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

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***Background and Hypothesis*: Long-acting injectable antipsychotic drugs (LAIs) are mainly used for relapse prevention but could also be advantageous for acutely ill patients with schizophrenia. *Study Design*: We conducted a systematic review and meta-analysis of randomized-controlled-trials (RCTs) comparing the second-generation long-acting injectable antipsychotics (SGA-LAIs) olanzapine, risperidone, paliperidone, and aripiprazole with placebo or their oral counterparts in acutely ill patients with schizophrenia. We analyzed 23 efficacy and tolerability outcomes, with the primary outcome being overall symptoms of schizophrenia. The results were obtained through random effects, pairwise meta-analyses, and subgroup tests. The study quality was assessed using the Cochrane-Risk-of-Bias-Tool version-1. *Study Results*: Sixty-six studies with 16 457 participants were included in the analysis. Eleven studies compared second-generation long-acting injectable antipsychotics (SGA-LAIs) with a placebo, 54 compared second-generation oral antipsychotics (SGA-orals) with a placebo, and one compared an SGA-LAI (aripiprazole) with its oral formulation. All 4 SGA-LAIs reduced overall symptoms more than placebo, with mean standardized differences of −0.66 (95% CI: −0.90; −0.43) for olanzapine, −0.64 (−0.80; −0.48) for aripiprazole, −0.62 (−0.76; −0.48) for risperidone and −0.42 (−0.53; −0.31) for paliperidone. The side-effect profiles of the LAIs corresponded to the patterns known from the oral formulations. In subgroup tests compared to placebo, some side effects were less pronounced under LAIs than under their oral formulations. *Conclusions*: SGA-LAIs effectively treat acute schizophrenia. Some side effects may be less frequent than under oral drugs, but due to the indirect nature of the comparisons, this finding must be confirmed by RCTs comparing LAIs and orals head-to-head.**

Key words: efficacy/depots/safety/oral antipsychotics

Introduction

Schizophrenia is a chronic and severe mental condition that has a significant impact on society. Oral antipsychotics (OAPs) have been the primary treatment for schizophrenia.[1] Unfortunately, non-adherence is frequent[2,3] and may compromise treatment efficacy.[4]

Long-acting injectable antipsychotics (LAIs) have been used as maintenance treatments for preventing relapse in patients with stable schizophrenia since 1960.[5–8] LAIs provide a unique advantage over OAPs as they have distinct pharmacokinetics. Compared to OAPs, LAIs can bypass hepatic and intestinal absorption and reach the circulatory system directly, decreasing the "first pass effect" and improving their bioavailability.[9,10] The slower absorption rate of LAIs leads to a prolonged half-life[11] and fewer peak-to-trough plasma concentration variations, which may contribute to better efficacy and tolerability compared to OAPs.[12]

The use of LAIs for the treatment of schizophrenia has been a topic of debate, with some studies showing their advantage over OAPs,[6,13–17] while others have not found this to be the case.[18–20] While being well studied as a maintenance treatment option,[5–8] evidence about the use of LAIs in the acute phase of schizophrenia has recently emerged.[13,16,21,22] In many settings, acutely ill patients are often treated as outpatients. However, this approach can

result in patients quickly discontinuing oral antipsychotics due to common symptoms of acute schizophrenia, such as suspiciousness or a lack of insight.[23] Furthermore, the financial pressures[24] of shorter hospital stays make LAIs useful for providing antipsychotic coverage when patients need to be discharged quickly.

Nevertheless, to our knowledge, no systematic review has examined the effects of LAIs in patients with acute schizophrenia. In general, 2 main questions exist: What are the efficacy and safety of LAIs compared to placebo, and how do LAIs compare to their oral counterparts in this context?

Thus, the purpose of the present meta-analysis was to compare the efficacy and safety of long-acting injectable second-generation antipsychotics with that of OAPs or placebo in patients with acute schizophrenia.

Methods

Search Strategy and Selection Criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol was published on the OSF (https://osf.io/7gj2s/).

We searched the Cochrane Schizophrenia Group's Study-Based Register, which includes https://clinicaltrials.gov/ and www.who.int/ictrp, from the database's inception to March 2022. We also assessed the references of all included trials for published and unpublished reports of further studies.

We included open, single-blind, double-blind, short-term, randomized-controlled-trials (RCTs), short-term being defined as three to thirteen weeks duration according to Cochrane reviews.[26] To avoid language bias, we included all studies irrespective of their language and origin.[27] To ensure data quality, we excluded trials performed in the mainland of China due to potential quality concerns,[28–30] except for studies conducted by international pharmaceutical companies.

We included only patients with acute schizophrenia irrespective of the diagnostic system used. Acute schizophrenia was defined as patients who had aggravated or active symptoms and who were at least at the beginning of the respective studies. If the authors described individuals as "acute" or did not explicitly mention their stability status, we presumed that these patients were acute.

We excluded maintenance (relapse prevention) studies in stable patients and dose-reduction trials. We excluded first-generation LAIs (FGA-LAIs), which produce more extrapyramidal symptoms (EPS) and tardive dyskinesia.[23] Most FGA-LAI studies have been published before the advent of second-generation antipsychotics. As such, they may involve stronger intervention effects than more recent RCTs, resulting in significant bias.[31,32] Moreover, FGA-LAIs are getting used less, at least in high-income countries.[33] Therefore, the present review included trials comparing SGA-LAIs (aripiprazole LAI, olanzapine LAI, risperidone LAI, and paliperidone LAI) with their oral versions or placebo. Concerning fixed dosage trials, we solely included those LAI doses authorized by the summary of product characteristics (SmPC).[34] For oral formulations, we included target to maximum fixed doses according to the International Consensus of Antipsychotic Dosing[35] (supplementary table S2). We also included all flexible-dose trials where physicians could adjust the dose.

