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REVIEW

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

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ABSTRACT

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

1. Introduction

Schizophrenia affects more than 24 million people globally, and it was the 20th leading cause of disability in 2019 (Collaborators, 2022). Oral antipsychotic drugs (OAPs) are the main form of treatment for schizophrenia (Ceraso et al., 2020; Huhn et al., 2020; Leucht et al., 2023). For relapse prevention, the most up-to-date meta-analysis showed that long-acting injectable formulations are superior to oral formulations in mirror-image studies, cohort studies, and randomized-controlled trials, although the superiority of LAIs in the latter two designs was relatively small(Kishimoto et al., 2021). LAIs offer advantages over OAPs, including improved adherence, less frequent dosing, knowing immediately when treatment is stopped, and then giving more time to react due to their longer half-life (Correll et al., 2021). LAIs do not undergo the first-pass effect in the liver enhancing bioavailability (Ragia et al., 2016), and their slower absorption and steadier blood concentrations might cause fewer side effects and provide better tolerance (Sheehan et al., 2012; Wang et al., 2023).

Some of these beneficial features of LAIs may also be useful in the treatment of acutely ill patients with schizophrenia. However, to the

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best of our knowledge, only one conventional pairwise meta-analysis has focused on the effects of LAIs in acutely ill patients (Wang et al., 2023). Pairwise meta-analysis is a method that can only combine trials comparing two treatments directly, of the design drug A vs drug B. In contrast, network meta-analysis is a technique that combines direct (e.g., drug A vs. drug B) and indirect evidence (e.g., drug A vs. drug B derived from drug A vs drug C and drug B vs drug C). It can, therefore, make use of all randomized data and increase precision(Salanti and Higgins, 2022). Moreover, the use of indirect evidence helps to fill gaps in the matrix of comparisons and ultimately derived hierarchies of which drug is likely to be the best, the second best, etc., for a given outcome.

In the present network meta-analysis, we thus investigated the comparative efficacy and tolerability of SGAs, which are available in both oral and long-acting injectable formulations in people with acute schizophrenia.

2. Experimental procedures

We conducted this NMA study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for NMA; see PRISMA checklist in eAppendix 1. A protocol was published on the Open Science Framework website (https://osf.io/f625j) and is presented in eAppendix 2.

2.1. Inclusion criteria

We included all relevant randomized controlled trials (RCTs) regardless of the degree of blinding. We excluded quasi-randomized designs like those using alternate day allocation and studies with a high risk of bias in randomization determined by the Risk of Bias tool 1 version (ROB 1)(Higgins et al., 2011). We excluded studies from mainland China, given documented quality problems (Leucht et al., 2022; Parry, 2017; Tong et al., 2018).

2.1.1. Participants

We focused on adults diagnosed with schizophrenia or related disorders (in particular schizoaffective disorder), using any diagnostic method. We only considered studies with at least 80 % of participants with such a diagnosis. We included acutely ill patients and excluded studies in stable patients (relapse prevention studies) and dose reduction studies. No restrictions were applied to the age, sex, ethnicity, or setting of the participants.

2.1.2. Types of interventions

We included studies that compared any two of the following interventions: risperidone LAIs (risperdal Consta, RBP-7000, and ISM risperidone); paliperidone LAIs (PP1M and PP3M); aripiprazole LAIs (Aripiprazole Maintena and Aripiprazole Lauroxil); olanzapine LAI (olanzapine pamoate); risperidone oral; paliperidone oral; aripiprazole oral; olanzapine oral; and placebo, either oral or injection.

2.1.3. Types of outcome measures

2.1.3.1. Primary outcomes. The main result was change of overall symptoms evaluated by the Positive and Negative Syndrome Scale (PANSS, (Kay et al., 1987)) or Brief Psychiatric Rating Scale (BPRS, (Overall and Gorham, 1988)).

2.1.3.2. Secondary outcomes. We examined positive, negative, and depressive symptoms, quality of life, and functioning, which were measured with published rating scales. The number of dropouts for any reason, side-effects and inefficacy were analyses as measures of overall acceptability, tolerability, and inefficacy, respectively. Side-effect outcomes encompassed weight gain (mean weight gain change/ kg, number of patients with weight gain, preferably defined as at least 7 %), extrapyramidal symptoms (number of patients using antiparkinsonian drugs), and akathisia (number of patients with akathisia), sedation, anticholinergic effects, increase in prolactin levels and increase of the QTc interval.

2.2. Search strategy

We reviewed previous meta-analyses(Huhn et al., 2019; Leucht et al., 2023; Wang et al., 2023), and we conducted update searches of the Cochrane Schizophrenia Group specialized register on June 14, 2021, September 21, 2021, March 6, 2022, and 25 June 2023 (eAppendix 3).

