Pediatric Drugs (2023) 25:135–149
https://doi.org/10.1007/s40272-023-00558-x

SYSTEMATIC REVIEW

What Role for Long-Acting Injectable Antipsychotics in Managing Schizophrenia Spectrum Disorders in Children and Adolescents? A Systematic Review

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Accepted: 8 January 2023 / Published online: 20 January 2023

Abstract

Background Long-acting injectable antipsychotics (LAIAs) are an efficacious and well-tolerated treatment in adults with schizophrenia spectrum disorders (SSD). However, there is less evidence for their use in children and adolescents.

Objectives The aim of this systematic review was to summarize findings regarding the effectiveness and side effects of LAIA in children and adolescents with SSD.

Methods Four databases (Web of Science, PubMed, MEDES, and Dialnet) were systematically searched for articles published between inception and 12 March, 2022, with the following inclusion criteria: (1) original articles or case reports; (2) providing data on efficacy/effectiveness or safety/tolerability of LAIA treatment in children and adolescents diagnosed with SSD (schizophrenia, schizoaffective disorder, schizophreniform disorder, non-affective psychotic disorder); (3) mean age of samples $\leq$ 18 years; and (4) written in English or Spanish. Exclusion criteria were review articles, clinical guides, expert consensus as well as posters or oral communication in conferences. The risk of bias was assessed using the ROBIS tool.

Results From 847 articles found, 13 met the inclusion criteria. These included seven single case reports or case series, four retrospective chart reviews, a 24-week open-label trial, and one observational prospective study, covering a total of 119 adolescents (aged 12–17 years) with SSD. Almost all the articles described data on second-generation LAIA (53 patients on risperidone [once every other week], 33 on paliperidone palmitate [once monthly], 10 on aripiprazole [once monthly], and two on olanzapine pamoate [once monthly]). Twenty-one patients were reported to be only on first-generation LAIAs. Non-adherence was the main reason for starting an LAIA. In all of the studies, the use of LAIAs was associated with improvement in the patients' symptoms.

Conclusions There are few studies assessing the use of LAIAs in adolescents with SSD. Overall, these treatments have suggested good effectiveness and acceptable safety and tolerability. However, we found no studies examining their use in children aged < 12 years. The problems and benefits linked to this type of antipsychotic formulation in the child and adolescent population require further study, ideally with prospective, controlled designs.

1 Introduction

Schizophrenia spectrum disorders (SSD) have a high impact on patients, their families and society [1–3]. When SSD begin in patients who are under the age of 18 years, they are known as early-onset [4] and their outcome has been reported to be worse than when onset of the disease takes place during adulthood [5]. Early-onset SSD has been linked to severe cognitive deficits [6], social impairment [7], relapses and hospitalizations [1] as well as deterioration in functioning [7] compared with adult-onset SSD.

In the treatment of early-onset SSD, antipsychotics (AP) are key [8]. Different systematic reviews and

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Key Points

There is a lack of randomized clinical trials and a scarce number of studies regarding long-acting injectable antipsychotics (LAIAs) in adolescents with schizophrenia spectrum disorders (SSD). The studies reviewed showed heterogeneous quality and no data was found concerning children < 12 years.

The studies have reported good effectiveness and acceptable tolerability of LAIAs when used to treat adolescents with SSD.

Non-adherence and lack of insight were the main reasons for starting LAIAs in these patients.

Based on the reviewed studies, the authors have made a series of recommendations for use of LAIAs in children and adolescents with SSD.

meta-analyses have confirmed the efficacy of some AP versus placebo in this population [9–11]. However, non-adherence to medication is prevalent among adult patients with schizophrenia, reaching rates of over 55% [12]. Risk factors associated with poor adherence include poor insight, negative attitude or subjective response toward medication, a history of previous non-adherence, substance abuse, shorter illness duration, lack of social support, and poorer therapeutic alliance [12, 13]. Adolescent age was described to increase the risk of non-adherence in one systematic review including bipolar disorder and SSD patients [14], but not in another which focused only on patients with SSD [13]. The use of long-acting injectable antipsychotics (LAIAs) is one of the most widely recommended strategies for improving adherence to treatment [15].

LAIAs have been approved as a treatment strategy for schizophrenia in adults, most often used according to patients' preferences or in order to avoid non-adherence [16, 17]. In adults, the benefits of LAIAs over oral AP have been observed in early psychosis, including first-episode patients [18]. Moreover, there is growing evidence that LAIAs are associated with higher quality of life, improved functional outcomes [19, 20] and reduced risk of relapse and hospitalizations compared with oral AP in adults with schizophrenia [21–24] and early psychosis [18].

The use of LAIAs in children and adolescents with schizophrenia has been recommended by both the American Academy of Child and Adolescent Psychiatry and the Spanish CIBERSAM guide in cases where there is a personal history of poor adherence to treatment and chronic psychotic symptoms [4, 25]. Nevertheless, LAIAs are not currently approved by regulatory agencies such as the Food and Drug Administration in the United States or the European Medicines Agency in the European Union for use in minors despite the fact that SSD often begin with an onset during childhood or adolescence [26].

Some case reports and mainly retrospective studies have reported on the use of LAIAs in children and adolescents with any psychiatric disorder such as anorexia nervosa, autism or conduct disorder [27–31]. In a literature review published in 2016 [32], of 36 cases involving LAIAs in this population, only seven (19.4%) were minors with schizophrenia, and the rest were diagnosed with bipolar disorder. The authors stated that LAIAs may improve clinical outcomes and adherence in children and adolescents, and found that the side effects were similar to those of oral formulations.

The objective of this systematic review was to summarize findings regarding the effectiveness and side effects of the use of LAIAs in children and adolescents with SSD.

2 Methods

2.1 Literature Search

To perform this systematic review, we followed the 2021 Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines [33]. The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42022304103.

A systematic literature search was carried out in Web of Science, PubMed, MEDES, and Dialnet databases from inception to March 12, 2022, using the following terms: (antipsychotic OR neuroleptic OR palmitate OR decanoate OR maintena OR pamoate) AND (long acting OR depot OR injectable OR injection) AND (schizophrenia OR psychotic disorder OR psychosis) AND (child OR adolescent OR minor OR youth OR young OR early onset).

2.2 Inclusion Criteria

The criteria for selecting the articles were the following: (1) original articles or case reports; (2) providing data on efficacy/effectiveness or safety/tolerability of LAIA treatment in children and adolescents diagnosed with SSD (schizophrenia, schizoaffective disorder, schizophreniform disorder, non-affective psychotic disorder); (3) mean age of samples ≤ 18 years; and (4) written in English or Spanish.

2.3 Exclusion Criteria

Review articles, clinical guides, expert consensus as well as posters or oral communication in conferences were excluded.

Grey literature as well as clinical trial registers were not searched.

2.4 Data Systematization

The electronic search was conducted in the following steps: first, two researchers (IB and AF) performed the electronic search. Second, both researchers reviewed one by one all of the references from the selected articles using a web platform (www.rayyan.ai) to help with classification. When discrepancies were found, articles were discussed until an agreement was reached. Third, IB and AF extracted the following data from the studies: bibliographic references, place where the study was conducted or the case visited, year of publication, type of study, description of the sample (number, sex, age, diagnoses), type of patient (outpatient/inpatient), type of LAIA, other pharmacological treatment, results of psychiatric assessment (questionnaires, interviews), and outcomes of the study (efficacy/effectiveness, safety/tolerability).