Furthermore, in studies that involved multiple dose arms, we combined the arms with appropriate formulae.[36] The same approach was used for different injection intervals (eg, olanzapine IM. biweekly and 4 weekly). In accordance with Leucht et al[37] post hoc sensitivity analyses only included near-to-maximum effective doses, comprising aripiprazole LAI of at least 440 mg 4 weekly, olanzapine LAI 210 mg biweekly, risperidone 50 mg biweekly, and paliperidone 100 mg 4 weekly.

We excluded studies comparing SGA-LAIs to a different oral drug (different compound) or LAI. Finally, we used the studies from an updated, previously published meta-analysis,[1] which included SGA-OAP placebo-controlled studies (aripiprazole, olanzapine, risperidone, and paliperidone), for subgroup analysis.

Data Analysis

Each study was characterized by extracting the following general data: Study name, publication year, and blinding type; trial duration; diagnostic criteria; intervention; application; dosing interval; mean dose and range (mg); the number of patients randomized; percentage of females; mean age in years; mean duration of illness in years; and mean baseline severity (SD) on a scale for overall symptoms.

The primary outcome was changed in the PANSS[38] or BPRS total score[39] from baseline to endpoint.

Secondary outcomes included response rate, discontinuation for any reason, inefficacy, depressive symptoms (eg, the Hamilton Depression Rating Scale,[40] the Montgomery Asberg Depression Scale,[41] or other published scales), quality of life (eg, Quality of Life Scale[42]), social functioning (eg, global assessment of functioning[43]), use of antiparkinsonian drugs, extrapyramidal symptoms (measured by the ESRS,[44] DIEPSS,[45] and SAS[46]), akathisia (Barnes Akathisia Scale,[47] DIEPSS Akathisia subscale,[45] and the akathisia subscale of the ESRS[44]), number of patients with akathisia, weight gain (continuous, kg; dichotomous, defined as >7%), prolactin, dry mouth, QTc prolongation, sedation, at least one anticholinergic side-effect, urinary retention, blurred vision, constipation, all-cause mortality, mortality for suicide.

All data were entered in duplicate into a specifically setup Microsoft ACCESS database, allowing an automatic comparison of the 2 independent extractions.

Dichotomous data were analyzed using odds ratios (OR), while continuous outcomes were analyzed using standardized mean differences (SMD, for rating scale results) or mean differences (MD), including their 95% CI. We evaluated between-study heterogeneity using χ^2 and I^2 statistics. Values of $P < .05$ and $I^2 > 50\%$ indicated considerable heterogeneity.

We meta-analyzed RCTs comparing LAIs with placebo and compared the effect sizes of different LAIs vs placebo by subgroup tests. We also meta-analyzed RCTs which compared LAIs and oral drug formulations directly. Moreover, we performed meta-analytic subgroup tests in which the effect sizes of LAIs compared to placebos were compared with the effect sizes of their oral counterparts vs placebo. In addition, different LAI formulations containing the same antipsychotic component (eg, aripiprazole maintena and lauroxil) were pooled in the main analysis and then separately analyzed in a subgroup analysis. In addition to the sensitivity analysis on the dose mentioned above, we performed sensitivity analyses using studies on LAIs whose results were reported closest to 6 weeks. This is because studies on acute phase LAIs typically last 12 weeks, whereas studies comparing OAPs with placebos typically last 6–8 weeks (primary outcome only). The few oral studies which lasted less than 6 and more than 8 weeks were excluded from this analysis.

Two authors (DW, SD) independently selected the studies, extracted data, and assessed the risk of bias for the included LAI studies using the Cochrane risk of bias method for randomized trials (RoB 1).[36] Discrepancies were resolved through discussion, with the assistance of SL when necessary.

All data analyses were conducted using the "meta" package[48] in R version 4.2.0.

Results

After screening 14 135 titles and abstracts, we examined 3424 full-text publications. Eleven placebo-controlled trials and one comparison of aripiprazole LAI vs aripiprazole oral yielded usable data from 4775 participants. Additionally, 54 placebo-controlled OAP studies with 11682 participants were included after updating and screening a previously published meta-analysis[1]; one study did not provide usable data. Overall, 66 studies with 16457 participants were included (for detailed information on the screening process, please refer to the flowchart in figure 1). The included studies were published between 1992 and 2022 (supplementary table S1). All detailed results can be found in the supplementary material.

Risk of Bias

The percentages of studies with high, unclear, and low risk of bias were as follows: 0%, 47%, and 53% for randomization; 0%, 53%, and 47% for allocation concealment; 3.03%, 31.82%, and 65.15% for blinding of patients and clinicians; 3.03%, 34.85%, and 62.12% for blinding of raters; 4.55%, 12.12%, and 83.33% for missing outcomes; 9.09%, 18.18%, and 72.73% for selective reporting; and 1.52%, 12.12%, and 86.36% for other biases (supplementary table S4).

Primary and Secondary Outcomes

Efficacy-Related Outcomes.

LAIs vs Placebo. All LAIs were found to be more efficacious than placebo concerning all efficacy-related outcomes: Overall symptoms (range of mean SMDs: −0.42 for paliperidone to − 0.66 for olanzapine), responders (range of mean ORs: 2.22 for paliperidone to 4.12 for risperidone), positive symptoms (range of mean SMDs: −0.40 for paliperidone to − 0.68 for olanzapine), negative symptoms (range of mean SMDs: −0.29 for paliperidone to − 0.54 for olanzapine), depressive symptoms (range of mean SMDs: −0.22 for risperidone to −0.43 for aripiprazole), dropout due to inefficacy (range of mean ORs: 0.52 for paliperidone to 0.25 for aripiprazole) and dropout due to any reason (range of mean ORs: 0.63 for risperidone to 0.47 for paliperidone), see table 1 and supplementary figures S1–S38.