2.3. Study selection and data extraction

The search results were screened by at least two reviewers (among DW, MQ, HW, and YZ) who retrieved full-text articles and checked the inclusion criteria. In case of uncertainty, a third reviewer was consulted. Two reviewers (DW and MQ) extracted the data and entered them in a Microsoft Access database, which uses an algorithm to check for discrepancies. Any incoherence was discussed, and a third reviewer (JS, SL) was consulted if no consensus was reached. In cases where important information was missing or unclear, study authors were contacted.

We preferred using mixed models with repeated measures or multiple imputations instead of last-observation-forward or completer-only analyses. We estimated missing standard deviations from test statistics or used the mean standard deviation of the included studies. Additionally, we extracted mean age, sex, baseline severity (PANSS total score), publication year, study duration, pharmaceutical sponsor, and whether completer-only analyses were performed. Two reviewers(DW, MQ) independently assessed risk of bias with the Cochrane Collaboration's Risk of Bias Tool, version 1. Overall risk of bias across domains was classified according to Furukawa et al. (Furukawa et al., 2016)

2.4. Data analysis

We conducted random-effects network meta-analyses in a frequentist framework with *netmeta* R(Rücker et al., 2016). The standardized mean difference (SMD) served as the effect size for mean values of rating scales. Mean differences (MDs) were used for prolactin levels, weight gain, and QTc prolongation. We analyzed dichotomous outcomes with odds ratios (ORs).

We assessed the transitivity assumption by comparing the distribution of potential effect modifiers across comparisons (baseline severity, mean age, and placebo response), based on all studies which provided data for the primary outcome of 'overall symptom change'.

We used a common heterogeneity parameter for all treatment comparisons and reported the between-study variance ($\tau 2$) for each outcome. We assessed statistical inconsistency by performing the SIDE-test for each comparison, where $p < 0.1$ was the threshold for a significant difference between direct and indirect evidence. We also applied the design-by-treatment interaction test, again considering p-values less than 0.1 as important(Veroniki et al., 2021).

We applied the CINeMA web application, which facilitates the grading of confidence in the results as high, moderate, low, and very low (Nikolakopoulou et al., 2020) for primary outcomes. We set the minimum relevant SMD to ± 0.1 for this purpose. All data are presented with 95 % confidence intervals (CIs).

Finally, we excluded the following studies in sensitivity analyses of the primary outcome: no use of operationalized diagnostic criteria, open RCTs, completer analyses, studies with over 50 % missing data, and high risk of bias studies according to RoB 1. We undertook a sensitivity analysis focusing solely on maximum-effective-doses according to Leucht et al.(Leucht et al., 2020). Finally, we conducted a sensitivity analysis in which only results at six-to-eight-weeks were included, because acute-phase LAI studies typically last 12 weeks, and OAP studies

usually 6 to 8 weeks.

3. Results

We identified 115 studies on the four second-generation antipsychotics which are available in oral and LAI formulations (PRISMA diagram of the search in eAppendix 4): aripiprazole LAI 4, aripiprazole oral 16; olanzapine LAI 1, olanzapine oral 44; paliperidone LAI 9, paliperidone oral 11; risperidone LAI 7, risperidone oral 36; placebo 62. Out of 115 studies, three eligible studies did not provide any usable data. 91 were double-blind trials, 4 were single-blind trials, and 17 were open-label trials. There were 25,550 participants with an average age of 38.46. The median (interquartile range) study duration was 6 weeks (6 to 12). The overall risk of bias, according to Furukawa et al.(Furukawa et al., 2016), was high in 17.4 % of the studies, unclear 41.4 %, and low in 40.9 % of the studies. Further study characteristics and the risk of bias are presented in eAppendix 5.

3.1. Primary outcome: change in overall symptoms

91 studies, involving 24,765 participants, were available for the primary outcome (Fig. 1). All drugs were significantly more efficacious than placebo with the ranked sequence of olanzapine LAI [SMD=−0.66; 95 %CI: −1.00 to −0.33], risperidone LAI[SMD= −0.59; 95 %CI: −0.73 to −0.46], olanzapine oral [SMD=−0.55; 95 %CI:−0.62 to −0.48], aripiprazole LAI [SMD=−0.54; 95 %CI: −0.71 to −0.37], risperidone oral [SMD=−0.48; 95 %CI:−0.55 to −0.41], paliperidone oral [SMD=−0.47; 95 %CI: −0.58 to −0.37], paliperidone LAI [SMD=−0.45; 95 %CI: −0.57;−0.33], aripiprazole oral [SMD=−0.40; 95 %CI: −0.50; −0.31] (Fig. 2a and eAppendix 6).

In terms of comparisons between antipsychotics, olanzapine oral [SMD= −0.15; 95 %CI = −0.25 to −0.05] and risperidone LAI [SMD= −0.19; 95 %CI = −0.35 to −0.03] were more efficacious than aripiprazole oral. Risperidone LAI was superior to paliperidone LAI [SMD= −0.14; 95 %CI = −0.27 to −0.01] (Table 1). The confidence in the evidence according to CINeMA was high for five comparisons, moderate for 6, low for 4 and very low for 2 comparisons (see Fig. 1, Fig. 2a and Table 1, details are presented in eAppendix6 1.3 Assessment of confidence in estimates). The results of the sensitivity analyses were overall consistent with these findings, including a post-hoc subgroup analysis pooled LAIs vs placebo versus pooled orals versus placebo ($p = 0.42$, see eAppendix 6, 1.2). There was no relevant inconsistency (eAppendix 6).

