Maintenance Treatment With Long-Acting Injectable Antipsychotics for People With Nonaffective Psychoses: A Network Meta-Analysis

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Objective: This study compared relapse prevention and acceptability of long-acting injectable (LAI) antipsychotics in the maintenance treatment of adults with nonaffective psychoses.

Methods: The authors searched MEDLINE, Embase, PsycINFO, CINAHL, CENTRAL, and online registers for randomized controlled trials published until June 2020. Relative risks and standardized mean differences were pooled using random-effects pairwise and network meta-analysis. The primary outcomes were relapse rate and all-cause discontinuation ("acceptability"). The quality of included studies was rated with the Cochrane Risk of Bias tool, and the certainty of pooled estimates was measured with GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

Results: Of 86 eligible trials, 78 (N=11,505) were included in the meta-analysis. Regarding relapse prevention, most of the 12 LAIs included outperformed placebo. The largest point estimates and best rankings of LAIs compared with placebo were found for paliperidone (3-month formulation) and aripiprazole. Moderate to high GRADE certainty for superior relapse prevention compared with placebo was also found for (in descending ranking order) risperidone, pipothiazine, olanzapine, and paliperidone (1-month formulation). In head-to-head comparisons of LAIs, only haloperidol was inferior to aripiprazole, fluphenazine, and paliperidone. For acceptability, most LAIs outperformed placebo, with moderate to high GRADE certainty for (in descending ranking order) zuclopenthixol, aripiprazole, paliperidone (3-month formulation), olanzapine, flupenthixol, fluphenazine, and paliperidone (1-month formulation). In head-to-head comparisons, only LAI aripiprazole had superior acceptability to other LAIs (bromperidol, fluphenazine, paliperidone [1-month formulation], pipothiazine, and risperidone).

Conclusions: LAI formulations of paliperidone (3-month formulation), aripiprazole, olanzapine, and paliperidone (1-month formulation) showed the highest effect sizes and certainty of evidence for both relapse prevention and acceptability. Results from this network meta-analysis should inform frontline clinicians and guidelines.

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Long-acting injectable (LAI) antipsychotics allow for a complete tracking of adherence and decrease the risk of misuse (1–4). Although they can be perceived as a last-resort option (5, 6), a broader and earlier use of LAIs has been emphasized in recent evidence-based guidelines (7–10), mainly based on the growing evidence of their effectiveness in preventing relapse and rehospitalization (2, 3, 11, 12), the well-established data on the negative consequences of poor adherence during the early phases of psychosis (13, 14), and their possible role in relieving the daily burden of oral antipsychotic administration (15, 16). However, although existing guidelines consider LAIs to be an important option for the maintenance treatment of schizophrenia, they do not provide any clear suggestion on which should be considered as first-choice options. Pragmatically, the U.K. National Institute for Health and Care Excellence recommends the use of the same criteria that are applied for the choice of oral antipsychotics (7), but this guidance does not consider practical differences in the administration modalities of individual LAIs that may account for different efficacy and acceptability profiles (e.g., long compared with short intervals of administration, the need for oral supplementation in the first few weeks of LAI administration, the need for monitoring after administration, or local pain) (1). Further, pharmacokinetic and pharmacodynamic differences between oral and LAI formulations may account for different efficacy and tolerability profiles (4, 17). Existing systematic reviews and meta-analyses have focused mainly on the comparison between oral and LAI antipsychotics, generally sorted into broad and heterogeneous groups (2, 3, 18, 19), without considering the different clinical profiles of

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the various LAIs. Randomized controlled trials comparing two or more LAIs in people with schizophrenia and other nonaffective psychosis have provided conflicting results (20, 21). Based on these considerations, we conducted a network meta-analysis to assess the differential efficacy and acceptability of individual LAIs among people with nonaffective psychoses.

METHODS

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines specific for network meta-analysis (22) (see Supplement A in the online supplement). The study protocol was registered in advance in PROSPERO (International Prospective Register of Systematic Reviews; registration number: CRD42019120240).