Data on social functioning were available only for aripiprazole and paliperidone, and both were found to be better than placebo (mean SMDs: −0.53 and − 0.23, respectively). A single trial[49] revealed that risperidone-LAI was not better than placebo regarding quality of life (SMD: −0.19, 95% CI − 0.41, 0.04) (table 1 and supplementary figures S1–S38).

Head-to-Head Comparisons of LAIs vs Their Oral Counterparts. Only one study[50] directly compared a LAI with its oral formulation (aripiprazole LAI vs aripiprazole oral formulation). There was no clear difference in the outcomes we addressed (supplementary figures S1–S38).

Subgroup Tests Comparing Different LAIs vs placebo. table 1 provides a summary of subgroup comparisons of various LAIs. A pattern emerged suggesting that paliperidone LAI was less efficacious than other antipsychotics in improving overall symptoms ($P = .03$), positive symptoms ($P = .04$), social functioning ($P < .01$), discontinuation for inefficacy ($P = .04$), and in responder rates ($P = .03$) (also see supplemental figures S1—S38).

Subgroup Tests Comparing Different Formulations of the Same LAI. We compared various LAI formulations using the same antipsychotic. There were no clear differences between aripiprazole LAI lauroxil and maintena, and between risperidone LAI subcutaneous, risperidone LAI ISM and risperidone LAI Consta (supplementary figures S64-S113).

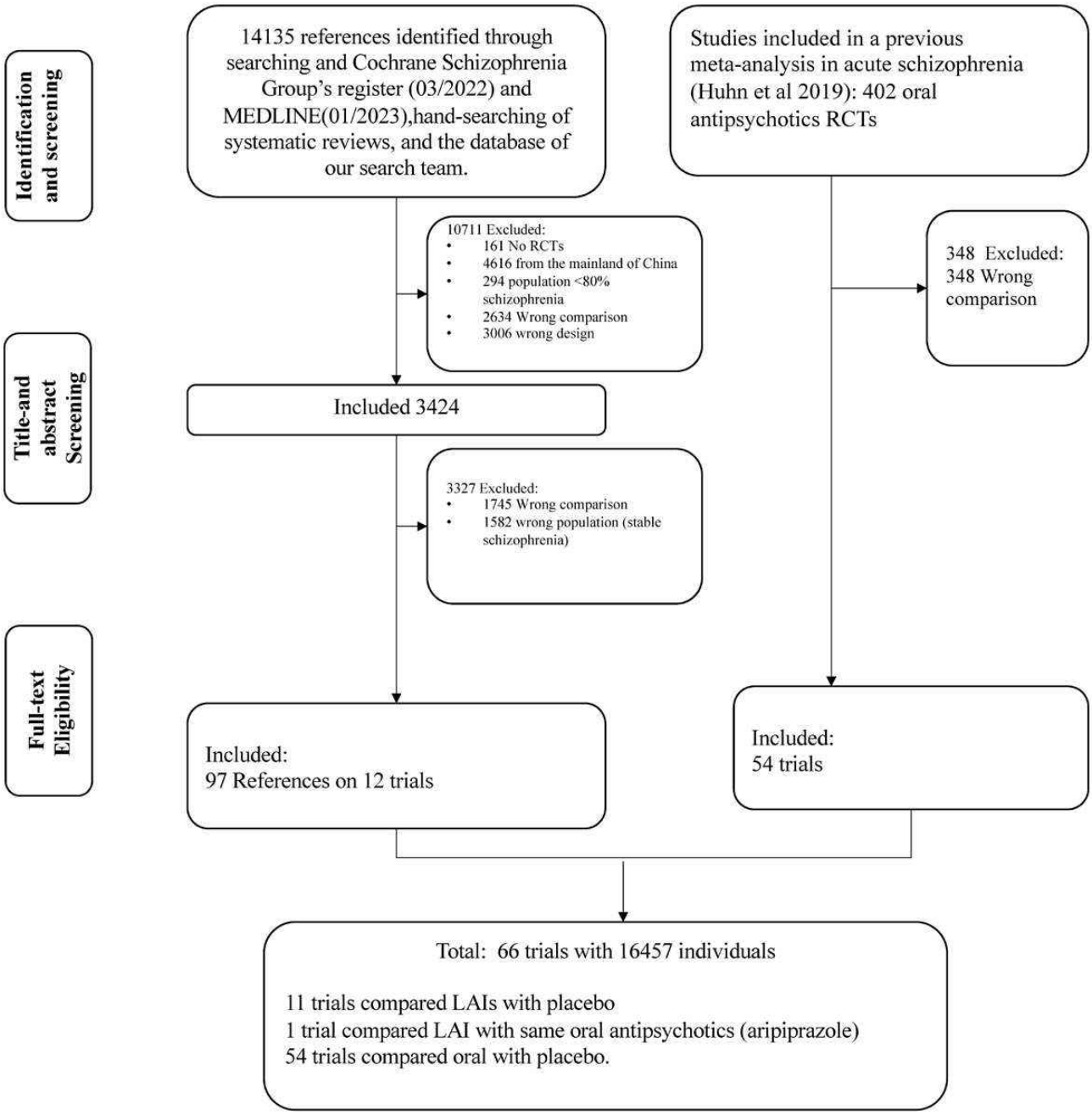

Fig. 1.

Subgroup Tests Comparing LAIs With Their Oral Counterparts Using Effect Sizes vs placebo. figure 2 shows the results of subgroup tests. Aripiprazole LAI was superior to its oral counterpart regarding overall symptoms and positive symptoms, response rate, and dropout for inefficacy. Risperidone LAI was better than its oral agent in response rate. In contrast, paliperidone oral was significantly better than its LAI in social functioning (supplementary figure S39-S62).