3.1.1. Secondary efficacy outcomes

3.1.1.1. Positive symptoms and negative symptoms. 73 studies involving 20,566 patients reported usable data in terms of positive symptoms. All antipsychotics were clearly better than placebo, with SMDs (95 %CI) ranging from −0.68 (−1.00 to −0.37) for olanzapine LAI to −0.37 (−0.48 to −0.27) for aripiprazole oral. In terms of between-drug differences, olanzapine oral [SMD=−0.15; 95 %CI=−0.27 to −0.03] and risperidone LAI [SMD=−0.20; 95 %CI: −0.36 to −0.04] outperformed aripiprazole oral. Moreover, risperidone LAI was significantly better than paliperidone LAI [SMD=−0.14; 95 %CI: −0.26 to −0.02] (Fig. 2b and eAppendix 7).

75 studies with 20,739 patients provided usable results for negative symptoms. All drugs were associated with significant improvement in negative symptoms compared to placebo, and SMDs (95 %CI) ranged from −0.54(−0.82 to −0.26) for olanzapine LAI to −0.32(−0.42 to −0.22) for paliperidone LAI (Fig. 2)c). Olanzapine oral showed a small advantage over paliperidone LAI [SMD = −0.12; 95 % CI: −0.24 to −0.0008] (eAppendix 8).

3.1.1.2. Depressive symptoms. The NMA based on 35 studies with 13,138 participants showed that all drugs were significantly superior to placebo, with SMDs (95 %CI) ranging from −0.43 (−0.69 to −0.17) for aripiprazole LAI to −0.21(−0.36 to −0.07) for risperidone oral (Fig. 2d). There were no usable data for olanzapine LAI. There were no clear between-drug differences (eAppendix 9).

3.1.1.3. Dropouts due to any reason, inefficacy, and side-effect. In the NMA of 92 RCTs with 27,102 participants all drugs, except olanzapine LAI which had a wide 95 %CI, were superior to placebo in terms of total dropout rates, ranging from [OR =0.50; 95 % CI: 0.43 to 0.58] for olanzapine oral to [OR= 0.65; 95 %CI: 0.52 to 0.80] for aripiprazole oral (Fig. 2e). Olanzapine oral was associated with a significantly lower risk than aripiprazole oral [OR = 0.77;95 % CI: 0.61 to 0.97] and risperidone oral [OR =0.83; 95 % CI: 0.69 to 0.99] (Fig. 2e and eAppendix 10).

The NMA of 81 RCTs and 25,149 participants on dropout for inefficacy showed low-to-moderate heterogeneity ($\tau^2 = 0.11$) and some incoherence (20 % inconsistent comparisons, design-by-treatment interaction test: $p = 0.167$) (eAppendix 23). Therefore, we only present the pairwise meta-analyses comparing antipsychotics with placebo. All drugs showed a significantly lower risk of dropouts for inefficacy than placebo, with OR (95 %CI) ranging from 0.32(0.25 to 0.41) for risperidone oral to 0.50(0.36 to 0.68) for paliperidone LAI (Fig. 2f and eAppendix 11).

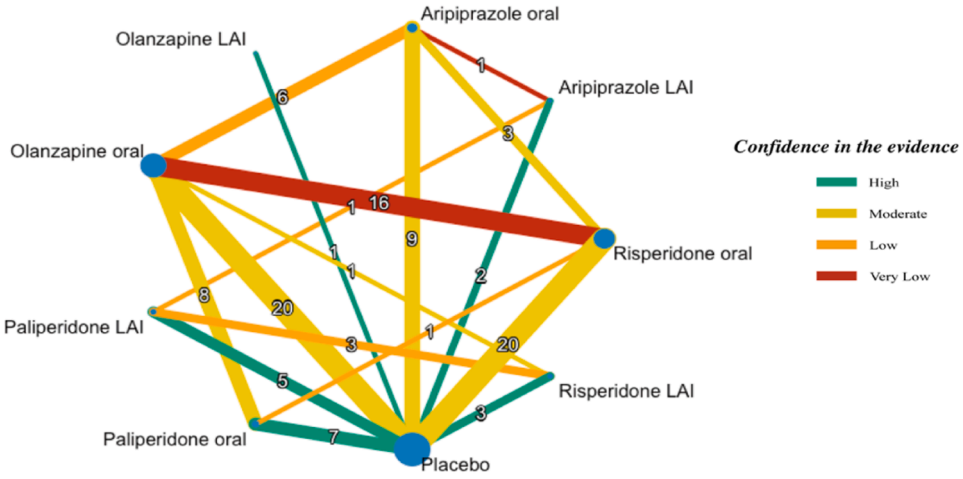

Fig. 1. Network plot for change in overall symptoms (primary outcome). The numbers on the lines represent the number of randomized controlled trials. Colors indicate the confidence in the evidence(CINeMA website): green=high, yellow=moderate, orange=low, red=very low.