Study Selection and Data Extraction

We searched for randomized controlled trials that included adults (≥18 years old) who were diagnosed with a nonaffective psychotic disorder according to any validated diagnostic criteria and who required antipsychotic maintenance treatment. No time or language restrictions were applied. All available LAIs, according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO) (https://www.whocc.no/atc_ddd_index), were eligible. Although the ultimate goal of this review was to compare LAIs with one another, we also included studies comparing LAIs with placebo and with oral antipsychotics to develop a more informative network of comparisons. First-generation oral antipsychotics were grouped according to chemical classes as defined by the ATC. We excluded studies comparing oral antipsychotics head to head or against placebo, considering clinical differences relative to LAI randomized controlled trials and also considering the risk of violating the transitivity assumption required for network meta-analyses (23). Studies comparing LAIs with a mixture of oral antipsychotics were also excluded. Finally, as relapse was a primary outcome, we excluded randomized controlled trials lasting <12 weeks, as has been suggested (24).

We searched the electronic databases MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL; online trial registers (e.g., ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform); and databases of regulatory agencies and pharmaceutical companies. We searched records from database inception to June 8, 2020 (for the full search strategy, see Supplement B in the online supplement). Two of us (G.O., F.B.) independently assessed titles, abstracts, and full texts of potentially relevant articles and extracted data following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (25). Two of us (F.B., C.G.) assessed the methodological quality of included studies using the Cochrane risk of bias tool. Disagreements were resolved by discussion and consensus with a third author (C.B.).

Outcomes

Two primary outcomes were considered: the number of patients who experienced at least one study-defined relapse by the end of the trial, as a proportion of the total number of patients who underwent randomized assignment (indicated as "relapse"); and the number of patients who dropped out by the end of the trial for any cause, as a proportion of the total number of patients who underwent randomized assignment (indicated as "acceptability").

Secondary outcomes included the mean change in scores on validated rating scales measuring psychopathology at study endpoint ("efficacy"), the number of patients who dropped out by study endpoint because of any adverse event ("tolerability"), and the mean change in scores on validated rating scales measuring quality of life at the end of the trial. Additional secondary outcomes, not included in the original protocol, were analyzed to provide further results on efficacy and side effects and were regarded as merely exploratory. These included functioning, hospitalization, sedation, QTc prolongation, weight gain, hyperprolactinemia, and extrapyramidal symptoms.

Statistical Analysis

We performed a standard pairwise random-effects meta-analysis for every comparison and, for each outcome, a network meta-analysis with a random-effects model in a frequentist framework, using the Stata *mvmeta* package. For dichotomous outcomes, we calculated and pooled relative risks with 95% confidence intervals. For continuous outcomes, we pooled the mean differences between treatment arms at the end of the study if all trials used the same rating scale; otherwise, we pooled standardized mean differences. We calculated dichotomous data on a strict intention-to-treat basis, considering as the denominator the total number of patients who underwent random assignment. For continuous variables, we applied a modified intention-to-treat analysis, whereby participants with at least one postbaseline measurement were represented by their last observations carried forward. The two primary outcomes were tested independently, without applying correction for multiple testing, as recommended by the Cochrane Handbook (26).

When a study included different arms of the same antipsychotic (LAI or oral) at different doses, we pooled these arms into a single one (25), provided that they were administered within a therapeutic dose range (27, 28). Very low doses of antipsychotics were considered as pseudo placebo, as endorsed by regulatory agencies (29), and were pooled together with placebo in the analysis. Furthermore, considering their pharmacological similarity (30), fluphenazine enanthate and decanoate, as well as clopenthixol and zuclopenthixol decanoate, were pooled together.

We asked trial authors to supply missing data or, alternatively, we imputed data with validated statistical methods

(25). We calculated missing standard deviations based on the standard error, t statistics, or p values (31). If this was not possible, we substituted missing standard deviations with a mean of those reported in the other included trials (32). As a last option, we used the standard deviation of the mean baseline score. Missing data for relapse were imputed according to commonly used cutoff scores of validated rating scales (namely, an increase ≥25% on scores on the Positive and Negative Syndrome Scale [PANSS], an increase ≥30% on scores on the Brief Psychiatric Rating Scale [BPRS], and an increase ≥2 points on scores on the Clinical Global Impressions severity scale [CGI-S]) (33–35), using a validated methodology (36).

For pairwise meta-analyses, we assessed heterogeneity by visual inspection of forest plots and by I^2 statistics. For the network meta-analysis, common heterogeneity across all comparisons was assumed and estimated in each network (37).

We evaluated the assumption of transitivity by extracting potential effect modifiers (e.g., blinding, sample size, follow-up length, antipsychotic doses) and comparing their distribution across comparisons in the network.

We evaluated the presence of incoherence by comparing direct and indirect evidence within each closed loop (38) and comparing the goodness of fit for a network meta-analysis model that assumes consistency with a model that allows for incoherence in a design-by-treatment framework (39–41), using the Stata commands *mvmeta* and *ifplot* (42, 43) and the Stata network suite (44). Incoherence was further investigated through node-splitting (45) and side-splitting (44) approaches between comparisons.