Sensitivity Analysis Using Only Maximum Effective Doses and Data Closest to 6–8 Weeks. This sensitivity analysis included only near to-maximum effective doses according to Leucht et al[37] The results did not change considerably (supplementary figure S118-S211).

Furthermore, since LAI studies had a longer duration (median 13 weeks) compared to their oral counterparts (median 6 weeks), we conducted the same subgroup analyses as above using LAI results closest to 6 weeks. Nonetheless, no apparent distinctions were observed in comparison to oral treatments (supplementary figures S114-S117).

Side-Effect-Related Outcomes.

LAIs vs Placebo. All LAIs had a significantly higher risk of clinically important weight gain (at least 7% increase)

Table 1. LAIs Compared to Placebo on all Outcomes

Outcomes	No. of Participants	No. of Studies	SMD/MD/ OR [95%CI]	Subgroup Analysis
Overall symptoms (continuous)				*P* = .03
Ari LAI VS Pla	925	2	−0.64 [−0.80; −0.48]	
Ola LAI VS Pla	402	1	−0.66 [−0.90; −0.43]	
Pal LAI VS Pla	2017	5	−0.42 [−0.53; −0.31]	
Ris LAI VS Pla	1010	3	−0.62 [−0.76; −0.48]	
Response rate (dichotomous)				*P* = .03
Ari LAI VS Pla	963	2	2.84 [2.07; 3.91]	
Ola LAI VS Pla	404	1	3.16 [1.84; 5.43]	
Pal LAI VS Pla	2098	5	2.22 [1.76; 2.78]	
Ris LAI VS Pla	738	2	4.12 [2.89; 5.88]	
Positive symptoms (continuous)				*P* = .04
Ari LAI VS Pla	925	2	−0.65 [−0.92; −0.38]	
Ola LAI VS Pla	402	1	−0.68 [−0.91; −0.45]	
Pal LAI VS Pla	2017	5	−0.40 [−0.50; −0.31]	
Ris LAI VS Pla	1010	3	−0.58 [−0.72; −0.43]	
Negative symptoms (continuous)				*P* = .12
Ari LAI VS Pla	925	2	−0.43 [−0.57; −0.30]	
Ola LAI VS Pla	402	1	−0.54 [−0.77; −0.31]	
Pal LAI VS Pla	2017	5	−0.29 [−0.38; −0.19]	
Ris LAI VS Pla	1010	3	−0.39 [−0.58; −0.21]	
Depressive symptoms (continuous)				*P* = .14
Ari LAI VS Pla	596	1	−0.43 [−0.60; −0.26]	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	2015	5	−0.22 [−0.35; −0.09]	
Ris LAI VS Pla	283	1	−0.36 [−0.61; −0.11]	
All-cause discontinuation (dichotomous)				*P* = .51
Ari LAI VS Pla	963	2	0.51 [0.39; 0.66]	
Ola LAI VS Pla	404	1	0.60 [0.38; 0.96]	
Pal LAI VS Pla	2098	5	0.47 [0.36; 0.63]	
Ris LAI VS Pla	1092	3	0.63 [0.47; 0.85]	
Discontinuation for inefficacy (dichotomous)				*P* = .04
Ari LAI VS Pla	963	2	0.25 [0.16; 0.39]	
Ola LAI VS Pla	404	1	0.40 [0.22; 0.71]	
Pal LAI VS Pla	2098	5	0.52 [0.42; 0.64]	
Ris LAI VS Pla	1092	3	0.46 [0.30; 0.71]	
Social function (continuous)				*P* < .01
Ari LAI VS Pla	936	2	−0.53 [−0.66; −0.39]	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	1459	3	−0.23 [−0.34; −0.11]	
Ris LAI VS Pla	—	—	—	
Quality of life (continuous)				—
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	—	—	—	
Ris LAI VS Pla	337	1	−0.19 [−0.41; 0.04]	
Weight gain (continuous)				*P* < .01
Ari LAI VS Pla	961	2	1.31 [0.14; 2.49]	
Ola LAI VS Pla	404	1	3.21 [2.11; 4.31]	
Pal LAI VS Pla	1605	4	1.32 [0.89; 1.75]	
Ris LAI VS Pla	624	2	2.18 [1.19; 3.16]	
Weight gain (dichotomous)				*P* = .91
Ari LAI VS Pla	963	2	2.21 [1.22; 3.99]	
Ola LAI VS Pla	404	1	2.85 [1.48; 5.47]	
Pal LAI VS Pla	2098	5	2.90 [1.76; 4.79]	
Ris LAI VS Pla	1092	3	2.53 [1.60; 4.00]	
QTc (continuous)				—
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	—	—	—	
Ris LAI VS Pla	637	2	3.40 [−0.44; 7.24]	