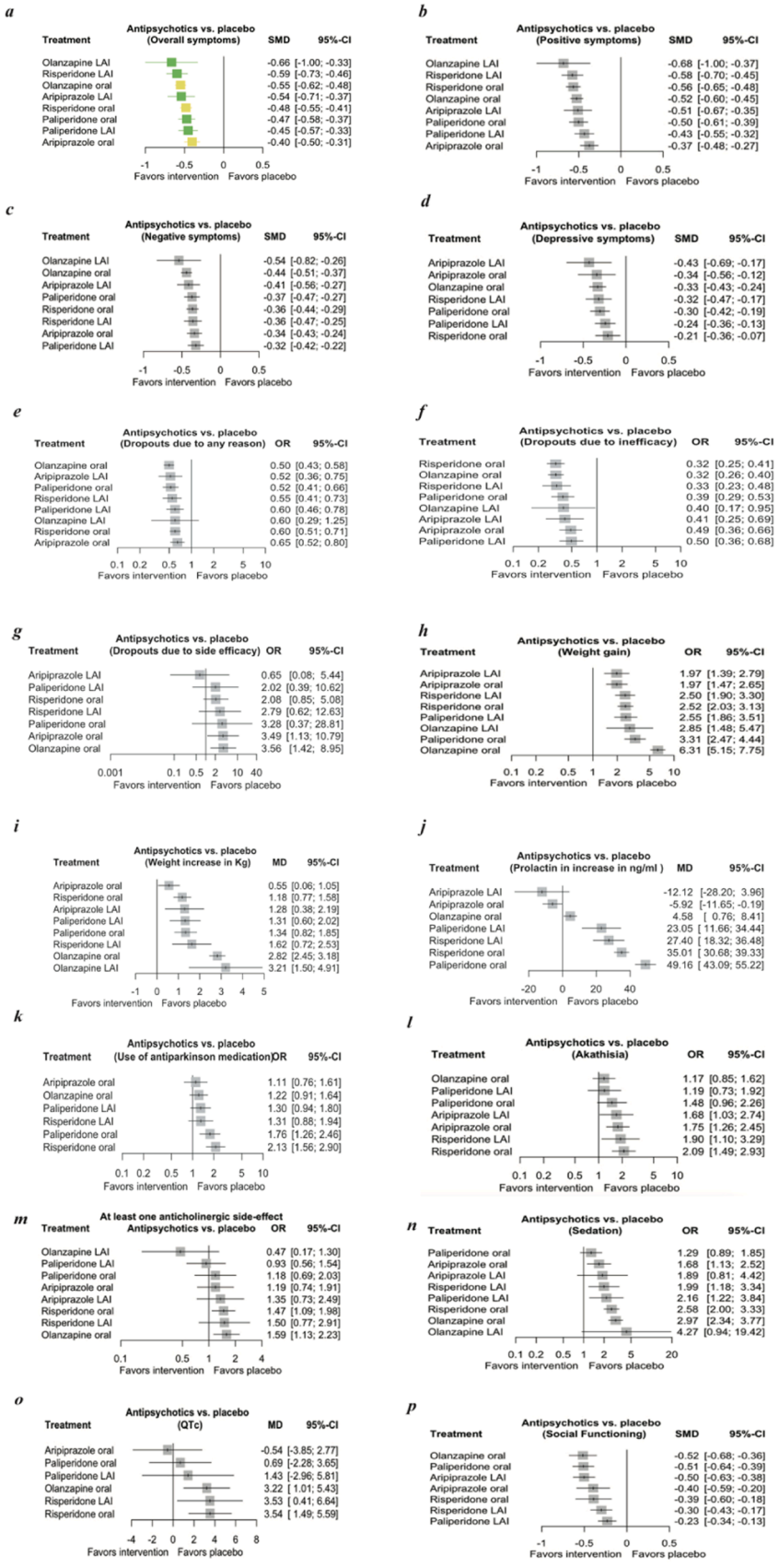

Fig. 2. Forest plots for comparing other drugs with placebo in terms of various outcomes. Note: For Fig. 2a changing overall symptoms, Colors indicate the confidence in the evidence(CINeMA website): green=high, yellow=moderate, orange=low, red=very low.

Table 1
League table for the change in overall symptoms (primary outcome).

