the above-mentioned open-label study with RLAI, patients with schizophrenia treated with RLAI in the early phase showed similar Positive and Negative Syndrome Scale (PANSS) total and Clinical Global Impressions–Severity (CGI-S) scores compared with patients treated with OAPs [65], whereas the PP1M study noted better treatment outcomes with PP1M versus OAPs on PANSS total scores but similar results for CGI-S scores versus OAPs [66].

In another open-label study, significant improvements in PANSS total and CGI-S scores were observed over the 18-month prospective period in patients with recent-onset schizophrenia who switched from OAPs to LAI (specifically, PP1M) [72, 73].

When LAI treatment outcomes for patients within 3 years of schizophrenia onset were compared with those for patients with longer illness duration (> 3 years), improved PANSS total scores [67–69, 71, 73], and CGI-S scores [68, 71, 73, 74] were observed. An exploratory post-hoc analysis by Brown et.al. reported significant improvements in PANSS total scores regardless of injection frequency (PP1M or PP3M) at all stages of schizophrenia (≤ 5, 6–10, and > 10 years) but the magnitude of benefits was larger in patients within the first 5 years compared with those with long-term schizophrenia [68]. Similar benefits were noted in another study wherein patients with schizophrenia duration of < 3 years versus ≥ 3 years and < 10 years versus ≥ 10 years showed the best improvements in clinical and functional outcomes [75]. Moreover, in patients hospitalized for the first time, significant improvements in CGI-S scores from baseline were noted with LAI treatment [76]. In patients within 2 years of diagnosis, Global Assessment of Functioning scores improved significantly from baseline [74].

A recent meta-analysis of 137 studies that included RCTs, cohort studies, and pre-post studies (pre vs post LAI use) found LAIs to be more effective than OAPs for relapse prevention [42]. In nine subgroup analyses from another meta-analysis of 11 RCTs [46], LAIs were superior to OAPs in patients with first episode and early phase schizophrenia when (i) studies employed a strict intention-to-treat approach (suggesting higher quality and more valid results), (ii) studies had a more pragmatic than explanatory design (suggesting greater applicability to usual care settings), (iii) when the oral comparator was selected based on a patient's prior treatment history (highlighting the value of LAIs, even when the oral antipsychotic choice could be tailored), and (iv) when patients were classified as clinically stable (suggesting benefits of a reasonably long OAP initiation phase before transitioning to an LAI) [46].

An integrated patient-level pooled analysis of two studies evaluated the risk of relapse in patients receiving PP1M or OAPs by different durations of illness (0–3 years, > 3–5 years, and > 5 years from diagnosis). PP1M treatment versus OAPs reduced risk of relapse by 33% for patients in the 0–3-year subgroup, by 43% in the > 3–5-year subgroup, and by 26% in the > 5-year subgroup, which supports the relevance of treating with LAIs within the first 5 years of illness [77].

In a post-hoc analysis of the RLAI study in patients with schizophrenia, the proportion of relapses was lower (10.5%) in recently diagnosed patients (< 3 years) than in patients with a longer disease duration (21.8%; > 3 years) [71]. A double-blind, placebo-controlled, relapse prevention study conducted in eight countries showed that PP3M significantly delayed time to relapse of schizophrenia symptoms compared with placebo [78]. In the post-hoc analysis of this study reporting on patients receiving PP3M within the first 5 years of schizophrenia diagnosis, PP3M led to significantly delayed time to relapse compared with placebo [79].

Many studies reported lower hospitalization rates and shorter hospital stays in patients receiving LAIs compared with those on OAPs (Table 2). In a recent meta-analysis, the risk of hospitalization with LAIs was significantly lower than with OAPs across RCTs, cohort studies, and pre-post (also known as mirror image) studies [42].

In a recent longitudinal observational study with a within-subject design, greater decreases in hospitalizations among patients with early phase psychosis were noted after implementation of LAI treatment compared with prior or subsequent OAP treatment [80].

Studies also reported a significant decrease in the proportion of patients with early phase psychosis who required hospitalization, and in cumulative hospital days, while receiving LAI treatment in comparison with OAP treatment [72, 81].

A post-hoc analysis of two observational studies, TIMORES and electronic Schizophrenia Treatment Adherence Registry (e-STAR), reported a reduction in the number of hospital stays at 12-month follow-up compared with pre-LAI initiation data [74]. The mean reduction from baseline in hospitalization days was more pronounced in patients with recent schizophrenia diagnosis at 12-month follow-up, and in patients with long-term schizophrenia at 24-month follow-up [74]. In a post-hoc analysis of another study that assessed patient outcomes after 1 year of LAI treatment, lower proportions of patients within 3 years of diagnosis (3.5%) were hospitalized due to worsening of symptoms compared with those with long-term schizophrenia (10.5%) [71].

A retrospective cohort study that evaluated in-hospital use of LAIs for first-admission schizophrenia in 56,211 patients from Taiwan indicated administration of LAIs with and without early discontinuation in 10.1% and 6.5% of patients, respectively. In addition, use of LAIs increased by 4% between 2004–2008 and 2013–2017. The risk of readmission decreased among patients receiving LAIs without early discontinuation when compared with patients not receiving LAIs [82].

In patients with schizophrenia, earlier illness is associated with lower antipsychotic adherence [32]. LAIs are associated with improved treatment adherence [32, 76], with a recent meta-analysis suggesting that adherence to LAI is 1.4 times higher than adherence to OAPs [83, 84]. Another large analysis of patients from the US Medicaid database showed that treatment adherence and persistence was better with second-generation LAIs than with first-generation LAIs [63]. Similar results were obtained in a recent analysis of