For the primary outcomes, we produced a treatment hierarchy by means of surface under the cumulative ranking curve (SUCRA) and mean ranks (46).

If ≥10 studies were included in a primary outcome, we assessed publication bias by visually inspecting the funnel plot, testing for asymmetry with the Egger's regression test (47), and investigating possible reasons for funnel plot asymmetry.

For each primary outcome, we assessed the certainty of evidence from network meta-analyses through the CINeMA application (https://cinema.ispm.ch), an adaptation of the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) (23, 48).

Finally, for each primary outcome, we conducted four sensitivity analyses excluding trials that did not employ a double-blind design; trials that compared LAIs with placebo; trials that involved ≤50 participants and were published before 1990; and trials that had a high risk of bias (i.e., ≥3 risk of bias items at "high risk").

RESULTS

Characteristics of Included Studies

Our database and manual searches identified 4,368 records. After removing duplicates and examining titles and abstracts, we selected 285 records for full-text assessment. Of these, 86 studies (49–134) (corresponding to 141 full-text articles) were eligible for inclusion. Of these studies, 78 (90.7%), which included 11,505 participants and 12 different LAIs, provided data for one or more outcomes of interest (see the PRISMA flowchart in Supplement C, as well as the list of included and excluded studies in Supplement D, in the online supplement).

Included studies were published across 50 years (1968 to 2018), and 43 (50%) were published before 1990 (for characteristics of included studies, see Supplement E in the online supplement). Forty-three studies (50%) compared LAIs head to head. Nineteen studies (22.1%) included placebo, and two studies (2.3%) included very low doses of LAIs, which were regarded as pseudo placebo (73, 91). In all cases, placebo was administered in an injectable form. Twenty-six studies (30.2%) included an oral antipsychotic comparator. Four studies (4.7%) had a three-arm design, and three (3.5%) had multiple arms that included different doses of LAIs (73, 91, 92). The mean follow-up length was 40.5 weeks (range=12–104). Sixty-six studies (76.7%) were double-blind, and the remaining were open-label, except for four studies where this information was missing. Overall, 12,065 individuals were included (range=12–1,065), with 36 studies (41.9%) including ≤50 participants. The mean age of included participants was 39.8 years (range=21.5–57.1). Four studies included only men. In the remaining studies, the mean proportion of included women was 40.1% (range=11.1%−83.3%). Most studies included only people with schizophrenia (86%), although three studies had additional inclusion criteria: patients whose symptoms were "highly resistant to treatment" (119), patients with comorbid alcohol abuse (79), and patients with comorbid obesity (60). One study included only patients with schizoaffective disorder (74), and the remaining nine studies (10.5%) included participants with various nonaffective psychosis diagnoses. In one of them, 11% of participants had bipolar disorder with psychotic features (62). Notably, diagnostic criteria varied between studies, reflecting the large time frame in which the studies were conducted. The most frequently employed diagnostic manuals were DSM-IV (16.3%) and DSM-III (12.8%). A high risk of attrition bias, reporting bias, and sponsorship bias emerged for several of the included studies (see Supplement F in the online supplement).

Primary Outcomes

The characteristics of studies included in the two primary outcome analyses are summarized in Table 1, and the corresponding network plots are shown in Figure 1. Every LAI was included in at least one closed loop. The results of the network meta-analysis for individual LAIs for the primary outcomes are shown in Figure 2 in the form of a net league table. For primary and secondary outcomes, all standard pairwise meta-analyses, network meta-analyses, and assessments of heterogeneity and incoherence are reported in the online supplement.