Olanzapine LAI	.	.	.	.	.	.	.	-0.66 [-1.00; -0.33]
-0.07 [-0.43; 0.29]	Risperidone LAI	-0.12 [-0.46; 0.22]	.	.	.	-0.10 [-0.27; 0.06]	.	-0.62 [-0.81; -0.43]
-0.11 [-0.45; 0.22]	-0.04 [-0.19; 0.10]	Olanzapine oral	.	-0.15 [-0.26; -0.03]	-0.09 [-0.21; 0.04]	.	-0.16 [-0.31; -0.01]	-0.52 [-0.61; -0.43]
-0.12 [-0.50; 0.25]	-0.05 [-0.26; 0.16]	-0.01 [-0.19; 0.17]	Aripiprazole LAI	.	.	-0.09 [-0.55; 0.38]	0.09 [-0.24; 0.41]	-0.64 [-0.86; -0.43]
-0.18 [-0.52; 0.15]	-0.11 [-0.26; 0.04]	**-0.07 [-0.15; 0.01]**	-0.06 [-0.24; 0.12]	Risperidone oral	0.37 [-0.28; 1.02]	.	-0.14 [-0.39; 0.11]	-0.52 [-0.61; -0.43]
-0.19 [-0.54; 0.15]	-0.12 [-0.29; 0.04]	-0.08 [-0.18; 0.02]	-0.07 [-0.27; 0.13]	-0.01 [-0.13; 0.11]	Paliperidone oral	.	.	-0.50 [-0.63; -0.37]
-0.21 [-0.56; 0.14]	**-0.14 [-0.27; -0.01]**	-0.10 [-0.23; 0.04]	-0.09 [-0.29; 0.11]	-0.03 [-0.17; 0.11]	-0.02 [-0.18; 0.14]	Paliperidone LAI	.	-0.42 [-0.57; -0.28]
-0.26 [-0.61; 0.08]	**-0.19 [-0.35; -0.03]**	**-0.15 [-0.25; -0.05]**	-0.14 [-0.32; 0.04]	-0.08 [-0.19; 0.03]	-0.07 [-0.20; 0.07]	-0.05 [-0.20; 0.10]	Aripiprazole oral	-0.38 [-0.51; -0.25]
-0.66 [-1.00; -0.33]	**-0.59 [-0.73; -0.46]**	**-0.55 [-0.62; -0.48]**	**-0.54 [-0.71; -0.37]**	**-0.48 [-0.55; -0.41]**	**-0.47 [-0.58; -0.37]**	**-0.45 [-0.57; -0.33]**	**-0.40 [-0.50; -0.31]**	Placebo

Pairwise (upper right portion) and network (lower left portion) meta-analytic results are shown for the secondary outcome. The left lower field presents the results of the network meta-analysis; the right upper field presents the results of pairwise meta-analyses. Treatments are in order of their point estimate compared to placebo. Each cell provides the standardized mean difference and the corresponding 95 % confidence interval (CI) of a comparison. Significantly different results are marked in bold. Colors indicate the confidence in the evidence(CINeMA website): green=high, yellow=moderate, orange=low, red=very low.

Based on 19 studies with 5490 participants aripiprazole oral and olanzapine oral showed a significantly higher risk of dropout from side effects compared to placebo, with [OR = 3.49; 95 % CI: 1.13 to 10.79] and [OR = 3.56; 95 % CI: 1.42 to 8.95], respectively (Fig. 2g). Moreover, olanzapine oral had a higher risk than risperidone oral [OR =0.58; 95 % CI: 0.39 to 0.87]. There were no usable data for olanzapine LAI. (Fig. 2g and eAppendix 12).

3.1.2. Secondary outcomes: side-effects

3.1.2.1. Patients with weight gain (≥ 7 % if available) and mean weight increase in kg. In 72 studies with 22,382 participants ≥ 7 % weight gain was clearly more frequent under all antipsychotics compared to placebo, with OR (95 %CI) ranging from 1.97(1.39 to 2.79) for aripiprazole LAI to 6.31(5.15 to 7.75) for olanzapine oral (Fig. 2h). Olanzapine oral had a significantly higher risk than all other drugs, including its LAI formulation. Aripiprazole LAI [OR= 0.59; 95 %CI 0.38 to 0.92] and oral [OR= 0.59; 95 %CI 0.41 to 0.86] had a lower risk than paliperidone oral (eAppendix 13).

As the NMA based on 61 studies with 18,645 participants on mean weight increase (kg) showed low to moderate heterogeneity (τ2 = 0.44), and some incoherence (28.6 % inconsistent comparisons, design-by-treatment interaction test: p = 0.036) (eAppendix 23), we only presented pairwise meta-analyses comparing antipsychotics with placebo. All drugs produced more weight gain than placebo, with MDs ranging from 0.55 kg (0.06 to 1.05) for aripiprazole LAI to 3.21 kg (1.50 to 4.91) for olanzapine LAI (Fig. 2i and eAppendix 14).