**Table 2** Efficacy and safety of LAIs when prescribed in patients with early phase schizophrenia

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| *Meta-analyses* | | | | | | | |
| Schneider-Thoma et al., 2022 [169] | 16,812 | Systematic review and Bayesian network meta-analysis of 501 studies | LAIs vs placebo in adults with stable schizophrenia or schizoaffective disorder | NR | Lower risk of relapse compared with placebo (RRs < 1.00)<br>Paliperidone oral had the lowest RR (0.20) | NR | N/A |
| Ostuzzi et al., 2022 [23] | 22,645 | Network meta-analysis of 92 studies | Adults with schizophrenia spectrum disorders | NR | Relapse prevention was significantly more effective with all antipsychotics—except clopenthixol-oral (OS), haloperidol-LAI, and (zu) clopenthixol-LAI—vs placebo<br>Tolerability (dropouts due to AEs) did not vary among antipsychotics | NR | N/A |
| Ostuzzi et al., 2021 [170] | 11,505 | Network meta-analysis of 78 studies | LAI in the maintenance treatment of adults with non-affective psychoses | NR | LAIs were significantly more effective vs placebo in relapse prevention and 'acceptability' (a measure of tolerability) | NR | N/A |
| Kishimoto et al., 2021 [42] | 397,319 | Comprehensive systematic review and meta-analysis of 137 studies | Adults with schizophrenia and related disorders | NR | Lower risk of hospitalization or relapse with LAIs vs OAPs (RCTs: $p = 0.033$; cohort studies: $p = 0.0044$; pre-post studies: $p < 0.0001$) | NR | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Lian et al., 2022 [171] | 10,584 | Meta-analysis of 15 studies | Early phase psychosis | ≤5 years | Significant advantage of LAIs over OAPs in terms of relapse rate reduction ($p = 0.05$), discontinuation due to non-adherence ($p = 0.03$), and inefficacy ($p = 0.04$)<br>No significant differences between LAIs and OAPs in all-cause discontinuation, hospitalization, and adherence rates | NR | N/A |
| Lian et al., 2022 [41] | 14,313 | Comprehensive review of 33 studies | Early phase schizophrenia | ≤5 years | LAIs showed benefits for early psychosis in terms of adherence, relapse reduction, and symptom improvements<br>Limited comparative data for fluphenazine decanoate, flupentixol decanoate, and aripiprazole | Reported as per the studies included such as insomnia, anxiety, headache, weight gain, depression, and hyperkinesia | N/A |
| Vita et al., 2024 [46] | 2374 | Systematic review and meta-analysis of 11 RCTs | LAI vs OAPs in patients with early phase schizophrenia | < 1 year | No differences between LAIs and OAPs for relapse/hospitalization prevention (RR 0.79) and acceptability (RR 0.92), but superiority of LAIs vs OAPs in both outcomes in several preplanned subgroup analyses of higher quality and more real-world studies | Common AEs: prolactin increase, body mass index change, weight increase, sedation, akathisia, and extrapyramidal side effects | N/A |