Table 1. Continued

Outcomes	No. of Participants	No. of Studies	SMD/MD/ OR [95%CI]	Subgroup Analysis
Use of antiparkinson medication (dichotomous)				*P* = .83
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	2098	5	1.18 [0.90; 1.53]	
Ris LAI VS Pla	1092	3	1.11 [0.72; 1.71]	
EPS scale (continuous)				*P* = .32
Ari LAI VS Pla	339	1	−0.10 [−0.31; 0.12]	
Ola LAI VS Pla	404	1	−0.21 [−0.44; 0.01]	
Pal LAI VS Pla	1730	4	0.01 [−0.10; 0.11]	
Ris LAI VS Pla	1075	3	−0.09 [−0.22; 0.03]	
Akathisia scale (continuous)				*P* = .57
Ari LAI VS Pla	339	1	0.00 [−0.21; 0.21]	
Ola LAI VS Pla	404	1	−0.20 [−0.42; 0.03]	
Pal LAI VS Pla	1735	4	−0.02 [−0.15; 0.11]	
Ris LAI VS Pla	787	2	−0.03 [−0.18; 0.11]	
Akathisia (adverse event)				*P* = .03
Ari LAI VS Pla	963	2	3.12 [1.75; 5.56]	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	2098	5	1.08 [0.61; 1.89]	
Ris LAI VS Pla	1092	3	1.59 [0.79; 3.19]	
At least once anticholinergic side effect				*P* = .11
Ari LAI VS Pla	963	2	1.02 [0.51; 2.07]	
Ola LAI VS Pla	404	1	0.47 [0.22; 1.02]	
Pal LAI VS Pla	2098	5	0.86 [0.55; 1.35]	
Ris LAI VS Pla	1092	3	1.81 [0.84; 3.88]	
Dry mouth(dichotomous)				*P* = .07
Ari LAI VS Pla	623	1	0.20 [0.04; 1.02]	
Ola LAI VS Pla	404	1	3.96 [0.51; 30.84]	
Pal LAI VS Pla	1527	3	1.79 [0.44; 7.37]	
Ris LAI VS Pla	300	1	3.48 [0.42; 28.70]	
Constipation (dichotomous)				*P* = .11
Ari LAI VS Pla	963	2	1.02 [0.51; 2.07]	
Ola LAI VS Pla	404	1	0.47 [0.22; 1.02]	
Pal LAI VS Pla	2098	5	0.86 [0.55; 1.35]	
Ris LAI VS Pla	1092	3	1.81 [0.84; 3.88]	
Blurred vision (dichotomous)				—
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	1527	3	0.25 [0.05; 1.28]	
Ris LAI VS Pla	—	—	—	
Urinary retention (dichotomous)				—
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	—	—	—	
Ris LAI VS Pla	—	—	—	
Sedation (dichotomous)				*P* = .84
Ari LAI VS Pla	963	2	2.51 [0.82; 7.71]	
Ola LAI VS Pla	404	1	4.27 [0.99; 18.37]	
Pal LAI VS Pla	1774	4	2.37 [0.98; 5.72]	
Ris LAI VS Pla	1092	3	1.96 [0.86; 4.47]	
Prolactin Level (continuous)				*P* < .01
Ari LAI VS Pla	—	—	—	
Ola LAI VS Pla	—	—	—	
Pal LAI VS Pla	451	1	18.85 [12.08; 25.62]	
Ris LAI VS Pla	742	2	29.17 [24.84; 33.50]	
All-cause mortality				*P* = .98
Ari LAI VS Pla	963	2	0.34 [0.03: 4.12]	
Ola LAI VS Pla	404	1	0.32 [0.01; 16.30]	
Pal LAI VS Pla	2098	5	0.49 [0.11; 2.16]	
Ris LAI VS Pla	1092	3	0.31 [0.04; 2.53]	

Table 1. Continued

Outcomes	No. of Participants	No. of Studies	SMD/MD/ OR [95%CI]	Subgroup Analysis
Mortality for suicide				$P = .99$
Ari LAI VS Pla	963	2	0.72 [0.04; 11.49]	
Ola LAI VS Pla	404	1	0.32 [0.01; 16.30]	
Pal LAI VS Pla	2098	5	0.67 [0.12; 3.55]	
Ris LAI VS Pla	1092	3	0.50 [0.05; 4.82]	

Note: Ris, risperidone; Pal, paliperidone; Ola, olanzapine; Ari, aripiprazole; PLA, placebo.
For continuous outcomes:
1.For effect-related outcomes, a negative value (−) indicates that the antipsychotic is favored over placebo.
2.For side-effect related outcomes, a negative value (−) indicates that the antipsychotic has fewer side effects than placebo.
For dichotomous outcomes:
1.For effect-related outcomes, an OR > 1 indicates that the antipsychotic is favored over placebo, for example, response rate.
2.For side-effect related outcomes, an OR < 1 indicates that the antipsychotic has fewer side effects than placebo.

than placebo (range of mean ORs: 2.21 for aripiprazole to 2.90 for paliperidone) and mean weight gain (range of mean MDs 1.31kg aripiprazole to 3.21kg olanzapine) (table 1 and supplementary figures S1–S38). Aripiprazole LAI was associated with a higher risk of akathisia (mean OR = 3.12) than placebo; paliperidone LAI (mean MD = 18.85) and risperidone LAI (mean MD = 29.17) produced more prolactin increase than placebo (table 1). There were no significant differences between LAIs and placebos in akathisia rating scale results (continuous), EPS scales (continuous), sedation, constipation, dry mouth, at least one anticholinergic side-effect, use of antiparkinsonian drugs, prolactin, all-cause mortality, and mortality for suicide (table 1 and supplementary figures S1–S38).

Head-to-Head Comparisons of LAIs With Their Oral Counterparts. Only one study[50] compared aripiprazole LAI with aripiprazole oral, and there was no significant difference between them in terms of any side effects (supplementary figure S1–S38).

Subgroup Tests Comparing Different LAIs vs Placebo. table 1 shows that the risk of akathisia (dichotomous) was highest for aripiprazole LAI ($P = .03$). Conversely, aripiprazole LAI was associated with a statistically significantly lower weight gain (continuous). In addition, prolactin increase was more pronounced when using risperidone LAI compared to paliperidone LAI ($P = .01$) (table 1 and supplementary figures S1—S38).

Subgroup Tests Comparing Different Formulations of the Same LAI. We compared various LAI formulations of the same antipsychotic. There were no clear differences between aripiprazole maintena and lauroxil, and between risperidone LAI subcutaneous, risperidone LAI ISM and risperidone LAI Consta in terms of side-effect outcomes (supplementary figure S64-S113).