2.5 Quality, Risk of Bias, and Evidence Assessments

The quality of assessment of each study (excluding case reports or case series) was evaluated with the Newcastle-Ottawa scale for case-control or cohort studies [34] with study-specific criteria [35] (Supplemental Table 1, see electronic supplementary material [ESM]).

The risk of bias was assessed for the same studies using the ROBIS tool [36] as is shown in Supplemental Table 2 (see ESM). The evidence of the recommendations was evaluated through the Grading of Recommendations Assessment, Development and Evaluations (GRADE) [37].

3 Results

Out of 847 articles retrieved, 13 articles met eligibility criteria and were reviewed in depth. The flowchart of the reviewed articles and the reasons for exclusion are shown in Fig. 1.

The included articles comprised one open-label trial [38], one observational prospective study [39], four retrospective chart review studies [28, 40–42], four single case reports [43–46], and three case series (of 2, 3, and 6 patients with SSD) [47–49]. One study included a patient age range of 13–18 years, but the mean age was < 18 years (15.9 ± 3.3) [38]. None of the studies included LAIA use in patients < 12 years. All patients were on second-generation LAIAs, except for one study [40] (which was based on prescription of first-generation LAIAs), one case in a case series [49], and a case series [48] in which patients were on a combination of LAIAs (second-generation and first-generation). In total, 119 patients with SSD were on LAIAs in the included articles. The distribution of patients on the different LAIAs is shown in Fig. 2.

3.1 Original Studies

Table 1 describes the main characteristics and results of the six original studies reviewed. The quality of the assessment scale scores for the studies were in the range of 4–9, with a mean and standard deviation of 5.8 ± 1.9. This shows that most of the studies were of low quality.

Of the six studies, three (50%) describe the use of LAI risperidone [38, 39, 42]. A 24-week open-label trial in which 31 adolescents with SSD who were clinically stable with oral AP (olanzapine or risperidone) were switched to LAI risperidone reported that the vast majority finished the study (one patient discontinued due to side effects and another for insufficient response) [38]. The use of LAI risperidone (mostly with 25 mg/2 weeks) was associated with improvement in all of the Positive and Negative Syndrome

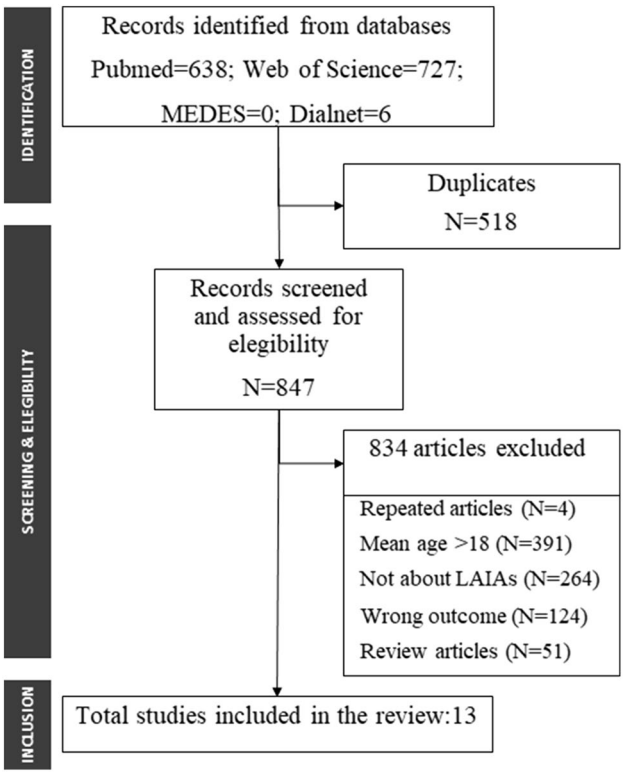

Fig. 1 Flow diagram of the article screening process

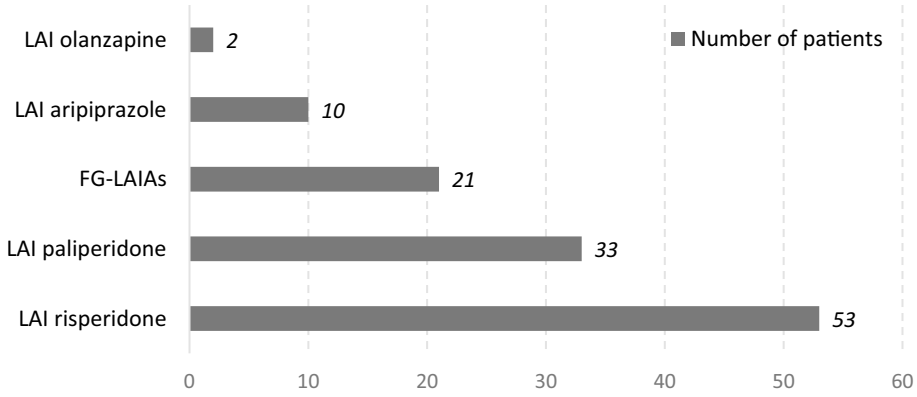

Fig. 2 Distribution of long-acting injectable antipsychotic agents in the 119 patients included in the studies reviewed

Scale (PANSS) domain scores and was well tolerated. In terms of extrapyramidal symptoms (EPS), one patient (3.2%) with akathisia and two (6.4%) with dystonia were reported, but the most frequent side effects were depression, anxiety, headache, and insomnia.

Ceylan et al. [39] conducted an observational prospective study (with a minimum 2-month follow-up) with hospitalized adolescents who were non-adherent to oral AP. Out of 42 included patients, only two were diagnosed with schizophrenia (one with an intellectual disability comorbidity). All patients were treated with LAI risperidone 25 mg/2 weeks, and a 50% clinical improvement (measured with the Clinical Global Impression [CGI] scale) was found in patients with SSD. Side effects were reported by all patients, and consisted of menstrual problems (39.2% of girls), swollen and tender breasts (28.6%, both sexes), weight gain (23.8%), and somnolence (23.8%). Dystonia was reported in 16.7% and fewer described other EPS such as slowing of movements (14.3%) and restlessness (7.1%). The authors stated that due to the small number of patients with SSD included in the study, it was difficult to draw conclusions about the effectiveness of LAI risperidone in this population.

The other retrospective study focusing on the use of LAI risperidone compared patients with early-onset and adult-onset SSD, finding that the continuation rate of the LAI treatment in early-onset patients was lower than in adult-onset patients, although this difference was not significant [42]. The dose of LAI risperidone was also lower in early-onset patients, although there was no difference in psychopathology severity between the groups. Thus, the authors were unable to find support for the benefits of using LAI risperidone for the treatment of patients with early-onset schizophrenia.

Using LAI paliperidone, Petrić et al. [41] conducted a retrospective study of adolescents with a first-episode of schizophrenia. This study compared patients using LAI paliperidone with others receiving oral risperidone. A total of 27.8% of the patients on LAIA and 22.2% of those on oral AP used cannabis. Although symptoms were associated with improvement with both treatments, total PANSS scores were significantly more reduced in patients on LAI paliperidone after 12 months of treatment, with fewer relapses and hospitalizations. Patients on LAI also showed greater improvement in personal and social functioning, with higher satisfaction with the therapy than patients on oral risperidone.