Relapse. The following LAIs (ordered from the largest to the smallest point estimate) were significantly more effective than placebo: paliperidone (3-month formulation) (relative risk=0.27, 95% CI=0.17−0.42), aripiprazole (relative risk=0.29, 95% CI=0.21–0.39), flupenthixol (relative risk=0.32, 95% CI=0.16–0.65), fluphenazine (relative risk=0.34, 95% CI=0.24–0.48), risperidone (relative risk=0.34, 95% CI=0.23–0.52), pipothiazine (relative risk=0.35, 95% CI=0.20–0.62), olanzapine (relative risk=0.37, 95% CI=0.26–0.53), paliperidone (1-month formulation) (relative risk=0.39, 95% CI=0.30–0.50), and haloperidol (relative risk=0.57, 95% CI=0.33–0.97) (Figure 3). Head-to-head comparisons showed paliperidone (3-month formulation), aripiprazole, and fluphenazine to be more effective than haloperidol (Figure 2). No relevant heterogeneity emerged from pairwise comparisons (i.e., I^2>50%), and the network did not show significant overall heterogeneity (estimated between-studies standard deviation, 0.07) or overall incoherence (design-by-treatment test, p=0.45). Intraloop incoherence emerged for four loops, all of them involving placebo and haloperidol. Results of the network meta-analyses were consistent with results from pairwise meta-analyses, except for the comparisons between haloperidol and placebo (favoring the latter in the direct estimate) and between fluphenazine and haloperidol (not significant in the direct estimate). Generally, there was statistical agreement between direct and indirect estimates, except for four comparisons: fluphenazine, haloperidol, and paliperidone (3-month formulation) relative to placebo, and paliperidone (1-month formulation) relative to paliperidone (3-month formulation).

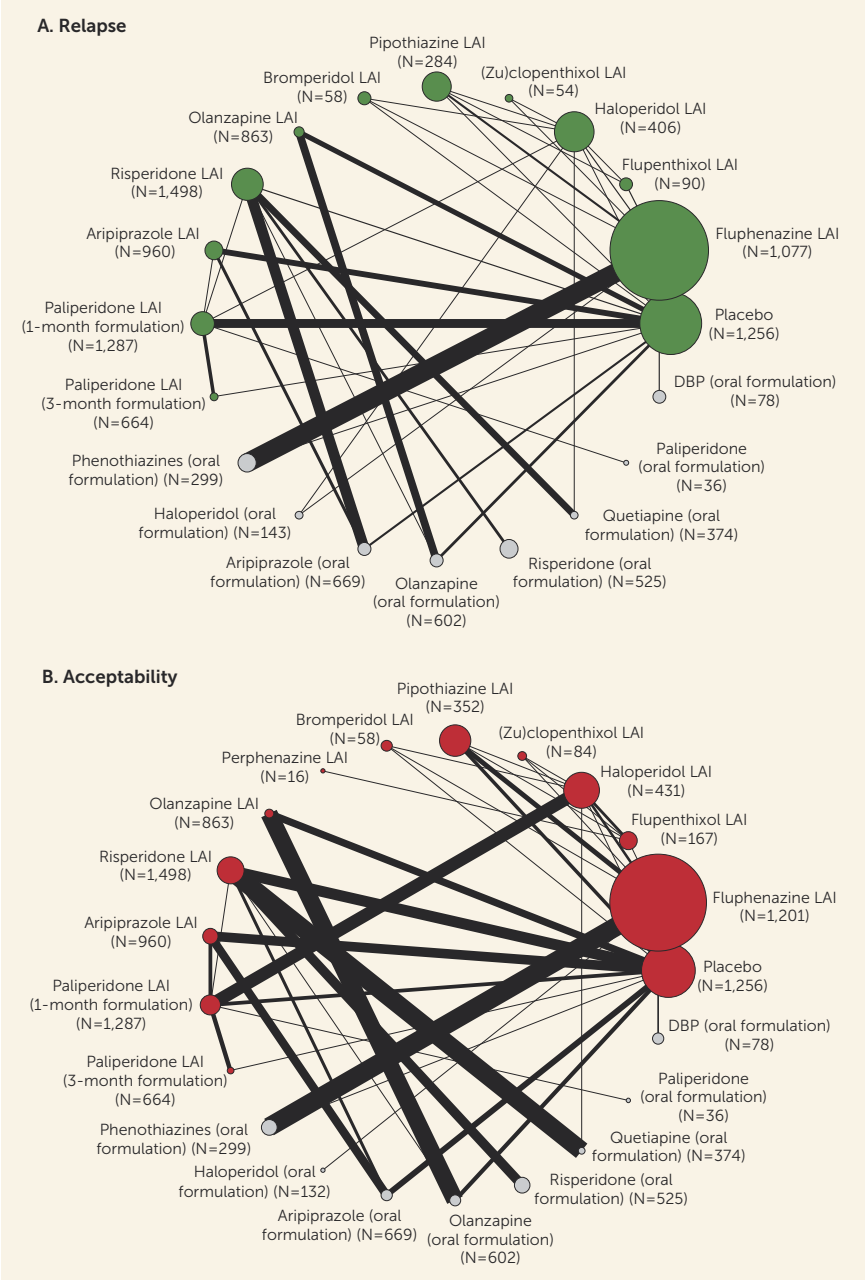
Paliperidone (3-month formulation), aripiprazole, and flupenthixol ranked best according to the mean SUCRA. Compared with placebo, the certainty of evidence was "high" for paliperidone (3-month formulation) and paliperidone (1-month formulation) and was "moderate" for aripiprazole, risperidone, pipothiazine, and olanzapine. The certainty of evidence was also "moderate" for the comparison between paliperidone (3-month formulation) and paliperidone (1-month formulation), while it was "very low" or "low" for most comparisons because of within-study bias, which includes high risk of reporting bias, attrition bias, and sponsorship bias (see Figure 3 and Supplement G in the online supplement). The results of sensitivity analyses generally confirmed those of the primary analysis, but they suggested that placebo-controlled studies might have been responsible formost of the observed intraloop incoherence. Further, statistical disagreement between direct and indirect estimates disappeared after placebo-controlled studies were removed from the analysis (see Supplements H–K in the online supplement).