Subgroup Tests Comparing LAIs With Their Oral Counterparts Using Effect Sizes vs Placebo. Compared to their oral formulations, olanzapine LAI had a significantly lower rate of at least one anticholinergic side-effect, aripiprazole LAI had a significantly lower frequency of dry mouth, paliperidone LAI had significantly lower prolactin levels, and aripiprazole LAI, paliperidone LAI, and olanzapine LAI had significantly lower EPS scores. In contrast, akathisia (dichotomous) was significantly more likely to develop with aripiprazole LAI than with its oral formulation. We did not find significant differences in other side effects, including weight gain, among the four LAIs and their oral formulations (figure 3 and supplementary figures S39–S62).

Sensitivity Analysis Using Maximum Effective Doses. These sensitivity analyses revealed no important difference (supplementary figure S118-S211).

Discussion

The present study is the first systematic review that compared the efficacy and safety of SGA-LAIs vs placebo and their oral counterparts in the treatment of acute schizophrenia. Based on 66 studies and 14 988 participants SGA-LAIs were clearly more effective than placebo, and they were generally as efficacious as their oral formulations. Certain side effects occurred less frequently under LAIs compared to oral antipsychotics, although this pattern was not fully consistent.

Some studies reported that psychiatrists prescribe paliperidone LAI more frequently than other LAIs[51,52] in patients who have indicators of higher severity of illness. For example, an analysis of the electronic health records of 1281 patients in London found that paliperidone palmitate was more likely to be prescribed in patients with more frequent and lengthy hospital admissions.[51] Similarly, an analysis of a Medicaid database revealed that clinicians were more likely to prescribe paliperidone LAI than aripiprazole LAI in patients with multiple hospitalizations.[52] Paliperidone could have been wrongly assumed to be a more effective LAI in this studies[51,52] because, in our meta-analysis, it had the smallest effect size compared

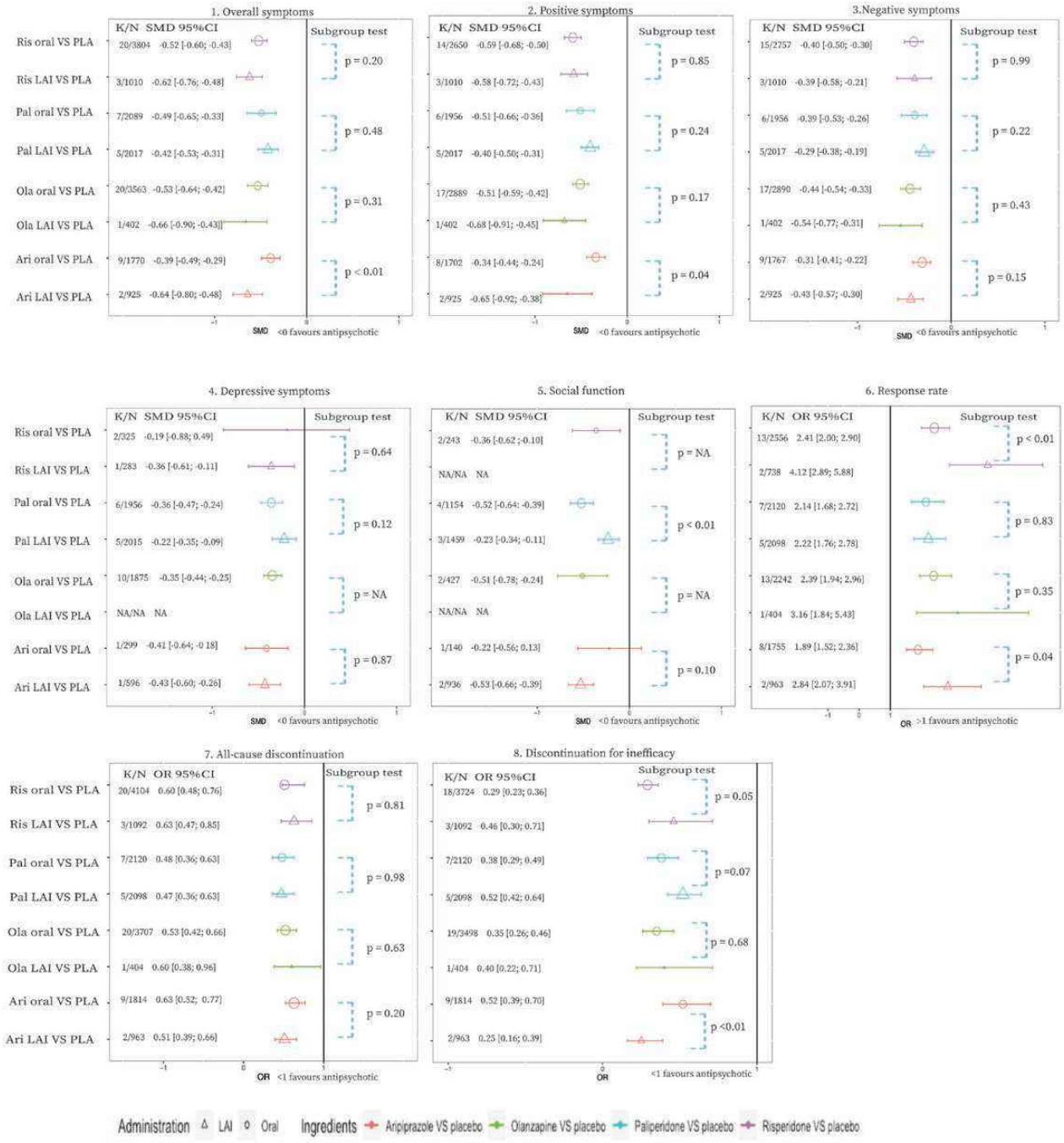

Fig. 2. Subgroup analysis for LAIs and the same oral formulations in terms of efficacy-related outcomes.