One study, using a retrospective design, compared adolescent inpatients on LAI risperidone, LAI paliperidone, and LAI aripiprazole, with 73%, 86%, and 58% of each group, respectively, having SSD [28]. Seven (23.3%) of the patients included were in foster care. Comorbid cannabis use was 40%, 86%, and 50% with each type of LAIA, respectively. The sample of patients with cannabis use were older than non-users. All patients were on LAIA due to a history of demonstrated non-adherence or concerns regarding future adherence to oral treatment. Clinical improvement was observed in patients on each LAIA from admission to discharge. Length of hospitalization was shorter in the LAI aripiprazole group compared with LAI risperidone and LAI paliperidone (13 ± 4 vs 20 ± 11 and 22 ± 9 days; $p = 0.08$), but an effect of differences in diagnoses and severity at admission could not be ruled out. Patients on LAI risperidone had significantly more side effects (45%) than patients on LAI aripiprazole (0%), with hyperprolactinemia being the most frequently reported one.

Finally, one retrospective study was conducted in India with adolescent inpatients with severe mental disorders (including 26 patients with SSD) who received first-generation LAI [40] for different reasons: 65.8% for failed or only partial response to oral AP; 34.2% for severe, aggressive behavior which did not respond to other drugs, and 31.6% for non-adherence with oral AP. They justified the use of first-generation LAIAs due to the cost of the medication. Most of the patients were on LAI fluphenazine (60.5%), but LAI flupentixol (34.2%) and LAI zuclopenthixol (18.4%) were also prescribed. As all of the patients were also on other treatments while on LAIAs, the authors acknowledged that it was difficult to disentangle the role of LAIA in clinical

Table 1 Original studies ($N = 6$) of children and adolescents on long-acting antipsychotics, listed alphabetically by first author

Study Country Setting	Year	Type of study	N, sex and diagnosis	Type of patient	Range and mean age (years) and SD	LAIA (mean dose) and other pharmacological treatment	Psychiatric assessment	Results
Ceylan et al. Turkey Ankara Yildirim Beyazit University Faculty of Medicine [39]	2017	Observational prospective study (with at least 2 months of follow-up)	2 SCZ 32 CD 14 BD (33.3% male)	Recruited as inpatients and the follow-up as outpatients	12–17 15.6 ± 1.5	LAI risperidone 25 mg 33% of patients were on mood stabilizers, 21.4% on stimulants and 16.7% on SSRIs.	K-SADS CGI LUNSERS WISC-R/WAIS-R Body weight	81% of all patients improved CGI at 2 months, but only in 1 (50%) of the patients with SCZ. The most frequent side effects in all patients were weight gain, difficulty staying awake during the day and muscle stiffness. In girls, the most frequent were menstrual problems and swollen or tender breasts. No specific side effects on patients with SCZ were reported.
Fortea et al. Spain Hospital Clínic de Barcelona [28]	2018	Retrospective (chart review from 2013 to June 2016)	11 patients on LAI risperidone ($N = 8$, 73% with any PD); 7 patients on LAI paliperidone ($N = 6$, 86% PD); 12 patients on LAI aripiprazole ($N = 7$, 58% PD) (46.7% male)	Inpatients	12.5–17.9 16.3 ± 1.3	Range of doses for LAI risperidone: 25–50 mg; for LAI paliperidone: 50–150 mg and for LAI aripiprazole: 300–400 mg. 19% of patients were on oral AP; 18% on medication for ADHD; 26.7% on mood stabilizers; and 17% on antidepressants.	CGAS	Clinical improvement measured with CGAS was observed with each LAI AP, with no differences between them. 45% of patients on LAI risperidone reported side effects as well as 19% of those on LAI paliperidone. None of the patients on LAI aripiprazole reported any. The most prevalent side effect was hyperprolactinemia.

Table 1 (continued)

Study Country Setting	Year	Type of study	N, sex and diagnosis	Type of patient	Range and mean age (years) and SD	LAIA (mean dose) and other pharmacological treatment	Psychiatric assessment	Results
Jacob et al. India National Institute of Mental Health and Neurosciences, Bangalore [40]	2021	Retrospective (chart review from 2010 to 2019)	20 SCZ 12 BD 4 PSI 2 SCZ-AFF (55.3% male)	Inpatients	Range for children and adolescents not specified, but the youngest was 10 years 14.7 ± 1.8	60.5% of patients were on fluphenazine decanoate (mean dose: 31 mg). 34.2% of patients were on flupentixol decanoate (mean dose: 25.3 mg). 18.4% of patients were on zuclopenthixol decanoate (mean dose: 200 mg). 23.7% of patients were on ECT, 13.2% on clozapine, 92.1% on oral AP, 39.5% on mood stabilizers, and 10.5% on SSRIs.	CGAS CGI	91.2% of patients improved in their follow-up, but it was difficult to ascertain whether this was associated with LAI or not. 47.6% of patients had side effects, with extrapyramidal ones being the most prevalent.

Table 1 (continued)

Study Country Setting	Year	Type of study	N, sex and diagnosis	Type of patient	Range and mean age (years) and SD	LAIA (mean dose) and other pharmacological treatment	Psychiatric assessment	Results
Petrić et al. Croatia Clinical Hospital Centre Rijeka [41]	2019	Retrospective, non-interventional, to assess LAI paliperidone vs oral risperidone during the first 12 months of treatment (chart review from 2014 to 2017)	18 first-episode SCZ on LAI paliperidone (55.6% male) 18 first-episode SCZ on oral risperidone (50% male)	Outpatients	No range specified <18 years Patients on LAI: 16.6 ± 0.6 Patients on oral risperidone: 16.2 ± 0.9	At the beginning, 72.2% received 150 mg of LAI-paliperidone and the rest 100 mg. At 12-month follow-up, the median dose was 75 mg. At the beginning, the initial dose of oral risperidone for all patients was 1 mg/day. At 12 months, the median dose was 3 mg/day. 77% of patients were on anxiolytics at the beginning of treatment and 19.4% of patients began taking anxiolytics during the follow-up.	CGI PANSS PSP TSQM Body weight Prolactin levels	At 12-month assessment, patients on LAI paliperidone had significantly greater reduction in total PANSS, CGI, personal and social functioning measured with PSP; they also had a lower number of hospitalizations and higher scores on convenience, global satisfaction, and overall result in TSQM compared with patients on oral risperidone. 22.2% of patients on oral risperidone had at least one side effect, while only 12.5% of those taking LAI paliperidone were similarly affected. Weight gain was significantly higher in patients on oral risperidone.

Table 1 (continued)

Study Country Setting	Year	Type of study	N, sex and diagnosis	Type of patient	Range and mean age (years) and SD	LAIA (mean dose) and other pharmacological treatment	Psychiatric assessment	Results
Ruan et al. China First Affiliated Hospital, College of Medicine, Zhejiang University, HangzhouSultan Qboos University [38]	2010	24-week open-label trial	31 SCZ (18 on oral olanzapine and 13 on oral risperidone; 41% male)	Outpatients	13–18 15.9 ± 3.3	Oral AP was switched to LAI risperidone (25 mg in 54.8% of patients, 37.5 mg in 29% and 50 mg in 16.1%) During the trial, 12.9% were on antidepressants, 6.5% on anti-parkinsonian agents, and 3.2% on sedative/hypnotics.	PANSS CGI ESRS Body weight Standard clinical laboratory tests Electrocardiography Patient assessment for pain after injection Investigator assessment for pain, redness and swelling after injection	80.6% of patients completed the study. PANSS decreased at least 20% in 67.7% of patients. The most frequent side effects were depression (12.9%), anxiety, and headache (9.7% each) as well as insomnia (6.4%).
Suzuki et al. Japan Fukui Kinen Hospital [42]	2017	Retrospective cohort study (chart review from July 2009 to November 2015)	12 early-onset SCZ (50% male) 20 adult-onset SCZ (45% male)	Inpatients and outpatients	Early-onset SCZ 16.8 ± 1.7 Adult-onset SCZ 23.2 ± 1.5	LAI risperidone (37.5 ± 12.5 vs 45.6 ± 8.4) Patients could take other psychopharmacology treatment but this was not reported in detail	Not reported	One-year continuation rate was low, with no significant differences between early and adult onset. Reasons for discontinuation were patient's decision, insufficient efficacy, and side effects.