*Mixed study design review*

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Ma et al., 2023 [172] | 158,740 | Scoping review of 15 cohort studies, 13 single-arm trials, 10 RCTs, 4 mirror image studies, 3 cross-sectional studies, and 1 controlled clinical trial | Asian patients with schizophrenia | ≤5 years | LAIs demonstrated lower relapse (0.0% to 12.4% vs 5.9% to 34.0%) / hospitalization rates (0.0% to 60.3% vs 20% to 66.1%) compared with OAPs<br>Comparable improvement in efficacy between LAIs and OAPs<br>Significant reduction in hospitalization length and outpatient visits/admissions after LAI initiation | AEs were similar between LAIs and OAPs | N/A |
| *Randomized controlled trials* | | | | | | | |
| Bell Lynum et al., 2019 [79] | 119 | RCT/PP | PP vs placebo in patients with early phase schizophrenia (DB phase) | ≤5 years | PANSS score significantly worsened in placebo group by 15%<br>CGI-S and PSP scores were significantly better in PP group compared with placebo (Difference: 7.1 and 2.1, respectively) | Common AEs: injection-site pain, headache, anxiety, nasopharyngitis, urinary tract infections, and increased weight | N/A |
| Bossie et al., 2017 [67] | 667 | RCT/PP | Patients with recent onset vs long-term schizophrenia treated with PP | ≤5 years vs >5 years | Significant improvements in PANSS scores vs baseline<br>Relapse rates were lower in both groups (10% and 18%) vs placebo (30% and 35.5%) | Reported AEs in recent onset and long-term illness groups were 56.8% and 65.1%<br>Common AEs: headache, injection-site pain, insomnia, suicidal thoughts, weight change, and increased weight | Early intervention with PP1M resulted in better symptom improvement, lower relapse rates, and better treatment outcomes in recently diagnosed patients |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Brown et al., 2020 [68] | 994 | RCT/PP | Patients with schizophrenia duration of illness ≤5 years, 6–10 years, > 10 years treated with PP during OL and DB phases vs baseline | Three categories: illness ≤5 years, 6–10 years, > 10 years | Significant improvements in PSP scale and PANSS scores compared with baseline in OL and DB phases<br>Relapse rate was 8–10% in all duration-of-illness groups | AEs varied between 50–54.9% in OL phase and 64.2–70.2% in DB phase<br>Common AEs: injection-site pain and increased weight | Significant symptomatic and functional improvements were observed in patients with early (≤ 5 years) and moderate (6–10 years) illness compared with those with long-term illness (> 10 years) |
| Dubois et al., 2014 [74] | 951 | RCT/RLAI | Recent vs long-term schizophrenia patients treated with RLAI | ≤3 years vs > 3 years | CGI-S scores were greater in patients with recent vs long-term schizophrenia<br>Reduced hospitalization rate by 61% in earlier-phase group | N/A | Recent diagnosis patients showed significant clinical improvements, better employment status, reduced hospitalization days at 12 months, and higher remission rates |
| Kane et al., 2023 [173] | 544 | Phase III, double-blind, placebo-controlled RCT of TV-46000 (subcutaneous risperidone) | Adult patients with schizophrenia treated with RLAI | 2 years | TV-46000 significantly prolonged time to impending relapse:<br>5.0-times longer with TV-46000 once monthly ($p < 0.0001$) vs placebo<br>2.7-times longer with TV-46000 once every 2 months ($p < 0.0001$) vs placebo | Common AEs: injection-site nodules, weight increase, and extrapyramidal disorder | N/A |
| Kane et al., 2020 [174] | 489 | RCT/long-acting AOM | AOM vs usual care in early phase schizophrenia | <5 years | Hospitalization rate decreased by 36% with AOM in first-episode and early phase patients vs those receiving usual care | NR | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Kim et al., 2023 [75] | 82 | RCT/long-acting injectable aripiprazole | Patients with recent onset vs long-term schizophrenia | ≤5 years vs >5 years | Significantly improved PANSS, PSP, and CGI scores in patients with recent-onset vs long-term schizophrenia | Common AE: increased body weight | Recent onset patients showed improvements in psychopathology and social functioning while long-term patients showed significant improvements in metabolic parameters |
| Malla et al, 2016 [65] | 77 | RCT/RLAI | RLAI vs OAP | <3 years | Significant improvements in PSP scale and PANSS scores compared with baseline with LAIs and OAPs<br>Relapse and hospitalization rates were 21% and 15.6%, respectively, with high proportion in RLAI group | Reported AEs: alcohol dependence syndrome, depression, nausea, and weight gain | N/A |
| Schreiner et al., 2015 [66] | 769 | RCT/PP | PP vs OAP | 1–5 years | Comparable improvement in PANSS total score was observed in both groups<br>Statistically significant improvement (vs baseline) in CGI-S total score and PSP for both groups<br>Time to relapse rate was significantly longer in PP (vs OAP) arm<br>Significantly fewer patients from PP (vs OAP) met relapse criteria | Commonly reported AEs (both groups): increase in body weight, insomnia, anxiety, headache, psychiatric disorders, and injection-site pain | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Subotnik et al., 2015 [81] | 83 | RCT/RLAI | RLAI vs OAP | 2 years | Relapse rate was lower for RLAI group vs oral risperidone group (5% vs 33%)<br>Hospitalization rate was 5% in RLAI group vs 18.6% in oral group<br>Significantly better adherence with RLAI than oral risperidone group | NR | N/A |
| Winter-van Rossum et al., 2023 [89] | 511 | RCT/LAI paliperidone, LAI aripiprazole | LAI vs OAPs in patients with early phase schizophrenia | 6 months to 7 years | Hospitalization rate was 20%<br>No difference between LAIs and OAPs in all-cause treatment failure, but randomization to LAIs before oral pretreatment phase and superiority of LAIs for discontinuation for "other" reasons | Common AEs: akathisia and Parkinson's | N/A |
| Zhang et al., 2015 [72] | 521 | Phase IIIb RCT/PP | Patients with recent-onset schizophrenia vs baseline | ≤5 years | Improved PANSS and CGI-S scores<br>Decrease in hospitalization rates with PP (vs baseline) 39.7% vs 24.6%, respectively | Common AEs: extrapyramidal symptom-related, injection-site pain, and insomnia | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Hargarter et al., 2016 [69] | 593 | RCT, post-hoc analysis/PP | Patients with recently diagnosed vs long-term schizophrenia | ≤3 years vs >3 years | Statistically significantly greater change in PANSS total score was noted in patients with recently diagnosed (vs long-term) schizophrenia<br>Statistically significant decrease in CGI-S scores at endpoint (vs baseline) noted for both groups<br>PSP scores increased significantly in both groups from baseline | Reported AEs: injection-site pain, insomnia, anxiety, headache, psychotic disorders, insomnia, akathisia, somnolence, depression, and increased weight | Recently diagnosed patients had a significantly higher treatment response and improved functioning compared with long-term patients |
| Macfadden et al., 2010 [71] | 323 | RCT, post-hoc analysis/RLAI | Patients with recently diagnosed vs longer duration schizophrenia | ≤3 years vs >3 years | Significant improvement in PANSS (−10.2 vs −3.8) and CGI-S (−0.5 vs −0.2) scores<br>Relapse rates were 10.5% in recently diagnosed vs 21.8% in patients with longer duration schizophrenia | Reported AEs: insomnia, anxiety, headache, psychiatric disorders, and influenza | Early treatment with RLAI resulted in greater improvement in symptoms and lower relapse rates compared with those with longer illness duration |
| *Nationwide cohort studies* | | | | | | | |
| Shin et al., 2021 [96] | 3790 | Korea National Insurance Claims Database study | Patients with schizophrenia treated with PP or ORPs; divided into early-PP (≤ 30 days), late-PP (> 30 days), and only ORP groups | ≤30 days vs > 30 days | Fewer rehospitalizations and shorter total stay in short-PP and only ORP groups ($p < 0.001$) | NR | N/A |
| Huang et al., 2021 [43] | 5228 | Taiwan National Health Insurance Research Database study | LAI vs OAP in patients with newly diagnosed schizophrenia | ≤3 years | Significantly lower all-cause mortality (aHR 0.66), natural-cause mortality (aHR 0.63), and suicide attempts (IRR 0.72) in LAI group compared with OAP group | NR | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Kheloussi et al., 2022 [175] | 238 | Real-world clinical outcomes study | Short-acting OAPs and LAI antipsychotics in patients with psychiatric conditions | < 5 years | Significant decrease in overall hospitalizations PMPY ($p < 0.001$) and psychiatric hospitalizations PMPY ($p < 0.001$) | NR | N/A |
| Sancho-Echeverria et al., 2024 [80] | 667 | Cohort study (naturalistic study) | LAI vs OAPs in patients with early psychosis | < 5 years | Significantly higher mean (SD) hospitalization in LAI vs oral arm (2.5 [2.61] vs 1.19 [1.69]), but reduction of hospitalization with LAI use compared with OAP use before and after LAI use | NR | N/A |
| Taipale et al., 2018 [106] | 29,823 | Retrospective nationwide cohort analysis | Patients aged 16–64 years with schizophrenia | NR | LAI use showed the lowest cumulative mortality (7.5%) | NR | N/A |
| Tiihonen et al., 2017 [176] | 29,823 | Retrospective nationwide database study | LAI vs OAPs in patients with schizophrenia | NR | LAIs showed the lowest risk of rehospitalization and treatment failure<br>LAIs reduced rehospitalization risk by 20–30% compared with oral antipsychotics | NR | N/A |
| Choon et al., 2019 [100] | 413 | Retrospective study | Patients with schizophrenia or schizoaffective disorder | ≤ 3 years | Significant decrease in IP and ER visits for early, NP group<br>NP patients on early therapy saved an average of HKD40,878 (USD5241) per year; late initiation yielded lower savings (HKD6224; USD798) | NR | N/A |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Kane et al., 2023 [93] | 306 | Retrospective claims-based study | Early vs late initiation and proactive vs reactive LAI | 1 year | Healthcare resource utilization and costs were significantly lower in proactive early LAI group | NR | N/A |
| Marcus et al., 2015 [88] | 3768 | Retrospective cohort study | OAP vs LAIs post-hospitalization in patients with schizophrenia | 6 months | Lower non-adherence ($p < 0.001$), fewer 60-day medication gaps ($p < 0.001$), and reduced rehospitalization ($p = 0.01$) in LAIs group | NR | N/A |
| Munday et al., 2019 [94] | 4366 | Claims-based cohort study | Early vs late initiation of LAI treatment in patients with new schizophrenia episodes | ≤1 year vs >1 year from diagnosis to treatment initiation | LAI initiators had lower all-cause hospitalization rates ($p = 0.002$) and psychiatric hospitalization rates ($p < 0.001$) | NR | Reduced psychiatric healthcare costs ($p < 0.001$) |
| Titus-Lay et. al., 2018 [87] | 47 | Retrospective cohort study | LAI vs OAP in patients with early psychosis | 2 years | Adherence was significantly greater in the LAI group | NR | N/A |
| Garcia-Portilla et al., 2022 [98] | 101 | Observational, multicenter, prospective study | PP3M in patients with recent schizophrenia diagnosis | 1 year | Improvement in PSP score from baseline to month 12 ($p < 0.001$)<br>Reduction in CGI-Sch severity score ($p < 0.001$)<br>Improved social and clinical outcomes | NR | N/A |
| Viala et al., 2012 [76] | 25 | Prospective study/ RLAI | Patients with recent-onset schizophrenia vs baseline | 6.8 mean years | CGI-S severity decreased from 5.44 at baseline to 3.14 with treatment<br>Relapse rate was 16%<br>Hospitalization rate was 16% with treatment | NR | N/A |
| *Non-nationwide cohort studies* | | | | | | | |