3.1.2.2. Prolactin. In 41 studies with 12,783 participants aripiprazole oral was significantly better than placebo [MD=−5.92; 95 %CI: −11.65 to −0.19]. The superiority of aripiprazole LAI compared to placebo was even larger, but the confidence interval overlapped with zero (MD= −12.12; 95 %CI: −28.20 to 3.96). All other drugs had more prolactin increase compared to placebo, with MDs ranging from 4.58 ng/mL (0.76; 8.41) for olanzapine oral to 49.16(43.09; 55.22) for paliperidone oral. There were no usable data for olanzapine LAI. Both formulations of aripiprazole were superior to all other medications with 95 %CIs excluding no effect. Moreover, olanzapine oral produce less prolactin increase than both formulations of paliperidone and risperidone. Finally, paliperidone LAI was associated with lower prolactin than its oral form (MD=−26.10; 95 %CI −39.00 to −13.20), and paliperidone oral increased prolactin levels less than risperidone LAI (MD= −21.76; 95 %CI −32.67 to −10.84) and oral (MD=−14.15; 95 %CI −21.43 to −6.87) (Fig. 2j and eAppendix 15).

3.1.2.3. Extrapyramidal side-effects (EPS): use of antiparkinsonian medication at least once and akathisia. In 45 studies with 14,800 participants only paliperidone oral [OR =1.76; 95 % CI: 1.26 to 2.46] and risperidone oral [OR =2.13; 95 % CI: 1.56 to 2.90] were associated with more antiparkinsonian mediation use than placebo (Fig. 2k). Moreover, risperidone oral had a significantly higher risk than aripiprazole oral [OR =0.52; 95 % CI: 0.33 to 0.81], olanzapine oral [OR =0.57; 95 % CI: 0.43 to 0.76] and paliperidone LAI [OR =0.61; 95 % CI: 0.39 to 0.95]. There were no usable data for olanzapine LAI and aripiprazole LAI (eAppendix 16).

The NMA based on 59 studies with 18,590 participants on akathisia showed moderate-to-high heterogeneity (τ2 = 0.08) and a number of incoherence (28.6 % inconsistent comparisons, design-by-treatment interaction test: p = 0.02) (eAppendix 23). Therefore, we present only pairwise meta-analyses compared to placebo. Both formulations of aripiprazole and risperidone had a higher risk of akathisia than placebo (Fig. 2l and eAppendix 17).

3.1.2.4. At least one anticholinergic adverse event. 57 studies with 18,554 participants provided data on at least one anticholinergic adverse event. Olanzapine oral [OR = 1.59; 95 % CI: 1.13 to 2.23] and risperidone oral [OR = 1.47; 95 % CI: 1.09 to 1.98] had a higher risk than placebo (Fig. 2m). In terms of differences between drugs, olanzapine LAI had a lower risk of anticholinergic adverse events than its oral formulation [OR = 0.30; 95 % CI: 0.10 to 0.86], and risperidone oral [OR = 0.32; 95 % CI: 0.11 to 0.92] (eAppendix 18).

3.1.2.5. Sedation. In 67 studies with 21,397 participants all drugs were more sedating than placebo and this finding was significant for olanzapine oral [OR = 2.97; 95 % CI: 2.34 to 3.77], risperidone oral [OR = 2.58; 95 % CI: 2.00 to 3.33], paliperidone LAI[OR = 2.16; 95 % CI: 1.22 to 3.84], risperidone LAI [OR = 1.99; 95 % CI: 1.18 to 3.34] and aripiprazole oral[OR = 1.68; 95 % CI: 1.13 to 2.52] (Fig. 2n). Olanzapine oral had a higher risk than oral formulations of aripiprazole [OR = 0.57; 95 % CI: 0.38 to 0.85] and paliperidone [OR = 0.43; 95 % CI: 0.31 to 0.61]. Risperidone oral had a higher risk than paliperidone oral [OR = 0.50; 95 % CI: 0.34 to 0.74] (eAppendix 19).

3.1.2.6. QTc prolongation. In 19 studies with 6372 participants, risperidone oral [MD =3.54; 95 % CI: 1.49 to 5.59], risperidone LAI [MD =3.53; 95 % CI: 0.41 to 6.64], and olanzapine oral [MD =3.22; 95 % CI: 1.01 to 5.43] produced more QTc prolongation than placebo (Fig. 2o). Data for aripiprazole LAI and olanzapine LAI were not available. Moreover, risperidone oral was significantly worse than aripiprazole oral [MD =−4.08; 95 % CI: −7.68 to −0.48] (eAppendix 20).

3.1.2.7. Quality of life and social functioning. Only 12 studies with 2885 participants provided data on quality of life. Therefore, no NMA was conducted. In pairwise meta-analyses, aripiprazole oral [SMD = −0.49;

95 %CI −0.72 to −0.26], olanzapine oral [SMD = −0.24; 95 %CI −0.46 to −0.03], and paliperidone oral [SMD = −0.18; 95 %CI −0.34 to −0.03] were significantly better than placebo. Risperidone LAI [SMD = −0.13; 95 %CI −0.30 to 0.03] was not significantly better than placebo. No data were available for aripiprazole LAI and olanzapine LAI (eAppendix 21).