AP antipsychotics, *BD* bipolar disorder, *CD* conduct disorder, *CGAS* Children's Global Assessment Scale, *CGI* Clinical Global Impression, *ECT* electroconvulsive therapy, *ESRS* Extrapyramidal Symptom Rating Scale, *K-SADS-PL* Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children Present and Lifetime, *LAIA* long-acting injectable antipsychotic, *LUNSERS* Liverpool University Neuroleptic Side Effect Rating Scale, *PANSS* Positive And Negative Syndrome Scale, *PD* psychotic disorder, *PSI* psychotic disorder, not otherwise specified, *PSP* Personal and Social Performance Scale, *SCZ* schizophrenia, *SCZ-AFF* schizoaffective disorder, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitors, *TSQM* Treatment Satisfaction Questionnaire for Medication, *WAIS-R* Wechsler Adult Intelligence Scale–Revised, *WISC-R* Wechsler Intelligence Scale for Children–Revised

improvement. Side effects were reported in almost 48% of patients, with EPS being the most prevalent one. The authors underscored the value of these LAI formulations in treating severe mental disorders in low and middle-income countries where the cost of treatment plays a significant role that can affect both treatment decisions and adherence.

3.2 Case Reports and Case Series

Pope and Zaraa [49] described nine adolescent inpatients receiving LAIA treatments, six of whom had SSD (two with a cannabis use comorbidity, one with PTSD and one with ADHD). Four (66.7%) of the SSD adolescents were on LAI paliperidone, one (16.7%) on LAI aripiprazole, and one (16.7%) on fluphenazine decanoate. A history of non-adherence was the reason for starting LAIAs in 83.3% of the patients that had this information documented. In all patients, CGI scores improved from admission to discharge. As for side effects, one patient on LAI paliperidone had EPS and needed benztropine and another patient on the same LAIA was on benztropine due to a previous history of dystonia with haloperidol. No other side effects were described with the other LAIAs.

A combination of LAIAs was reported in three cases of adolescents with severe psychosis and aggression admitted in an adolescent forensic psychiatric unit [48]. All were males aged 16–17 years; one was already on LAIA, and the other two refused oral AP during their current hospitalization. One of them had a comorbid substance use disorder (glue sniffing and cannabis smoking). The AP used were the following: one patient was on LAI olanzapine 405 mg fortnightly together with LAI zuclopenthixol decanoate 600 mg fortnightly, another was on LAI paliperidone 150 mg monthly and LAI zuclopenthixol decanoate 400 mg fortnightly, and the last one on LAI paliperidone 150 mg monthly and LAI zuclopenthixol 600 mg fortnightly. Both LAI were administered the same day for all patients. These combinations decreased the Brief Psychiatric Rating Scales (BPRS) scores of each patient by almost 40 points. One patient showed mild parkinsonism and another showed polydipsia and polyuria without diabetes mellitus or diabetes insipidus. The other patient did not report any side effects.

Two cases of LAI paliperidone in adolescent inpatients were described by Fàbrega et al. [47]. One was diagnosed with undifferentiated schizophrenia and mild intellectual disability, and the other with psychotic disorder not otherwise specified (NOS) and conduct disorder. Both patients started treatment with oral paliperidone and then switched to LAI paliperidone 50 mg every 28 days (due to concerns about adherence and lack of insight), which was associated with an improvement of symptoms and a decrease in PANSS scores. LAIAs were begun due to the concerns regarding treatment adherence or a history of previous non-adherence. One patient did not report any side effects, and the other experienced an oculogyric crisis, after which oral biperiden 4 mg/day was added.

Looking at the single case reports, two of them were based on the description of side effects [44, 45]. Mirza et al. [45] described a male adolescent inpatient with schizophrenia who developed a severe acute-onset delirium after the second dose of LAI paliperidone (first dose: 150 mg and second: 100 mg). The treatment was associated with an improvement of his symptoms, but 10 days after the second dose the patient needed an admission due to fluctuating levels of consciousness and additional symptoms of delirium. No other cause for delirium was found. The case reported by Solfanelli et al. [44] focused on a skin rash, which was developed by an adolescent with schizophreniform disorder and comorbidity with juvenile idiopathic arthritis. After tolerating oral olanzapine, LAI olanzapine was initiated at a dosage of 300 mg every 3 weeks. Eight days after the first dose, a skin eruption was observed, with no other signs or symptoms, except for an increase in some liver function test results. After the administration of intramuscular betamethasone and oral chlorphenamine, the rash gradually disappeared and liver function test results returned to normal within a week.

In terms of effectiveness, the case of a 15-year-old incarcerated male diagnosed with schizophrenia and conduct disorder was described by Aggarwal and Lindegaard [43]. The subject was on oral aripiprazole 20 mg/day, with good response and tolerability, but after releasing from the center the patient stopped taking the medication and was reincarcerated after 3 months for other illegal behavior. After reintroducing oral aripiprazole, the LAI formulation was administered to improve adherence. After the new release, the patient continued being adherent and at 12-month follow-up the patient showed clinical stability, good tolerability, and no reincarceration.

Lastly, the case of an adolescent with schizophrenia starting LAI aripiprazole with two injections was reported [46]. A 16-year-old inpatient male experienced clinical improvement of the psychotic symptoms with aripiprazole 30 mg/day and clozapine 100 mg/day. Due to poor insight and comments about not taking medication after being discharged, LAI aripiprazole 800 mg (2 injections of 400 mg the same day) was administered as a fast way to reach the dose of 400 mg/monthly without oral supplementation. No side effects were observed. At 1-month follow-up, global functioning and insight had improved, as well as positive psychotic symptoms.

4 Discussion

This is, to our knowledge, the first systematic review conducted regarding the use of LAIA exclusively in children and adolescents with SSD. Despite the fact that this is a very important issue in clinical practice, we found few studies and case reports on this topic, as well as a scarce number of high quality studies. The largest number of reported cases were for LAI risperidone followed by LAI paliperidone. Clinical improvement was observed in almost all of the studies and case reports in the short and medium term (up to 12 months' follow-up), with adequate tolerability. The existence and profile of side effects depended on the type of LAI prescribed. History of previous non-adherence, concern about poor treatment adherence, as well as lack of insight, were the main reasons for initiating LAIAs in all of the studies.

4.1 Efficacy/Effectiveness

LAIAs were linked to an improvement of clinical symptoms in most of the studies included, both with first-generation [40, 49] and second-generation drugs [28, 39–46] or with a combination of both [48]. Better functional outcome, and a smaller number of hospitalizations than with adolescents on oral AP were also reported after 12-month follow-up [37]. Only the study assessing the 1-year continuation rate described a higher number of discontinuations of LAI risperidone in early-onset versus adult-onset SSD, as an indirect way to measure effectiveness [42].

The use of LAIAs in adults with SSD has been consistently associated with improvement in clinical psychopathology, functionality and fewer relapses and hospitalizations compared with oral medication [18–24, 50]. It has to be taken into account that avoiding relapses and hospitalizations is important to elude clinical deterioration [51].