**Table 2** (continued)

| Author, year [ref.] | No. of patients | Study design/drug | Patient population | Duration of illness | Efficacy outcomes | Safety outcomes | Benefits in early vs long-term illness |
|---|---|---|---|---|---|---|---|
| Basu et al., 2023 [99] | 1132 | DREaM study, in a real-world population | PP in patients with recentonset schizophrenia or schizophreniform disorder | ≤2 years | Significantly low psychiatric hospitalizations and healthcare costs with early use of PP | NR | N/A |
| Olivares et al., 2009 [95] | 2028 | Electronic Schizophrenia Treatment Adherence Registry (e-STAR) RLAI study | Patients with schizophrenia | 2 years | Greater CGI-S and GAF improvements in recent vs long-term diagnosis<br>Reduced hospitalizations, stays, and LOS recent vs long-term | Common AEs: psychiatric, GI, musculoskeletal, reproductive disorders | N/A |
| *Mirror image study* | | | | | | | |
| Peitl et al., 2022 [97] | 112 | Mirror image study/ PP1M | PP1M treatment in patients with recent-onset schizophrenia (ROS) | 1.6 mean years | Significant reductions in CGI-S and CRDPSS scores ($p < 0.001$)<br>Decreased number and length of hospitalizations ($p = 0.002$ and $p < 0.001$, respectively) | NR | N/A |

*AE* adverse event, *aHR* adjusted hazard ratio, *AOM* aripiprazole once-monthly (long-acting aripiprazole monohydrate), *CGI* Clinical Global Impression, *CGI-S* Clinical Global Impressions Scale–Severity, *CGI-Sch* Clinical Global Impression–Schizophrenia scale, *CRDPSS* Clinician-Rated Dimensions of Psychosis Symptom Severity, *DB* double-blind, *ER* emergency room, *GAF* Global Assessment of Functioning, *GI* gastrointestinal, *IP* inpatient, *IRR* incidence rate ratio, *LAI* long-acting injectable, *LOS* length of stay, *N/A* not applicable, *NP* non-polypharmacy, *NR* not reported, *OAP* oral antipsychotic, *OL* open-label, *ORP* oral formulations of risperidone and paliperidone, *PANSS* Positive and Negative Syndrome Scale, *PMPY* per member per year, *PNS* peripheral nervous system, *PP* paliperidone palmitate, *PP1M or PP3M* paliperidone palmitate 1- or 3-monthly, *PSP* Personal and Social Performance scale, *RCT* randomized clinical trial, *RLAI* risperidone long-acting injectable, *RR* risk ratio, *SD* standard deviation

the Swedish health care register data [85] and a more recent observational study in the US Medicare population [86].

The improved adherence to LAIs compared with OAPs has also been noted in early phase schizophrenia. In a randomized head-to-head study of oral versus RLAI, adherence to the LAI formulation was significantly better on a 5-point scale (1 = perfect adherence; 5 = complete non-adherence; mean [SD]: 1.1 [0.5] vs 1.9 [0.8]; $p < 0.001$) and was associated with greater prevention of disease exacerbations and/or relapse [81]. In a retrospective analysis of patients with a new diagnosis of a psychotic disorder, the use of LAI was associated with a trend of better medication persistence and adherence [87] compared with the use of OAPs [81, 87]. The average proportion of days on medication was higher for patients treated with LAI (76%) than in the OAP group (32%) and was comparable to those on combination treatment with LAI + OAPs [87]. In a large retrospective analysis of patients receiving LAIs or OAPs within 6 months of hospitalization for schizophrenia, LAIs were associated with better adherence, fewer medication gaps, and a lower risk of rehospitalization than those receiving OAPs [88]. On the other hand, EULAST, a randomized study of oral versus LAI aripiprazole and oral versus LAI paliperidone found no differences in the overall rates of treatment discontinuation for any reason across OAP and LAI arms [89]. However, methodological issues have been raised, including that patients were directly randomized to OAP or LAI use, without prior stabilization on the oral antipsychotic, thereby increasing discontinuations and not mirroring the clinical initiation practices of LAIs that usually follow an oral lead in the stabilization period [90]. In EULAST, LAI performance to prevent treatment discontinuation was found to be better than that of OAP, but the study lacked the statistical power needed to demonstrate significance [91]. Notably, when discontinuation data were separated by reason (due to safety, efficacy, or other reasons), discontinuation of the two OAPs for 'other reasons' was significantly higher than discontinuation of the two LAIs [89].

Real-world evidence (RWE) studies have demonstrated benefits of early initiation of LAIs in terms of the reduction in the risk of hospitalizations and deaths. A recent study of patients with newly diagnosed schizophrenia from the Taiwan National Health Insurance Research Database indicated that the use of LAIs within the first 2 years after diagnosis was associated with decreased all-cause mortality and suicide risk over the 16-year follow-up period [43]. In an observational study of patient records from the Clinical Database Analysis and Reporting System of the Hong Kong Hospital Authority, treatment with LAIs was associated with a reduction in hospitalizations and suicide attempts compared with OAPs; risk reduction was substantially more pronounced in the subgroup of patients who initiated an LAI within 2 years of their schizophrenia diagnosis [92].