In 20 studies and 7931 participants all drugs, except for olanzapine LAI which did not have usable data, outperformed placebo in functioning, with SMDs ranging from −0.52(−0.68 to −0.36) for olanzapine oral to −0.23(−0.34 to −0.13) for paliperidone LAI. In terms of differences between drugs, aripiprazole LAI was superior to risperidone LAI [SMD = −0.20; 95 %CI −0.38 to −0.03] and paliperidone LAI [SMD = −0.27; 95 %CI −0.44 to −0.11]. Olanzapine oral was better than paliperidone LAI [SMD = −0.29; 95 %CI −0.48 to −0.09] and risperidone LAI [SMD = −0.22; 95 %CI −0.42 to −0.01]. Paliperidone oral was better than its LAI formulation [SMD =−0.28; 95 %CI −0.44 to −0.12], and risperidone LAI [SMD =−0.21; 95 %CI −0.39 to −0.03] (Fig. 2p and eAppendix 22).

4. Discussion

To our knowledge, this is the first NMA to comprehensively compare SGAs in both oral and LAI forms of administration for acute schizophrenia. In contrast to a previous pairwise meta-analysis which included 66 RCTs and 16.457 participants(Wang et al., 2023) the evidence-base could be extended to 115 RCTs with 25.550 participants. All drugs were more efficacious than placebo. LAIs were generally on par with their oral counterparts in terms of efficacy. Furthermore, certain adverse effects were less common with some LAIs than with oral antipsychotics, though this trend was not uniformly observed.

All antipsychotic drugs in both formulations reduced *overall symptoms* more than placebo, with mean SMDs between –0·66 for olanzapine LAI and –0·40 for aripiprazole oral at the bottom of the hierarchy, and all were associated with fewer drop-outs due to inefficacy than placebo. However, only olanzapine oral and risperidone LAI were significantly more efficacious than aripiprazole oral, all other 95 % CIs for comparisons between antipsychotics overlapped. It is noteworthy that olanzapine was also the most efficacious drug in a NMA examining the effects of antipsychotics in long-term studies of initially acutely ill patients (Leucht et al., 2023), and that it came close to clozapine in a NMA in treatment-resistant patients(Dong et al., 2023). Similar hierarchies were also observed in terms of *positive symptoms, and negative symptoms*; and all drugs were superior to placebo in *depressive symptoms*. This finding may be explained by the fact that second-generation antipsychotics do not only affect dopamine but also the serotonin (Kuroki et al., 2008), norepinephrine (NE), and glutamate systems (Abi-Dargham and Laruelle, 2005). These neurotransmitters play a key role in mood regulation (Ressler and Nemeroff, 1999), cognition(Hoshino, 2005) and perception (Mather et al., 2016). In particular, the effects of serotonin receptors have been linked to antidepressant effects(Yohn et al., 2017).

Premature study discontinuation (“dropout”) is an important outcome, because it reflects broader effectiveness rather than efficacy or single side-effects. All-cause discontinuation combines dropout for inefficacy and side-effects and can thus be considered to be a proxy for acceptability. Except for olanzapine LAI, all drugs were superior to placebo. In comparisons of drugs, olanzapine oral was associated with a lower risk of all-cause discontinuation than aripiprazole oral and risperidone oral.

In terms of overall tolerability, except for aripiprazole LAI, all antipsychotics were associated with more dropouts due to side-effects than placebo, and this difference was significant for aripiprazole oral (OR = 3.49; 95 % CI: 1.13 to 10.79) and olanzapine oral (OR = 3.56; 95 % CI: 1.42 to 8.95). Few studies presented data on *quality of life and social function*, which are critical patient-centered outcomes. However, where such data were available, most antipsychotics had superior effects in comparison to placebo. Quality of life and social functioning should be consistently analyzed in the future.

Regarding specific side-effects, all drugs were associated with more patients experiencing significant weight gain than placebo. Olanzapine oral had the highest risk (OR 6.31 (95 % CI = 5.15 to 7.75). This finding aligned with previous studies (Huhn et al., 2019; Leucht et al., 2023). Interestingly, olanzapine LAI showed a lower risk of weight gain than its oral counterpart. One explanation may be that LAI formulations lead to smaller fluctuations in plasma levels (Sheehan et al., 2012). The higher plasma level peaks of oral medication may trigger appetite, leading to increased food intake (He et al., 2013). The main limitation is that only one olanzapine LAI study was available. We could not corroborate the difference between oral and LAI in terms of continuous weight increase in kg. The results were very inconsistent, so that we restricted to pairwise meta-analyses compared to placebo.