Mortality rates are also considered to be an important outcome for determining the long-term effectiveness of a medication [52]. LAIAs have been associated with less mortality than oral AP. In a nationwide register study conducted in Sweden including patients with schizophrenia aged from 16 to 64 years, second-generation LAIAs were associated with 33% less mortality than equivalent oral AP [53]. In a similar study (same age range and diagnosis) conducted with registry data in Taiwan, patients on LAIAs had lower risks of all-cause mortality, including natural-case mortality, and fewer suicide attempts compared with patients who were on the equivalent oral AP [54].

4.2 Safety/Tolerability

LAIAs have been reported to be a treatment option with a good tolerability profile in children and adolescents [32]. Reviewed studies on second-generation LAIAs described rates of side effects ranging from 0 (LAI aripiprazole) to 45% (LAI risperidone) [28, 38, 39, 41, 42], but only one study compared different LAIAs [28]. This study which used first-generation LAIAs showed side effect rates of 47.6% [40]. Weight gain, sedation, EPS, hyperprolactinemia and depression were the most prevalent side effects in the reviewed second-generation LAIA studies [28, 38, 39, 41], while EPS were the most frequent in first-generation LAIAs [40]. None of the studies reviewed compared patients with first-generation LAIA to those on second-generation LAIAs. When comparing first- to second-generation LAIAs in adults with SSD, no differences were observed in tardive dyskinesia and parkinsonism; however, second-generation LAIAs were associated with less prescription of antiparkinsonian agents [50]. On the other hand, long-term weight gain and body mass index were greater with second-generation than with first-generation LAIAs [50].

4.3 First Episode of Psychosis

First episode of psychosis is an earlier stage of a possible severe mental disease [55], after which most patients go on to develop either SSD or bipolar disorder, although 58% of cases develop no further episodes over 5.5 mean years of follow-up, according to a systematic review and meta-analysis of studies with adult patients [56]. In this stage, the prevention of relapses is decisive to help avoid deterioration and improve clinical and functional outcomes [55]. In a recent study in adults, patients in the early stage of their disease who had indicators of poor prognosis such as homelessness, legal problems or substance use disorder seemed to benefit from the early prescription of LAIAs, with a reduction and delay in relapses and rehospitalizations compared to patients with good prognosis on oral AP [51]. Moreover, in a systematic review and meta-analysis of studies with adults, patients with first-episode psychosis on LAIAs had less risk of relapse, with a relative risk (RR) of 0.58 (95% confidence interval [CI] 0.34–1.01), and with no differences between first-generation and second-generation LAIAs [18]. However, rates of hospitalization were similar between patients on LAIAs and oral AP, with an OR of 0.57 (95% CI 0.30–1.08) [18]. In adolescents, Petrić et al. observed fewer hospitalizations and higher personal and social functioning in patients with first-episode psychosis on LAI paliperidone compared with those on oral risperidone [41].

4.4 Resistant Schizophrenia Spectrum Disorders (SSD)

The definition of resistant SSD includes an inadequate response to at least two AP trials of sufficient dose and duration and having ruled out non-adherence to treatment [57].

The American Academy of Child and Adolescent Psychiatry specifies the importance of reviewing (apart from the child's clinical status) the treatment history, in order to ensure that the case is effectively considered to be resistant SSD [4]. The Indian guidelines also set out that if a patient fails to respond to particular antipsychotic medication, adherence to medication needs to be evaluated before changing the medication [58]. Clozapine is the treatment recommended for resistant SSD, both in adults [59] and in minors [4, 25]. When patients are resistant to clozapine, the use of LAIAs has been proposed as an augmentation strategy for children and adolescents with resistant SSD [60]. In adults, a mirror-image retrospective study showed that adding a first- or second-generation LAIA to clozapine treatment reduced the number of relapses, as well as the number and length of hospitalizations. Furthermore, no changes in analytical parameters, such as neutrophil counts or prolactin levels, were observed with the combination of treatments [61]. In a similar design also with adult patients, Bioque et al. [62] reported that adding LAI paliperidone to clozapine improved clinical symptoms, functionality, number and length of hospitalizations, number of visits to emergency services, and severity of side effects.

In the studies reviewed, no response or only partial response to multiple oral medication trials, which is generally considered resistant SSD, was one of the reasons for prescribing LAIAs [40].

4.5 Comorbid Substance Use

The comorbidity of a substance use disorder with SSD is high, reaching 41.7% in a systematic review [63]. It has been consistently reported that patients with substance use disorders have an earlier age at onset of SSD [63, 64]. In our reviewed studies, some of the studies reported substance use [28, 41, 48, 49] with rates ranging between 27.8% and 86% of the samples. Only one study had a diagnosis of substance dependence 3 months before initiating the study as an exclusion criterion [38].

Substance use comorbidity leads to poorer outcomes for SSD patients and the best prognosis is achieved when combined AP treatment and psychosocial intervention are implemented [65]. In a 3-year study comparing patients with a first-episode of psychosis and comorbid substance use who started LAIAs as a first-line medication versus those on oral AP, patients on LAIAs had a significantly lower relapse rate and higher relapse-free survival time, as well as trends for reduced rehospitalization rates and hospitalization-free survival time [66].

4.6 Reasons for Starting Long-Acting Injectable Antipsychotics (LAIAs)

In all but one [38] of the studies reviewed, a previous history of non-adherence, concerns about adherence to medication or lack of insight were the main reasons for starting LAIAs [28, 39–49]. Aggressive behavior as well as severe resistant psychopathology were also reasons for starting LAIAs [40, 48].

Initially, LAI formulations of AP were developed to improve adherence [67], which is crucial in order to guarantee effective treatment of patients [68]. Pediatric patients, particularly adolescents, have a higher risk of non-adherence to psychotropic medication [68]. This is a problem of particular clinical importance among adolescents, since a median of 33% (ranging from 6 to 62%) of non-adherence in this age group was reported in a systematic review [69]. A study in adolescents, including 53.7% with SSD, reported 9% of poor and 25.4% of moderate treatment adherence, showing a highly significant association between a patient's attitude towards the drug and adherence [70]. Other situations such as substance abuse, violence or legal conflicts are also risk factors for lack of adherence [12, 13, 71, 72]. Adolescents placed in foster care could be another indicator for considering the use of LAIA, due to a higher risk of non-adherence, and increased incidence of behavioral difficulties and substance use comorbidities [73]. In fact, youth in foster care comprised 23.3% of the patients included in one of the studies reviewed [28] and 16% of the children and adolescents with at least one prescription of LAIA in the study conducted in the Indiana Medicaid system [74].

An additional factor to be taken into account regarding the prescription of LAIAs is lack of insight. This is a frequent clinical characteristic of patients with early-onset SSD [75, 76], and usually refers to subjects' lack of awareness regarding their mental disorder and the need for treatment [77]. Insight is associated with adherence to treatment [77]. Worse insight has been associated with more severe symptoms, increased risk of discontinuing treatment, and poorer outcomes [74, 78, 79]. Significantly, it has also been suggested that younger patients may have less insight than adults with SSD [75, 76, 80].