Analyses of a claims database reported that early versus late use of LAIs in patients with newly diagnosed schizophrenia indicated reduced healthcare costs (mainly associated with ER and other outpatient visits) [93] and reduced all-cause hospitalization rates and rates of psychiatric hospitalizations [94]. An observational study, e-STAR, reported greater improvement in CGI-S scores among recently diagnosed patients (≤2 years) receiving LAI, who also had lower hospitalization rates and shorter hospital stays, compared with those with >2 years of schizophrenia [95]. Further, nationwide RWE studies reporting the benefits of early initiation of LAIs were conducted in Finland [31], South Korea [96], Croatia [97], Spain [98], the US [40, 99], and Hong Kong [100].

## 4 Long-Term Benefits of Early LAI Adoption

While the benefits of LAIs when initiated within the first 5 years of schizophrenia onset are well documented, very few studies have reported on their long-term effectiveness in patients with early phase schizophrenia. In a population-based cohort study, patients who switched to an LAI within 3 years after initiating OAPs experienced significantly lower mortality (all-cause and natural cause but not unnatural cause [suicide, homicide, and accidents]) and lower risks of rehospitalization, psychiatric hospitalization, and psychiatric ER visits compared with those who continued OAPs [101].

A simulation model predicted 10-year benefits of starting an LAI within the first 3 years of disease after failing second OAP treatment versus oral-only treatment in a hypothetical patient cohort. The model estimated that oral-only treatment would reduce the likelihood of competitive employment and independent living and increase hospital admissions compared with early initiation of LAI [102]. In a 10-year mirror image observational study, patients who completed 5 years of PP1M demonstrated an overall reduction in hospitalization rates and the mean length of hospitalization compared with the 5-year period before the initiation of PP1M; furthermore, more than half of the patients were not hospitalized at all during the 5-year PP1M treatment period [103].

In a subgroup analysis of long-term outcomes in Chinese patients within 5 years of schizophrenia onset, treatment with PP1M resulted in clinically meaningful changes from the baseline in PANSS total scores and medication satisfaction questionnaire scores at the end of the treatment period (day 548) [104].

LAIs may also provide long-term neuroprotection by maintaining steady therapeutic drug levels, reducing relapses, and thereby limiting the cumulative neurobiological damage of repeated psychotic episodes [105]. Clinical and real-world data show LAIs are associated with lower rates of relapse and rehospitalization compared with oral

antipsychotics, which could translate into better preservation of cognitive function, improved long-term functional outcomes, and attenuation of illness-related structural brain changes [105, 106].

## 5 Safety Profile of LAIs

The safety profiles of LAI and OAP formulations of the same active agent are generally similar in all patients, regardless of the duration of illness [107]. Adverse events (AEs) common to both LAIs and OAPs include increased body weight, insomnia, anxiety, and headache [65, 66, 108, 109]. The incidence of insomnia, headache, anxiety, administration-site conditions, and injection-site pain reported with LAIs was similar in patients with early or long-term schizophrenia [71]. AEs of special interest, including extrapyramidal symptoms, tardive dyskinesia, and prolactin increases were found to be less frequent with LAI treatment in a systematic review that compared the efficacy and safety of second-generation LAIs and their OAP counterparts versus placebo [109]. The lower likelihood of prolactin increases and hyperprolactinemia with LAI treatment than with the same oral treatment had been shown before and is likely due to reduced antipsychotic peak levels and subsequent marked postsynaptic dopamine blockade with LAIs versus OAPs [107]. A post-hoc analysis of a double-blind relapse prevention study with open-label extension revealed that most AEs were reported at a similar frequency between patients with recent-onset and long-term schizophrenia; however, prolactin-related events were higher in recently diagnosed patients [110].

Considering earlier adoption of LAIs might imply use in younger patient populations in some cases, it should be noted that early use of antipsychotics in younger patients such as children and adolescents have been also associated with adverse effects such as weight gain, development of diabetes, increased prolactin levels, and an increased QT interval [111–115].

## 6 Economic Benefit of LAIs

A systematic review and meta-analysis of 25 real-world studies compared healthcare utilization, costs, and adherence between patients with schizophrenia treated with LAI versus oral medications in the United States. Although the initiation of LAI was associated with an increase in pharmaceutical expenses per patient per year, there was no significant difference in the overall healthcare expenditure between patients treated with LAIs and OAPs considering the lower medical costs compensated for the higher pharmacy expenses [116]. A retrospective observational cohort study that evaluated costs following 6 months of treatment of schizophrenia with an LAI also reported significant reduction in inpatient costs and an increase in outpatient pharmacy costs, resulting in no changes in total healthcare costs over 6 months [117]. A budget impact analysis of increased use of LAIs for the treatment of schizophrenia in Japan from a healthcare payor perspective over 5 years revealed minimal impact on budget. Increased drug acquisition and administration visit costs were compensated for by the decreased hospitalization costs [118]. A similar analysis in Egyptian representative healthcare settings also revealed potential cost savings with LAIs compared with the standard of care in people with chronic schizophrenia [119]. Another systematic review of 10 studies suggested lower total costs, medical costs, and all-cause inpatient costs in patients with schizophrenia treated with LAIs when compared with OAPs [120].

According to another retrospective claims data study, treatment with LAIs in commercially insured young adults with schizophrenia was associated with significant cost savings to commercial payers [121]. Mirror image analysis of claims data from German patients with schizophrenia treated with LAIs suggested an increase in medication costs post-switching to LAI, while there was a decrease in hospitalization costs contributing to an overall reduction in total costs [122]. A study that compared cost effectiveness of LAIs versus OAPs in patients with schizophrenia from a rural community in South India indicated LAIs to be cheaper than OAPs [123]. Another retrospective observational single-arm study that utilized administrative health data from Alberta, Canada also reported lower health resource utilization and costs with second-generation LAIs [124]. Similarly, use of LAIs for treatment of patients with schizophrenia from Korea was associated with increased annual outpatient costs but significantly reduced inpatient admissions contributing to an overall reduction in total annual healthcare costs [125].