to placebo in various efficacy outcomes. Nevertheless, we derived the efficacy inferiority of paliperidone from subgroup tests vs *placebo*. Firm evidence of differences between LAIs can only be derived from head-to-head RCTs, of which very few are available. In the double-blind RCT by Fleischhacker et al,[53] paliperidone LAI was inferior to risperidone LAI in acutely ill patients, but there was no paliperidone booster injection after eight days of treatment which subsequently became part of the SoPC. Pandina et al[54] and Li et al[55] confirmed the non-inferiority of paliperidone LAI compared to risperidone LAI, and there was no clear difference between aripiprazole LAI and paliperidone LAI in the EULAST study[56] which can be described as a hybrid between an acute phase and relapse prevention study. Aripiprazole once-monthly and aripiprazole 2 monthly were similarly effective in acutely ill patients.[57] Network meta-analyses on relapse prevention did also not find clear differences between the 4 LAIs in question.[5,7,58] More head-to-head trials between LAIs are needed to characterize their relative efficacy.

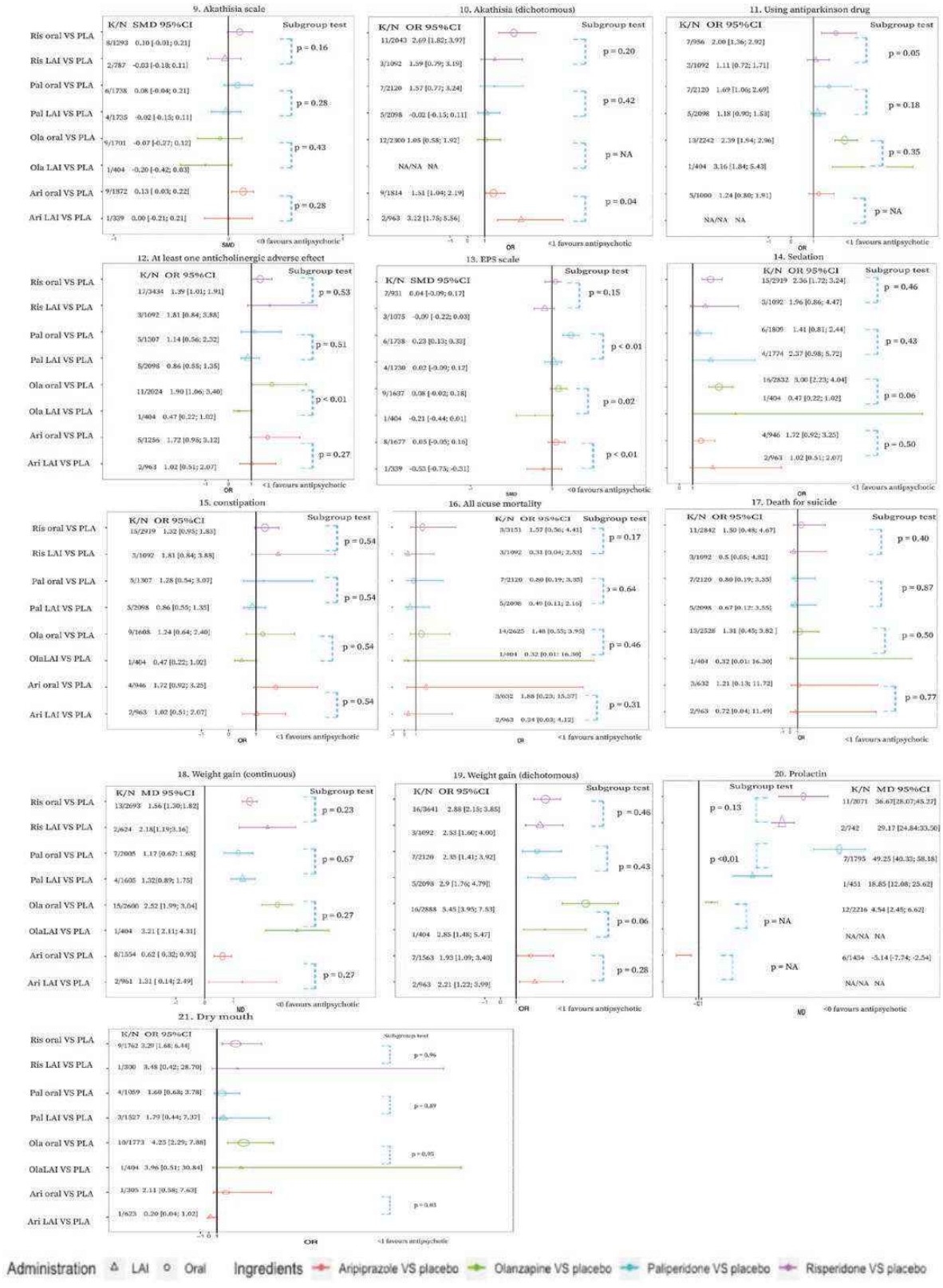

Fig. 3. Subgroup analysis for LAIs and the same oral formulations in terms of safetyrelated outcomes.

Regarding drug safety compared to placebo, all SGA-LAIs caused weight gain, which is one of the most common side effects of SGAs. This side effect has been attributed to histamine receptor inhibition and 5-HT2A receptor inhibition.[59] Blocking hypothalamic H1 receptors may activate AMP-activated protein kinase (AMPK), which is known to be a feeding regulator.[60] It can also activate AMPK-carnitine palmitoyltransferase-1 signaling, which is associated with caloric intake and, ultimately, weight gain.[61] Furthermore, blockade of the 5-HT_{2A} receptor has been associated with feeding behavior[62] and insulin resistance.[63] As expected, olanzapine's mean weight gain was most pronounced (3.2 kg). The numbers of patients with at least 7% weight gain were not significantly different between groups. However, differences in the underlying rates must be considered. For example, 28% of olanzapine-treated patients vs 12% in the placebo group gained weight compared to paliperidone LAI 8% vs 3% in its placebo groups (supplementary figure S18). The weighted mean relative risks were the same, RR 2.85 for olanzapine and RR 2.9 for paliperidone (table 1), but olanzapine's weight gain occurred at a higher level.