4.7 The Potential Role of LAIAs in the Treatment of Children and Adolescents with SSD

Several recommendations can be put forward based on existing knowledge concerning the use of LAIAs in children and adolescents with SSD (aged >12 years). The strength of the evidence of the recommendations are rated below:

1. LAIAs could be a helpful option for young people who are non-adherent with oral antipsychotic medication (Low).
2. Patients with poor insight could be monitored for non-adherence, and LAIAs should be kept in mind as a possible treatment option (Low).
3. If, with oral medication, patients experience side effects while showing an improvement in terms of symptoms and functioning, a switch to the same medication in an LAI formulation may improve tolerability. If the existing oral AP does not have an LAI formulation, a switch to a different oral AP with an available LAI formulation may also be beneficial (Very low).
4. Comorbid substance use could be taken into account when an AP is initiated, keeping in mind that LAIAs can be a helpful option in the presence of this comorbidity (Low).
5. Patients with a recent or first episode of psychosis may also benefit from the use of LAIAs. This treatment option need not only be considered an option for patients with a long duration of their disease (Low).
6. In resistant or severe SSD, a switch to LAI formulation may help improve the effectiveness of AP treatment in some patients (either in monotherapy or combined with oral AP) (Very low).

Apart from the potential role of LAIAs that has been pointed out, it is important to remember that patients and caregivers' preferences should be taken into account to help promote shared decision making [81]. Patients and their caregivers should be consulted about LAIAs when a therapeutic plan is being developed.

4.8 Limitations and Strengths

The main limitations of this systematic review are the lack of randomized controlled trials (RCTs), the heterogeneity of the designs of the studies (open-label trial, observational prospective, observational retrospective, case series, case reports), and the small number of articles included. Moreover, some of the original studies were of low quality and had an unclear risk of bias according to the rating scales we used, and none of the studies reviewed was a randomized control trial. Furthermore, the studies examined a limited number of young patients with SSD on LAIAs, none were < 12 years of age, and there was a narrow range of different LAIAs and doses used (i.e., only two patients were on LAI olanzapine), but this could reflect typical clinical practice. Also, one study included stable patients who switched from oral AP to LAI risperidone [38] while in the other studies patients on LAIA, or switched to LAIA, were actively psychotic [28, 39–49]. Lastly, the means by which adverse events were evaluated as part of these reports may have led to the under-reporting of these events. Apart from body weight measure and prolactin levels in some of the studies and three original studies which used a scale [38, 39, 41], adverse events were self-reported. Among the strengths of our study is the fact that the review looks at the use of LAIA exclusively in children and adolescents with SSD. Also, the review followed the internationally accepted PRISMA criteria and was registered in the PROSPERO database.

5 Conclusion

To our knowledge, this is the first systematic review to address exclusively the role of LAIAs in the treatment of children and adolescents with SSD. Overall, although no RCT studies were found and the quality of most of the studies was low, they documented good effectiveness and acceptable tolerability in treating these patients, with a different pattern of side effects according to the type of LAIA. No studies included patients younger than 12 years. The use of this type of AP formulation in this population requires further study, ideally with other prospective and controlled designs, in order to more fully understand the potential role that LAIAs could play in the treatment of children and adolescents with SSD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40272-023-00558-x.

Acknowledgments The authors would like to thank Mr A. D. Pierce for his linguistic assistance and review of the text.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature.

Declarations

Funding No funding was received to conduct this study or for the publication of this article.

Conflict of interest IB has received honoraria and travel support from Angelini, Otsuka-Lundbeck, and Janssen and grants from the Spanish Ministry of Health, Instituto de Salud Carlos III supported by ERDF Funds from the European Commission (PI18/0242/PI21/0391). AF has received travel and educational support from Janssen Cilag and Otsuka-Lundbeck. DI has received continuing medical education support from Rubió and Angelini. GS has received speaker fees from Angelini, and has received funding from the Alicia Koplowitz Foundation, the Brain and Behaviour Research Foundation and the Instituto de Salud Carlos III supported by ERDF Funds from the European Commission (PI1800976, PI21/00330), the Catalonia Government (2017SGR881, PERIS SLT006/17/00346), and Fundació Clínic Recerca Biomèdica (Ajut a la Recerca Pons Bartran).

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.

Authors' contributions IB had the idea for the article, IB and AF performed the literature search and extracted the information. All the authors contributed to the interpretation of the data for the work. The first draft of the manuscript was written by IB and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript, and agreed to be accountable for the work.

References

1. Immonen J, Jääskeläinen E, Korpela H, Miettunen J. Age at onset and the outcomes of schizophrenia: a systematic review and meta-analysis. Early Interv Psychiatry. 2017;11:453–60. https://doi.org/10.1111/eip.12412.
2. Jin H, Mosweu I. The societal cost of schizophrenia: a systematic review. Pharmacoeconomics. 2017;35:25–42. https://doi.org/10.1007/s40273-016-0444-6.
3. Latorre V, Messeni Petruzzelli A, Uva AE, Ranaudo C, Semisa D. Unveiling the actual cost of schizophrenia: an activity-based costing (ABC) approach. Int J Health Plann Manage. 2021. https://doi.org/10.1002/hpm.3405.
4. McClellan J, Stock S. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013;52:976–90. https://doi.org/10.1016/j.jaac.2013.02.008.
5. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry. 1994;151:1409–16. https://doi.org/10.1176/ajp.151.10.1409.
6. Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2009;195:286–93. https://doi.org/10.1192/bjp.bp.108.060723.
7. Harvey PD, Isner EC. Cognition, social cognition, and functional capacity in early-onset schizophrenia. Child Adolesc Psychiatr Clin N Am. 2020;29:171–82. https://doi.org/10.1016/j.chc.2019.08.008.
8. Mattai AK, Hill JL, Lenroot RK. Treatment of early-onset schizophrenia. Curr Opin Psychiatry. 2010;23:304–10. https://doi.org/10.1097/YCO.0b013e32833b027e.
9. Harvey RC, James AC, Shields GE. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. CNS Drugs. 2016;30:27–39. https://doi.org/10.1007/s40263-015-0308-1.
10. Pagsberg AK, Tarp S, Glintborg D, Stenstrøm AD, Fink-Jensen A, Correll CU, et al. Acute antipsychotic treatment in children and adolescents with schizophrenia spectrum disorders: a systematic review and network meta-analysis. J Am Acad Child Adolesc Psychiatry. 2017;56:191–202. https://doi.org/10.1016/j.jaac.2016.12.013.
11. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol. 2018;28:659–74. https://doi.org/10.1016/j.euroneuro.2018.03.008.
12. Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A. Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. Syst Rev. 2020;9(1):17. https://doi.org/10.1186/s13643-020-1274-3.
13. Sendt KV, Tracy DK, Bhattacharyya S. A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. Psychiatry Res. 2015;225:14–30. https://doi.org/10.1016/j.psychres.2014.11.002.
14. García S, Martínez-Cengotitabengoa M, López-Zurbano S, Zorrilla I, López P, Vieta E, et al. Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: a systematic review. J Clin Psychopharmacol. 2016;36:355–71. https://doi.org/10.1097/JCP.0000000000000523.
15. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas. 2014;5:43–62. https://doi.org/10.2147/PROM.S42735.
16. Citrome L. New second-generation long-acting injectable antipsychotics for the treatment of schizophrenia. Expert Rev Neurother. 2013;13:767–83.
17. NICE, 2014. Psychosis and Schizophrenia in Adults. The National Institute for Health and Clinical Excellence Guideline on Treatment and Management [WWW Document]. URL http://www.nice.org.uk/guidance/cg178/
18. Lian L, Kim DD, Procyshyn RM, Fredrikson DH, Cázares D, Honer WG, et al. Efficacy of long-acting injectable versus oral antipsychotic drugs in early psychosis: a systematic review and meta-analysis. Early Interv Psychiatry. 2021. https://doi.org/10.1111/eip.13202.
19. Montemagni C, Frieri T, Rocca P. Second-generation long-acting injectable antipsychotics in schizophrenia: patient functioning and quality of life. Neuropsychiatr Dis Treat. 2016;12:917–29. https://doi.org/10.2147/NDT.S88632.
20. Olagunju AT, Clark SR, Baune BT. Long-acting atypical antipsychotics in schizophrenia: a systematic review and meta-analyses of effects on functional outcome. Aust N Z J Psychiatry. 2019;53:509–27. https://doi.org/10.1177/0004867419837358.
21. Brissos S, Veguilla MR, Taylor D, Balanzá-Martinez V. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Ther Adv Psychopharmacol. 2014;4:198–219. https://doi.org/10.1177/2045125314540297.
22. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence. 2013;7:1171–80. https://doi.org/10.2147/PPA.S53795.
23. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. J Clin Psychiatry. 2013;74:957–65.

24. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia-A critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res. 2011;2011(127):83–92. https://doi.org/10.1016/j.schres.2010.11.020.
25. Grupo de trabajo del CIBERSAM para la elaboración de una guía clínica y terapéutica para primeros episodios psicóticos. Guía clínica y terapéutica para primeros episodios psicóticos en la infancia y la adolescencia. Informe de consenso de recomendaciones. Centro de Investigación Biomédica en Red-CIBER 2015. https://www.ciberisciii.es/ficheros/SAM/Gu%C3%ADaPEPinfanciaAdolescencia_v5.0.pdf
26. Driver DI, Gogtay N, Rapoport JL. Childhood onset schizophrenia and early onset schizophrenia spectrum disorders. Child Adolesc Psychiatr Clin N Am. 2013;22:539–55. https://doi.org/10.1016/j.chc.2013.04.001.Childhood.
27. Carlone C, Pompili E, Silvestrini C, Nicolò G. Aripiprazole once-monthly as treatment for psychosis in Turner syndrome: literature review and case report. Riv Psichiatr. 2016;51:129–34. https://doi.org/10.1708/2342.25114.
28. Fortea A, Ilzarbe D, Espinosa L, Solerdelcoll M, de Castro C, Oriolo G, et al. Long-acting injectable atypical antipsychotic use in adolescents: an observational study. J Child Adolesc Psychopharmacol. 2018;28:252–7. https://doi.org/10.1089/cap.2017.0096.
29. Kowalski JL, Wink LK, Blankenship K, Habenicht CD, Erickson CA, Stigler KA, et al. Paliperidone palmitate in a child with autistic disorder. J Child Adolesc Psychopharmacol. 2011;21:491–3. https://doi.org/10.1089/cap.2011.0035.
30. Perinpanayagam MS, Haig RA. Use of depot tranquillisers in disturbed adolescent girls. Br Med J. 1977;1:835–6.
31. Umehara H, Iga J, Ohmori T. Successful treatment of anorexia nervosa in a 10-year-old boy with risperidone long-acting injection. Clin Psychopharmacol Neurosci. 2014;12:65–6.
32. Lytle S, McVoy M, Sajatovic M. Long-acting injectable antipsychotics in children and adolescents. J Child Adolesc Psychopharmacol. 2017;27:2–9. https://doi.org/10.1089/cap.2016.0055.
33. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178–89. https://doi.org/10.1016/j.jclinepi.2021.03.001.
34. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2013; https ://www.ohri.ca/programs/clini cal_epide miolo gy/oxfor d.asp. Accessed 22 April 2022.
35. Pozzi M, Ferrentino RI, Scrinzi G, Scavone C, Capuano A, Radice S, et al. Weight and body mass index increase in children and adolescents exposed to antipsychotic drugs in non-interventional settings: a meta-analysis and meta-regression. Eur Child Adol Psychiatry. 2020. https://doi.org/10.1007/s00787-020-01582-9.
36. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225–34. https://doi.org/10.1016/j.jclinepi.2015.06.005.
37. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013;66:151–7. https://doi.org/10.1016/j.jclinepi.2012.01.006.
38. Ruan L, Hu S, Huang M, Hu J, Cai W. Efficacy and safety of long-acting risperidone on early onset schizophrenia in adolescent patients. Afr J Pharm Pharmacol. 2010;4:184–92.
39. Ceylan MF, Erdogan B, Tural Hesapcioglu S, Cop E. Effectiveness, adverse effects and drug compliance of long-acting injectable risperidone in children and adolescents. Clin Drug Investig. 2017;37:947–56. https://doi.org/10.1007/s40261-017-0555-7.
40. Jacob P, Shere S, Kommu JVS. The use of first-generation long-acting injectable antipsychotics in children and adolescents-A retrospective audit from India. Asian J Psychiatr. 2021;61: 102663. https://doi.org/10.1016/j.ajp.2021.102663.
41. Petrić D, Rački V, Gačo N, Kaštelan A, Graovac M. Retrospective analysis of the effectiveness and tolerability of long-acting paliperidone palmitate antipsychotic in adolescent first-episode schizophrenia patients. J Child Adolesc Psychopharmacol. 2019;29:197–204. https://doi.org/10.1089/cap.2018.0044.
42. Suzuki H, Hibino H, Inoue Y, Takaya A. Treatment retencion of risperidone long-acting injection in patients with early-onset schizophrenia in Japan. Asian J Psychiatry. 2017;27:137–8.
43. Aggarwal A, Lindegaard V. Can a "shot" help prevent youth re-incarceration? Case report on use of a long-acting injectable antipsychotic in incarcerated youth. Psychopharm Bull. 2021;53:2.
44. Solfanelli A, Curto M, Dimitri-Valente G, Kotzalidis GD, Gasperoni C, Sani G, et al. Skin rash occurring with olanzapine pamoate, but not with oral olanzapine, in a male with juvenile idiopathic arthritis. J Child Adolesc Psychopharmacol. 2013;23(3):232–4. https://doi.org/10.1089/cap.2012.0121.
45. Mirza H, Harding D, Al-Balushi N. Paliperidone palmitate-induced delirium in an adolescent with schizophrenia: case report. Sultan Qaboos Univ Med J. 2018;18(2):e208–10. https://doi.org/10.18295/squmj.2018.18.02.014.
46. Salvi V, Appignanesi C, Marpepa B, Orsolini L, Volpe U. Aripiprazole LAI two-injection start in a 16 year-old adolescent with schizophrenia. Neuropsychopharmacol Rep. 2022. https://doi.org/10.1002/npr2.12240.
47. Fàbrega M, Sugranyes G, Baeza I. Two cases of long-acting paliperidone in adolescence. Ther Adv Psychopharmacol. 2015;5:304–6. https://doi.org/10.1177/2045125315600141.
48. McInnis P, Kasinathan J. Combination long-acting injectable (LAI) antipsychotic medication in adolescents with severe psychosis and aggression: a case series. Australas Psychiatry. 2019;27(2):160–4. https://doi.org/10.1177/1039856218815744.
49. Pope S, Zaraa SG. Efficacy of long-acting injectable antipsychotics in adolescents. J Child Adolesc Psychopharmacol. 2016;26:391–4. https://doi.org/10.1089/cap.2015.0091.
50. Saucedo E, Carranza F, Guerrero AF, García-Cervantes KI, Álvarez Villalobos NA, Acuña VD, et al. Preliminary efficacy and tolerability profiles of first versus second-generation Long-Acting Injectable Antipsychotics in schizophrenia: A systematic review and meta-analysis. J Psychiatr Res. 2020;129:222–33.
51. Abdel-Baki A, Medrano S, Maranda C, Ladouceur M, Tahir R, Stip E, et al. Impact of early use of long-acting injectable antipsychotics on psychotic relapses and hospitalizations in first-episode psychosis. Int Clin Psychopharmacol. 2020;35:221–8. https://doi.org/10.1097/YIC.0000000000000310.
52. Ahrens B. Mortality studies and the effectiveness of drugs in long-term treatment. Pharmacopsychiatry. 1997;30(Suppl 1):57–61. https://doi.org/10.1055/s-2007-979518.
53. Taipale H, Mittendorfer-Rutz E, Alexanderson K, Majak M, Mehtälä J, Hoti F, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. Schizophr Res. 2018;197:274–80. https://doi.org/10.1016/j.schres.2017.12.010.
54. Huang CY, Fang SC, Shao YJ. Comparison of long-acting injectable antipsychotics with oral antipsychotics and suicide and all-cause mortality in patients with newly diagnosed schizophrenia. JAMA Netw Open. 2021;4: e218810. https://doi.org/10.1001/jamanetworkopen.2021.8810.
55. McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and treatment of the first episode and