## 7 Current Treatment Guidelines and Recommendations for Schizophrenia

A summary of clinical guidelines and pharmacological treatment recommendations for early-onset schizophrenia is provided in Table 3. In brief, most guidelines recognize the benefits of using LAIs in improving adherence and reducing relapse rates. Only some guidelines explicitly recommend the early use of LAIs in treating schizophrenia, particularly in the early phase or after a first episode. LAIs are specifically recommended for patients who prefer an injectable antipsychotic or those with poor adherence to other medication or with a history of poor response to OAPs, in order to uncover potential non-adherence-related "pseudo" treatment resistance [126]. A recent systematic review of clinical practice

**Table 3** Clinical guidelines and pharmacological treatment recommendations for early phase schizophrenia

| Country | Organization | Year | Recommendations for first-episode or early phase schizophrenia |
|---|---|---|---|
| Australia and New Zealand | The Royal Australian and New Zealand College of Psychiatrists [177] | 2016 | Consider LAIs if it is the patient's preference or if adherence has been poor or uncertain or if a poor response to oral medication<br>Early use of LAIs should be considered and offered, especially in patients with a high risk of non-adherence to oral agents |
| Canada | The Canadian Psychiatric Association (CPA) and the Schizophrenia Society of Canada (SSC) | 2017 | Support early consideration of LAIs for individuals experiencing first-episode schizophrenia, particularly for those with adherence challenges |
| | Canadian Consortium for Early Intervention in Psychosis [178] | 2013 | Recommend LAI antipsychotic therapy during all phases of psychotic disorders, including early phase |
| EU | European Psychiatric Association guidelines [179] | 2022 | While the guidelines recognize the superior performance of LAIs vs OAPs in terms of risk of relapse and hospitalizations, they do not provide specific recommendations on when LAIs should be used |
| France | French Association for Biological Psychiatry and Neuropsychopharmacology (AFPBN) [180] | 2013 | LAIs should be offered as first-line treatment for patients that require long-term treatment |
| Germany | The German Association for Psychiatry, Psychotherapy, and Psychosomatics [181] | 2019 | Use LAI antipsychotics as a maintenance treatment option in those individuals with early phase schizophrenia who have adherence issues |
| India | Expert group on Clinical Practice Guidelines for Management of Schizophrenia [182] | 2017 | Choose a first-generation or second-generation antipsychotic medication (oral/parenteral/depot or long-acting preparations) based on past treatment response, history of side effects, cost, comorbidity, patient/family preference, preferred route of administration, availability, current metabolic profile, history of compliance, treatment resistance |
| Kenya | National Clinical Guidelines for Management of Common Mental Disorders [183] | 2024 | Low dose of LAIs (haloperidol, fluphenazine, zuclopenthixol) to be initiated; dose titration based on clinical response and tolerability<br>Any one medication to be provided—avoid switching unless poor tolerance to side effects and poor response to treatment after at least 6 weeks |
| LMICs | WHO mhGAP [184] | 2023 | LAI antipsychotic medicines—namely fluphenazine, haloperidol, paliperidone, risperidone, and zuclopenthixol—should be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side effects, and personal preference |
| Singapore | Ministry of Health of Singapore, Clinical Practice Guidelines Workgroup on Schizophrenia [185] | 2011 | Long-acting depot antipsychotics may be indicated in patients in whom treatment adherence is an issue or when a patient expresses a preference for such treatment<br>Long-acting depot antipsychotics should not be used for acute episodes because it may take 3–6 months for medications to reach a steady state |
| South Africa | Standard Treatment Guidelines and Essential Medicines List for South Africa [186] | 2019 | Treatment to be initiated with haloperidol<br>If good response/tolerability to haloperidol, or patient preference, can depot zuclopenthixol |
| Turkey | Schizophrenia Treatment Guideline of Psychiatric Association of Turkey [187] | 2010 | Recommends prioritizing SGAs rather than FGAs in patients with first-episode psychosis<br>Intramuscular injections in case patients do not comply with oral treatments at the start of treatment or when psychomotor agitation to be calmed<br>Haloperidol is the most used agent. Intramuscular zuclopenthixol can be used every 24–72 hours |

**Table 3** (continued)

| Country | Organization | Year | Recommendations for first-episode or early phase schizophrenia |
|---|---|---|---|
| UK | National Institute for Health and Care Excellence [188] | 2014 | Offer OAPs in addition to psychological interventions (family intervention, individual CBT)<br>Offer LAIs to patients with schizophrenia who prefer such treatment after an acute episode or avoiding non-adherence to antipsychotic treatment |
| USA | American Psychiatric Association [189] | 2020 | Offer LAIs to patients with schizophrenia who prefer such treatment or those who have a history of poor adherence<br>First-episode patients to be treated within a coordinated specialty care program integrating several evidence-based interventions to form comprehensive treatment |
| | Schizophrenia Patient Outcomes Research Team (PORT) [97, 190] | 2009 | Offer LAIs to enhance adherence |
| | National Council for Mental Wellbeing [191] | 2019 | Offer LAIs as a first-line treatment option to patients with psychotic disorders and encourage increased use of LAIs |
| World | World Federation of Societies of Biological Psychiatry (WFSBP) Clinical Guidelines for Schizophrenia [192] | 2017 | Use LAIs in those patients with schizophrenia who prefer an injectable formulation or with high risk of non-adherence |

*CBT* cognitive behavioral therapy, *FGAs* first-generation antipsychotics, *LAI* long-acting injectable, *LMICs* low- and middle-income countries, *OAPs* oral antipsychotics, *SGAs* second-generation antipsychotics, *WHO mhGAP* World Health Organization's Mental Health Gap Action Programme

guidelines for schizophrenia management reported that nearly all guidelines (94.7%), except the one from Italy, discussed the use of LAIs, primarily recommending them for non-adherence (77.8%), maintenance care (72.2%), and patient preference (66.7%). However, only 27.8% contained a specific recommendation of using LAIs for first-episode schizophrenia [1]. Another systematic review and comparison of recommendations from pharmacological guidelines for the first episode of schizophrenia also indicated an increasing interest in the use of LAI antipsychotics early in the treatment of schizophrenia to address non-adherence, reduce relapse, and improve psychosocial functioning [127]. Nevertheless, expert consensus [128] and Delphi panels [129] have included patients with first-episode and early phase schizophrenia among their recommended patient groups for LAI discussion and initiation. Further, a consensus guideline focused on the pharmacological treatment of schizophrenia, developed in collaboration by International Guidelines for Algorithmic Treatment (INTEGRATE) authors from all UN regions, recommends LAIs as an early intervention, also considering patient preferences [130].