TABLE 1. Characteristics of randomized controlled trials included in each network of primary outcomes in a meta-analysis of long-acting injectable (LAI) antipsychotics for nonaffective psychoses

Characteristic	Relapse Network		Acceptability Network	
Number of studies	69		74	
Number of patients included	11,176		11,385	
	Mean	SD	Mean	SD
Age (years)	40	12.7	39	12.7
	N	%	N	%
Women	3,663	32.8	3,700	32.5
Study follow-up duration				
12–26 weeks	22	31.9	26	35.1
27–52 weeks	35	50.7	35	47.3
≥53 weeks	12	17.4	13	17.6
Study blinding				
Double-blind	52	75.4	15	20.3
Open-label	15	21.7	55	74.3
Unclear or not reported	2	2.9	4	5.4
Year of publication				
Through 1989	32	46.4	35	47.3
1990–2009	18	26.1	20	27
2010–2019	19	27.6	19	25.7
Type of comparison				
LAI compared with placebo	18	26.1	20	27
LAI compared with oral antipsychotics	25	36.2	24	32.4
LAI compared with LAI	25	36.2	29	39.2
LAI compared with oral antipsychotics and placebo	1	1.5	1	1.4
Setting				
Inpatient	15	21.7	15	20.3
Outpatient	35	50.7	38	51.3
Mixed	14	20.3	14	18.9
Unclear or not reported	5	7.3	7	9.5

Acceptability. The following LAIs (ordered from the largest to the smallest point estimate) were significantly more acceptable than placebo: (zu)clopenthixol (relative risk=0.33, 95% CI=0.13–0.84), aripiprazole (relative risk=0.49, 95% CI=0.41–0.58), paliperidone (3-month formulation) (relative risk=0.60, 95% CI=0.43–0.84), olanzapine (relative risk=0.62, 95% CI=0.48–0.79), flupenthixol (relative risk=0.62, 95% CI=0.44–0.89), haloperidol (relative risk=0.64, 95% CI=0.50–0.81), fluphenazine (relative risk=0.67, 95% CI=0.55–0.81), risperidone (relative risk=0.70, 95% CI=0.57–0.85), paliperidone (1-month formulation) (relative risk=0.70, 95% CI=0.58–0.85), and pipothiazine (relative risk=0.73, 95% CI=0.56–0.96) (Figure 3). Head-to-head comparisons showed aripiprazole to be significantly superior to bromperidol, fluphenazine, paliperidone (1-month formulation), pipothiazine, and risperidone (Figure 2). Moderate heterogeneity was detected for three pairwise comparisons (olanzapine LAI relative to olanzapine oral formulation, placebo relative to haloperidol LAI,

FIGURE 1. Network plots of evidence for relapse and acceptability in a meta-analysis of long-acting injectable (LAI) antipsychotics for nonaffective psychoses[a]



[a] The thickness of lines is proportional to the precision of each direct estimate, and the size of circles is proportional to the number of studies that included the treatment. The N indicates the number of participants who were randomly assigned to each treatment, and the phenothiazines are fluphenazine, trifluoperazine, and chlorpromazine. DBP=diphenylbutylpiperidine derivatives (pimozine, penfluridol).