Hyperprolactinemia is associated with various adverse effects, ranging from menstrual disorders in women and sexual dysfunction in both sexes to serious, but unfortunately not recorded, long-term complications such as osteoporosis (Koch et al., 2023). As observed in prior studies (Huhn et al., 2019; Lu et al., 2022; Zhu et al., 2021), both aripiprazole LAI and oral formulations were associated with a reduction in prolactin levels when compared to placebo. Aripiprazole acts as a partial agonist at D2 receptors, rather than as an antagonist like many other antipsychotics, reducing the risk of hyperprolactinemia. Unlike other atypical antipsychotics, aripiprazole favors D2 receptors over 5-HT2A receptors, and it also possesses stronger 5-HT1A partial agonist properties than its 5-HT2A antagonism, contributing to its relatively good tolerability (Stahl and Djokic, 2023). Aripiprazole LAI had a higher mean effect size (MD= −12.12, 95 %CI −28.20 to 3.96) than oral (MD=−5.92; 95 %CI: −11.65 to −0.19] in this regard, but the difference was not significant due to a wide confidence interval. Olanzapine oral was associated with a small, but statistically significant prolactin elevation compared to placebo (MD=4.58; 95 %CI: 0.76 to 8.41], unfortunately, no data on olanzapine LAI were available. Paliperidone and risperidone were associated with most prolactin increase, but possibly again, due to more stable plasma levels under LAIs, this increase was more pronounced in their oral formulations.

The oral formulations of risperidone and paliperidone are well known to produce more extrapyramidal side-effects than placebo(Huhn et al., 2019) and our NMA confirmed this finding. Olanzapine oral and aripiprazole oral were neutral in this regard. Interestingly, however, the LAI formulations of paliperidone and risperidone were not associated with more antiparkinsonian medication use than placebo, and with less use than their oral counterparts. Both formulations of risperidone and aripiprazole produced akathisia, but not olanzapine oral, paliperidone LAI, and oral. Akathisia is considered the most problematic side-effect of aripiprazole.

Olanzapine LAI was also associated with a significantly lower risk of anticholinergic side-effects, a dangerous problem when it is severe, than its oral counterpart and risperidone oral. All antipsychotics were more sedating than placebo. This side-effect was most pronounced for olanzapine oral and LAI, probably due to their strong binding to histamine receptors(Bymaster et al., 1999). For paliperidone oral, aripiprazole LAI, and olanzapine LAI the increase did not reach the conventional 5 % significance level. Finally, some drugs increased the QTc interval, but the mean differences to placebo were only 3–3.55 msec for risperidone oral, risperidone LAI, and olanzapine, thus all small.

There are several limitations to our study. First, most differences between LAIs and orals were derived from indirect evidence. Olanzapine LAI came out as the most efficacious antipsychotic in several outcomes, but it must be noted that only one trial was available (Lauriello et al., 2008) and that therefore its confidence intervals were usually large. Second, we only included RCTs which minimize the possibility of showing efficacy superiorities compared to oral drugs. The main question about LAIs has so far been whether they reduce relapse rates compared to oral drugs in maintenance trials. The most up-to-date systematic review found a large LAI superiority in pre-post (“mirror

image") studies but only a small difference in RCTs (Kishimoto et al., 2021). One reason for only small differences in RCTs is that patients who consent to double-blind, randomized-controlled trials are relatively adherent per se. Third, LAI studies were usually longer. We addressed this problem by a sensitivity analysis including only data between 6 and 8 weeks which confirmed the results on the primary outcome (e-Appendix 6, 1–15). We could perform this sensitivity analysis on side-effects because they are rarely reported at different time points. Nevertheless, most side-effect occur early after initiation of treatment, so a longer study duration may not be a major problem. Overall, olanzapine LAI was associated with less weight gain and less anticholinergic side-effects than olanzapine oral, but this evidence was based on a single olanzapine LAI trial. Paliperidone LAI produced less prolactin increase and fewer EPS than its oral counterpart, and strong trends in favour of risperidone LAI compared to risperidone oral was apparent for the same outcomes. Fourth, although we examined a relatively broad range of side-effects, antipsychotic drugs can also produce other ones. Fifth, we excluded studies from mainland China because of frequently raised quality concerns (Leucht et al., 2022; Parry, 2017; Tong et al., 2018). Nevertheless, this criterion could reduce the applicability to Chinese patients who, for example, are usually smaller and lighter. Finally, the confidence in the evidence for the primary outcome ranged between high and very low, but it was moderate for most comparisons according to CINeMA (Fig. 1, Fig. 2a, eAppendix 6.1.3 Assessment of confidence in estimates).

Traditionally, LAIs had been reserved for the most challenging cases of schizophrenia. However, current trends advocate for their early use, already at the first episode, to prevent disease progression and avoid complications related to non-adherence (Stahl and Djokic, 2023). Our study supports this shift, showing that LAIs are as efficacious as oral agents in the acute-phase of schizophrenia, and some may have advantages in terms of lower occurrence of some side-effects .

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Contributors

DW and SL designed the study. DW, MQ, HW and YZ screened the articles and extracted data. DW, JST, and SS did the statistical analysis. SL and JP supervised the work. DW drafted the article. SL, JP, JD, YZ, JST, and SS reviewed and revised manuscript.

Declaration of competing interest

S.L. has received honoraria as a consultant and/or advisor and/or for lectures and/or for educational material from Alkermes, Angelini, Apsen, Eisai, Gedeon Richter, Janssen, Karuna, Kynexis, 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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Supplementary materials

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