## 8 Barriers to Early Adoption of LAIs

Despite substantial evidence from clinical and real-world studies, significant barriers to LAI adoption persist (Fig. 1), particularly in the early phase, which is associated with increased disease complexity (Fig. 2) [50, 131–134]. Physician surveys in Japan [132], Canada [131, 135], and European countries [136, 137] showed that barriers to LAI use are often rooted in the negative perception of LAIs by patients and physicians and the associated stigma [47, 136]. Consequently, LAIs are often viewed as a last-resort option for patients with a history of non-adherence. Physicians may also delay prescribing LAIs for first-episode patients, believing they may not relapse and that LAIs are meant for longer-term treatment [138]. While guidelines mention LAIs as a viable treatment option, there is a lack of strong support for their use early in the course of the disease where they could have the greatest impact. This situation contributes to the continued underutilization of LAIs, despite their potential to significantly reduce early relapses caused by non-adherence and treatment discontinuation, at least in clinically meaningful subgroups of studies [46]. Additional practical challenges also hinder uptake, including AEs [139], lack of regular availability of certain LAI formulations [47, 108, 140, 141], and logistical difficulties such as the need to travel for injections or inadequate storage facilities for LAI medications [141]. Additionally, dosing flexibility with LAIs is inevitably reduced, and dose adjustments occur more slowly than with OAPs [55, 142].

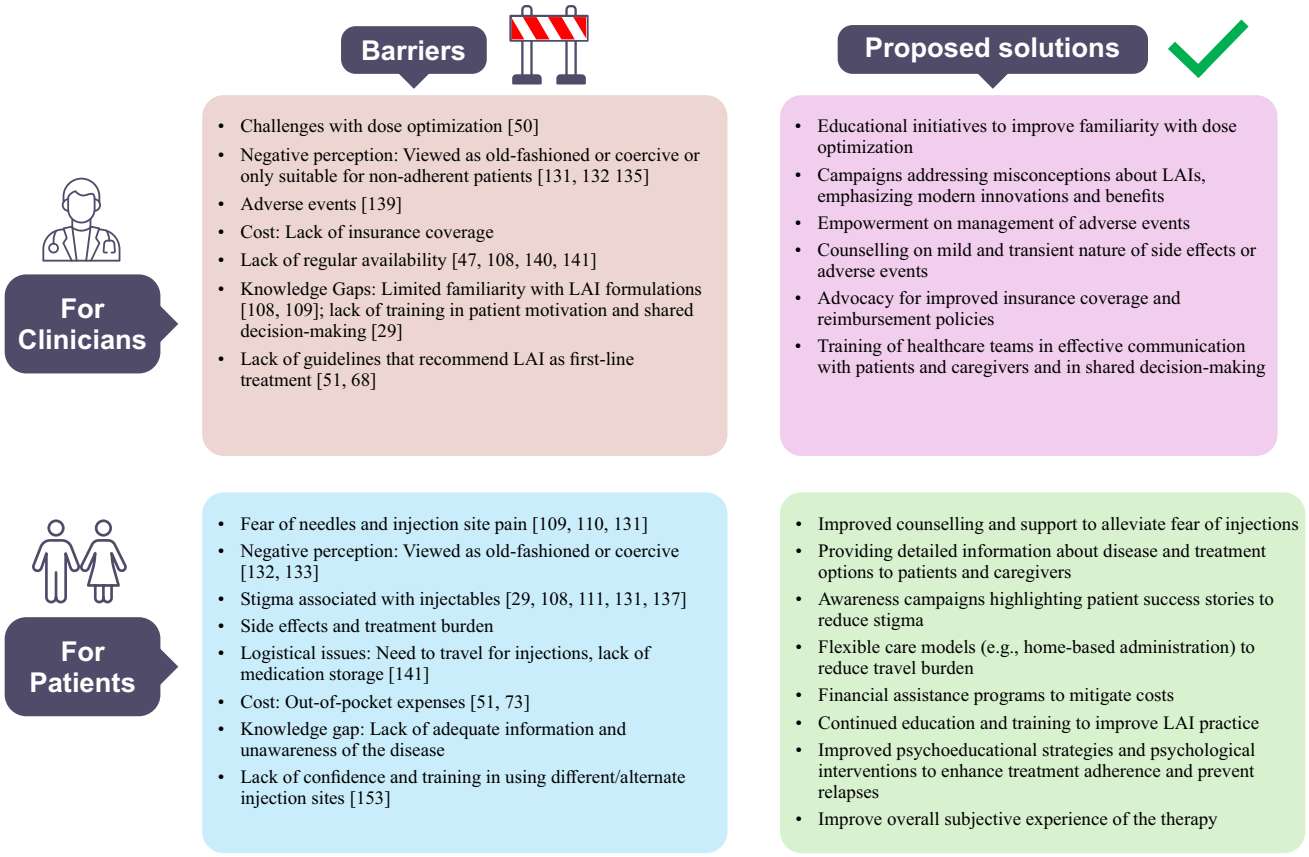


**Fig. 1** Barriers to long-acting injectable (LAI) antipsychotic adoption and proposed solutions

Nevertheless, in a pre-implementation evaluation of contextual determinants of early intervention programs, participants including prescribers, non-prescribers, administrators, clients, and caregivers were supportive of LAIs despite barriers like transportation or insurance coverage [143].

First-generation LAIs did important work historically and remain inexpensive, but are associated with the well-known drawbacks of first-generation antipsychotics, including extrapyramidal symptoms, tardive dyskinesia, and prolactin effects, and are frequently delivered as older oil-based depot formulations with limited dose options, injection-site issues, and less flexible pharmacokinetics [144–146]. These safety- and formulation-related limitations reduce the acceptability for some patients and clinicians and act as a real barrier to broader LAI use despite the cost advantage.