the critical early stages. Med J Aust. 2007;187(S7):S8-10. https://doi.org/10.5694/j.1326-5377.2007.tb01327.x.
56. Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. Br J Psychiatry. 2017;211:350–8. https://doi.org/10.1192/bjp.bp.117.201475.
57. Correll CU, Howes OD. Treatment-resistant schizophrenia: definition, predictors, and therapy options. J Clin Psychiatry. 2021;82(5):96. https://doi.org/10.4088/JCP.MY20096AH1C.
58. Grover S, Avasthi A. Clinical Practice Guidelines for the management of schizophrenia in children and adolescents. Indian J Psychiatry. 2019;61(Suppl 2):277–93. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_556_18.
59. Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am J Psychiatr. 2020;177:868–72. https://doi.org/10.1176/appi.ajp.2020.177901.
60. Chakrabarti S. Clozapine resistant schizophrenia: newer avenues of management. World J Psychiatry. 2021;11:429–48. https://doi.org/10.5498/wjp.v11.i8.429.
61. Caliskan AM, Karaaslan M, Inanli I, Caliskan S, Arslan M, Esra Cicek I, et al. The effects of adding long-acting injectable antipsychotic drugs to clozapine on relapse and hospitalization in patients with treatment-resistant schizophrenia: a mirror-image retrospective study. Int Clin Psychopharmacol. 2021;36:30–3. https://doi.org/10.1097/YIC.0000000000000336.
62. Bioque M, Parellada E, García-Rizo C, Amoretti S, Fortea A, Oriolo G, et al. Clozapine and paliperidone palmitate antipsychotic combination in treatment-resistant schizophrenia and other psychotic disorders: A retrospective 6-month mirror-image study. Eur Psychiatry. 2020;63: e71. https://doi.org/10.1192/j.eurpsy.2020.72.
63. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. Drug Alcohol Depend. 2018;1(191):234–58. https://doi.org/10.1016/j.drugalcdep.2018.07.011.
64. Sugranyes G, Flamarique I, Parellada E, Baeza I, Goti J, Fernandez-Egea E, et al. Cannabis use and age of diagnosis of schizophrenia. Eur Psychiatry. 2009;24:282–6. https://doi.org/10.1016/j.eurpsy.2009.01.002.
65. Crockford D, Addington D. Canadian schizophrenia guidelines: schizophrenia and other psychotic disorders with coexisting substance use disorders. Can J Psychiatry. 2017;62:624–34. https://doi.org/10.1177/0706743717720196.
66. Abdel-Baki A, Thibault D, Medrano S, Stip E, Ladouceur M, Tahir R, et al. Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder. Early Interv Psychiatry. 2020;14:69–79. https://doi.org/10.1111/eip.12826.
67. Arango C, Baeza I, Bernardo M, Cañas F, de Dios C, Díaz-Marsá M, et al. Long-acting injectable antipsychotics for the treatment of schizophrenia in Spain. Rev Psiquiatr Salud Ment (Engl Ed). 2019;12:92–105. https://doi.org/10.1016/j.rpsm.2018.03.006.
68. Dinnissen M, Dietrich A, van der Molen JH, Verhallen AM, Buiteveld Y. Guideline adherence of monitoring antipsychotic use for nonpsychotic indications in children and adolescents: a patient record review. J Clin Psychopharmacol. 2021;41:13–8. https://doi.org/10.1097/JCP.0000000000001322.
69. Häge A, Weymann L, Bliznak L, Märker V, Mechler K, Dittmann RW. Non-adherence to psychotropic medication among adolescents—a systematic review of the literature. Z Kinder Jugendpsychiatr Psychother. 2018;46:69–78. https://doi.org/10.1024/1422-4917/a000505.
70. Molteni S, Giaroli G, Rossi G, Comelli M, Rajendraprasad M, Balottin U. Drug attitude in adolescents: a key factor for a comprehensive assessment. J Clin Psychopharmacol. 2014;34(1):99–108. https://doi.org/10.1097/JCP.0000000000000035.
71. Czobor P, Van Dorn RA, Citrome L, Kahn RS, Fleischhacker WW, Volavka J. Treatment adherence in schizophrenia: A patient-level meta-analysis of combined CATIE and EUFEST studies. Eur Neuropsychopharmacol. 2015;25:1158–66. https://doi.org/10.1016/j.euroneuro.2015.04.003.Treatment.
72. Parellada E, Bioque M. Barriers to the use of long-acting injectable antipsychotics in the management of schizophrenia. CNS Drugs. 2016;30:689–701. https://doi.org/10.1007/s40263-016-0350-7.
73. Solerdelcoll M, Ilzarbe D, Fortea A, Morer A, Lazaro L, Sugranyes G, Baeza I. Psychopathology and mental health service use among youth in foster care admitted to a psychiatric inpatient unit: a 4-year retrospective controlled study. Eur Child Adolesc Psychiatry. 2022;21:1–12. https://doi.org/10.1007/s00787-022-02104-5.
74. Modesitt T, Kubascik E, Ott C. Extent of use of long-acting injectable antipsychotics in children and adolescents within Indiana Medicaid. Ment Health Clin. 2018;8(5):202–7. https://doi.org/10.9740/mhc.2018.09.202.
75. Parellada M, Fraguas D, Bombín I, Otero S, Castro-Fornieles J, Baeza I, et al. Insight correlates in child- and adolescent-onset first episodes of psychosis: results from the CAFEPS study. Psychol Med. 2009;39:1433–45. https://doi.org/10.1017/S0033291708004868.
76. Parellada M, Boada L, Fraguas D, Reig S, Castro-Fornieles J, Moreno D, et al. Trait and state attributes of insight in first episodes of early-onset schizophrenia and other psychoses: A 2-year longitudinal study. Schizophr Bull. 2011;37:38–51. https://doi.org/10.1093/schbul/sbq109.
77. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. Am J Psychiatry. 1993;150:873–9.
78. Lincoln TM, Lüllmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia. A systematic review Schizophr Bull. 2007;33:1324–42. https://doi.org/10.1093/schbul/sbm002.
79. Osatuke K, Ciesla J, Kasckow JW, Zisook S, Mohamed S. Insight in schizophrenia: a review of etiological models and supporting research. Compr Psychiatry. 2008;49:70–7. https://doi.org/10.1016/j.comppsych.2007.08.001.
80. McEvoy JP, Johnson J, Perkins D, Lieberman JA, Hamer RM, Keefe RS, et al. Insight in first-episode psychosis. Psychol Med. 2006;36:1385–93.
81. Hamann J, Heres S. Why and how family caregivers should participate in shared decision making in mental health. Psychiatr Serv. 2019;70:418–21.