There was no clear difference between paliperidone LAI and risperidone LAI vs placebo in extrapyramidal side-effect scales and in the use of antiparkinson medication. This finding is important because their oral formulations clearly produce more EPS than placebo.[1] Aripiprazole LAI resulted in more akathisia adverse events than placebo. This finding was not substantiated by mean scores of the Barnes Akathisia scale, but only one aripiprazole study[64] reported Barnes Akathisia scale data that were useable for meta-analysis. Paliperidone LAI and risperidone LAI led to substantial hyperprolactinemia, which can cause sexual dysfunction and dys-/amenorrhea.[65] Prolactin data were not available for olanzapine LAI and aripiprazole LAI. In a previous network meta-analysis of oral antipsychotics, aripiprazole was associated with a reduction of prolactin levels compared to placebo, and olanzapine led to only a small increase.[1]

All four LAIs were sedating, but some uncertainty remained because 95% CI included a small possibility of no effect. There were no clear differences between LAIs and placebo in terms of various anticholinergic side-effects, QTc prolongation, and mortality.

When we compared LAIs with their oral counterparts by subgroup tests, the former were superior in several instances (figure 3): LAI formulations of aripiprazole, olanzapine, and paliperidone had lower extrapyramidal symptom rating scale scores than their oral counterparts, and patients on risperidone LAI needed almost less antiparkinsonian medication than those on oral ($P = .05$). The prolactin increase of paliperidone LAI was less pronounced than that of its oral formulation, and there was the same trend for risperidone LAI. Aripiprazole LAI was associated with fewer patients reporting dry mouth than those receiving aripiprazole orally, and fewer olanzapine LAI-treated patients experienced at least one anticholinergic side effect. These results may be due to the smaller peak-to-trough fluctuations and more stable plasma concentrations of LAIs compared to oral formulations.[12,66–68] Moreover, as LAIs avoid the first-pass effect in the liver, lower actual doses of LAIs compared to oral medication[10] may be needed for the same bioavailability and efficacy, and this effect may result in fewer side effects.[69] It is, however, also possible that the doses of the LAIs were actually lower than those of their oral counterparts. Pharmaceutical companies try to produce LAI doses that are equivalent to oral doses, but these relationships are not straightforward and can, for example, depend on the injection site (gluteal vs deltoid), frequency of injections (eg, 2 weekly or 4 weekly) and vehicle medium.[10] It is also important to mention that weight gain did not differ between LAIs and orals, and that except for prolactin increase, sexual side-effects such as amenorrhea were rarely reported and not analyzed by us.

These results should be interpreted with the following limitations. First, there was one exception to the rule in that aripiprazole LAI had a higher risk of akathisia compared to placebo than oral. The validity of this finding is unclear because, in the single head-to-head comparison of aripiprazole LAI and oral, the trend was in the other direction (more akathisia with oral).[50] Second, regarding efficacy, subgroup tests via placebo only provide indirect evidence; and the number of LAI studies was usually much smaller than that of the oral compounds. We could not conduct a sensitivity analysis at six to eight weeks for side effects because, in the LAI studies, these outcomes were only measured at the endpoint, which was usually 13 weeks. It is known that patients can get accustomed to their medications over time. Thus, given the longer duration of the LAI studies, fewer adverse effects may have been reported at endpoint. This issue is more likely in continuous outcomes such as scale-rated EPS and prolactin because they are measured at baseline and at endpoint. In contrast, side effects reported as adverse events usually occur early after the initiation of treatment. Third, ideally, there would be a large, randomized study including all SGAs (LAIs and oral), but it is unlikely that such a study could be conducted. A step forward could be a network meta-analysis, but it would mainly be star-shaped, using a placebo as a common comparator. Fourth, we only considered randomized-controlled-trials, the participants of which can differ substantially from those of real-world registry studies.[70] Fifth, we did not include studies from the mainland of China because it has been shown that most of them are not adequately randomized.[71] Usually, Chinese publications are very short, making it difficult to judge their quality.[28–30] Sixth, there was no study in acutely ill first-episode patients which limits generalizability. In this important subgroup with little previous drug exposure, severe side effects which require immediate cessation, such as neuroleptic malignant

syndrome[72] or priapism may be an even greater concern than in chronic patients.

Despite its limitations, the present study provides clinicians with important information on the effects of LAIs in acute schizophrenia. In clinical practice, the early use of LAIs offers an option with less volatility of peak and trough levels which could eventually lead to fewer adverse effects compared to their oral equivalents, but this needs to be confirmed by head-to-head comparisons. Finally, LAIs may bridge the often-difficult initial treatment phase when patients are especially skeptical of their treatment.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflicts of interests: In the last 3 years, Stefan Leucht has received honoraria as a consultant and/or advisor and/or for lectures and/or for educational material from Alkermes, Angelini, Eisai, Gedeon Richter, Janssen, Lundbeck, Medichem, Medscape, Merck Sharpp and Dome, Mitshubishi, Neurotorium, NovoNordisk, Otsuka, Recordati, Roche, Rovi, Sanofi Aventis, TEVA. The other authors have no conflict to declare.

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Author Contribution

DW, AK, SD, HW, and YZ screened the articles and extracted data. DW, JST, and SS did the statistical analysis. DW drafted the article. Profs Leucht, Priller, and Davis critically revised the article.

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