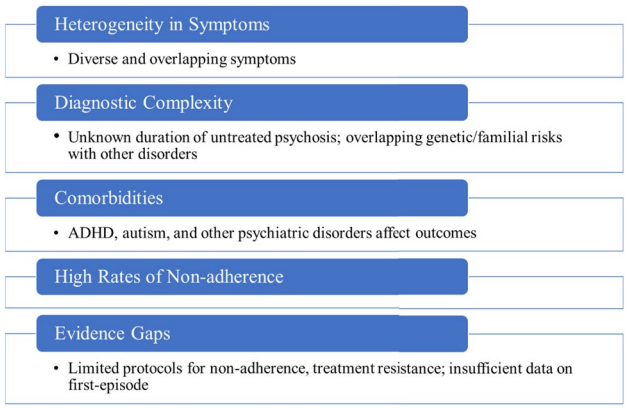


**Fig. 2** Challenges in treating early phase schizophrenia. *ADHD* attention-deficit/hyperactivity disorder

## 9 Increasing Physician Confidence/Reduced Barriers

Attitudes of health professionals towards LAIs have been identified as playing a crucial role in whether patients take antipsychotics [53, 147, 148]. Clinicians are more likely to prescribe LAIs in the following cases: greater number of monthly switches within OAPs and greater monthly schizophrenia-related hospitalization and ER visits [141, 149]; the patient is at a high risk of relapse [141]; to improve treatment adherence [150, 151]. In addition, health care professional–administered LAIs serve as a practical adherence signal with missed injections as an immediate, actionable flag for nonadherence [42, 145].

Given the improved clinical outcomes, treatment adherence, and overall QoL associated with the early use of LAIs in schizophrenia, clinicians and patients may want to consider LAI treatment during the earliest phase of schizophrenia. Figure 1 outlines proposed solutions to address clinician- and patient-specific barriers that hinder the early adoption of LAIs. Training the entire treatment team on the value of LAIs, shared decision making, and strategies to communicate effectively with patients and their caregivers has demonstrated great success in facilitating LAI prescribing in patients with first-episode and early phase schizophrenia [152]. Among physicians, limited confidence in training in using different or alternate injection sites may act as a barrier to early adoption [153]. In addition, counselling patients on the mild transient nature of AEs can improve acceptance of LAIs. Improved psychoeducational strategies and psychological interventions can help improve the subjective experience of therapy [153].

A recent US-based survey, the DECIDE study, examined attitudes and preferences among mental healthcare providers with regards to the use of LAIs in patients with schizophrenia [154]. Overall and across subgroups, side effects were ranked as the most important consideration while clinician preference was ranked as the least important consideration for LAI selection. Clinicians from the high-LAI use subgroup considered product characteristics [141], including multiple injection sites, small/on-par needle size, and less frequent dosing for LAI selection that can contribute to simplified administration [155]. On the other hand, among the clinicians from the LAI-mindset subgroups, the LAI-hesitant subgroup of clinicians prioritized patient preference for LAI selection and deprioritized product attributes [139].

## 10 Limitations

The results of this review need to be interpreted within several limitations. First, this was a guided pragmatic review and not a systematic literature review. Second, no quantitative meta-analytic calculation of results was conducted. Instead, results are summarized and presented descriptively. Third, given the heterogeneity of study designs, population and treatment characteristics, treatment settings, comparator groups, outcomes, and sample sizes of the included studies, which also drive the choice of LAIs, we restricted the level of analysis and presentation to LAIs as a group without comparing individual LAIs, as this could have led to biased comparisons. Fourth, data informing specific outcomes differed regarding quantity and quality of the available results. Finally, large RCTs enrolled patients from high-income/middle-income countries, indicating that future studies should also collect data in less resourced treatment and healthcare settings (low-income countries) in order to assess similarities and potential differences of the outcomes when LAIs are used across geographic and economic regions.

## 11 Conclusions

Adoption of LAIs during early phase schizophrenia is associated with improved patient outcomes, reduced relapse risk, and lower hospitalizations (number and length of stay), in addition to comparable safety profiles with OAPs. However, LAIs remain underutilized during this period and are still reserved for use in the later stages of illness following multiple relapses or after demonstrated medication non-adherence. Current treatment guidelines and recommendations mention LAIs as an alternative to OAPs, particularly if the treatment goal is to improve adherence. The efficacy and safety data of LAIs in early phase (vs long-term) schizophrenia along with lower healthcare resource use, especially when used proactively before non-adherence and relapse have occurred [40], may support recommending LAIs as a first-line treatment after stabilization of the first episode with OAPs and in patients with early phase schizophrenia.

Guidelines may need to be updated to further encourage and emphasize the importance of early adoption of LAIs, possibly as early as first-line treatment during the early phase of schizophrenia to improve outcomes and QoL of patients. Finally, mental health care providers would be better equipped to offer LAIs if they had access to educational initiatives that focus on the early benefits of LAIs while addressing clinician- and patient-specific barriers to early adoption [156]. These programs could also include training health care providers in shared decision making and effective communication with patients and caregivers.

**Acknowledgements** We acknowledge Himabindu Gutha PhD, CMPP (SIRO Medical Writing Pvt. Ltd., India) for medical writing assistance (funded by Johnson & Johnson) and Ellen Baum, PhD (Johnson & Johnson) for additional editorial support.

**Funding** This study was supported by Johnson & Johnson.

## Declarations

**Conflict of Interest** Dr Correll reports that he has been a consultant and/or advisor to or has received honoraria from AbbVie, Alkermes, Allergan, Angelini, Aristo, Autobahn, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Draig, Eli Lilly, Eumentis Therapeutics, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Johnson & Johnson, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neuraxpharm, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Response Pharmaceutical, Reviva, Rovi, Saladax, Sanofi, Seqirus, Servier, Sumitomo Pharma America,

Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris and Xenon Pharmaceuticals. He provided expert testimony for Johnson & Johnson, Lundbeck and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, IntraCellular Therapies, Relmada, Reviva, Rovi. He has received grant support from Boehringer-Ingelheim, Johnson & Johnson and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, and Terran. Dr Sanchez reports that he has been a consultant and/or advisor to or has received honoraria from Angelini, Casen-Recordati, Johnson & Johnson, Lundbeck, Osakidetza, Otsuka, Rovi, and University of Deusto. All the other authors are employees of Johnson & Johnson and may hold company stocks or stock options in Johnson & Johnson.

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Availability of Data and Material** Not applicable.

**Code Availability** Not applicable.

**Author Contributions** Conception and design: all authors. Acquisition of data: all authors. Data analysis and interpretation: all authors. Manuscript writing and editing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data, and approved submission to the journal.



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