and fluphenazine LAI relative to oral formulations of phenothiazines), although the network did not show significant overall heterogeneity (estimated between-studies standard deviation, 0.08) or overall incoherence (design-by-treatment test, p=0.22). The test for intraloop incoherence was statistically significant for the loop including placebo, haloperidol LAI, and paliperidone LAI (1-month formulation). Results of the network meta-analyses were consistent with those from pairwise meta-analyses, except for haloperidol and pipothiazine relative to placebo and aripiprazole relative to paliperdone (1-month formulation) (not significant in the direct estimate). There was statistical agreement between direct and indirect estimates, except for haloperidol and paliperidone (1-month formulation) relative to placebo. Among those LAIs significantly superior to placebo, (zu)clopenthixol, aripiprazole, and paliperidone (3-month formulation) ranked best according to the SUCRA. Compared with placebo, the certainty of evidence was "high" for paliperidone (3-month formulation) and "moderate" for (zu)clopenthixol, aripiprazole, olanzapine, flupenthixol, fluphenazine, and paliperidone (1-month formulation). For most of the head-to-head comparisons, the certainty of evidence was "very low" or "low" because of within-study bias and imprecision of results (see Figure 3 and Supplement L in the online supplement). Results of sensitivity analyses generally confirmed those of the primary analysis, but they suggested that placebo-controlled studies and older and smaller studies may have been responsible for most of the observed intraloop incoherence and that studies with high overall risk of bias also contributed to the overall incoherence of the network. Statistical disagreement between direct and indirect estimates disappeared after placebo-controlled studies were removed from the analysis (see Supplements M–P in the online supplement).

Secondary Outcomes

Regarding dropouts due to adverse events (tolerability), paliperidone (1-month formulation) was less tolerable than placebo, while for other LAIs, no differences relative to placebo emerged (Figure 4). Aripiprazole was more tolerable

FIGURE 2. Net league table of head-to-head comparisons for relapse and acceptability in a meta-analysis of long-acting injectable (LAI) antipsychotics for nonaffective psychoses[a]

Aripiprazole LAI	**2.10 (1.03, 4.28)**	1.27 (0.86, 1.88)	**1.37 (1.06, 1.76)**	1.30 (0.99, 1.71)	1.26 (0.93, 1.71)	1.43 (1.14, 1.79)	**1.23 (0.87, 1.75)**	0.64 (0.06, 6.58)	**1.50 (1.09, 2.05)**	**1.42 (1.11, 1.82)**	0.68 (0.27, 1.73)	**2.05 (1.71, 2.44)**
0.57 (0.24, 1.39)	Bromperidol LAI	0.61 (0.29, 1.28)	0.65 (0.33, 1.29)	0.62 (0.31, 1.24)	0.60 (0.29, 1.25)	0.68 (0.34, 1.37)	0.58 (0.28, 1.24)	0.30 (0.03, 3.41)	0.71 (0.35, 1.46)	0.68 (0.33, 1.38)	0.32 (0.10, 1.00)	0.97 (0.49, 1.94)
0.90 (0.41, 1.95)	1.57 (0.58, 4.25)	Flupenthixol LAI	1.07 (0.76, 1.52)	1.02 (0.75, 1.39)	0.99 (0.64, 1.53)	1.12 (0.78, 1.61)	0.97 (0.62, 1.51)	0.50 (0.05, 5.01)	1.18 (0.80, 1.73)	1.12 (0.76, 1.65)	0.54 (0.22, 1.32)	**1.61 (1.12, 2.30)**
0.83 (0.53, 1.31)	1.45 (0.67, 3.14)	0.93 (0.49, 1.75)	Fluphenazine LAI	0.95 (0.75, 1.21)	0.92 (0.67, 1.26)	1.05 (0.82, 1.34)	0.90 (0.63, 1.29)	0.47 (0.05, 4.79)	1.10 (0.86, 1.40)	1.04 (0.80, 1.35)	0.50 (0.20, 1.25)	**1.50 (1.23, 1.82)**
0.51 (0.28, 0.93)	0.88 (0.37, 2.12)	0.56 (0.26, 1.20)	**0.61 (0.37, 0.99)**	Haloperidol LAI	0.97 (0.69, 1.36)	1.10 (0.89, 1.36)	0.94 (0.67, 1.33)	0.49 (0.05, 4.99)	1.15 (0.85, 1.56)	1.09 (0.83, 1.44)	0.52 (0.21, 1.29)	**1.57 (1.24, 1.99)**
0.77 (0.49, 1.22)	1.34 (0.54, 3.32)	0.86 (0.39, 1.90)	0.92 (0.57, 1.51)	1.53 (0.80, 2.89)	Olanzapine LAI	1.13 (0.83, 1.55)	0.98 (0.65, 1.47)	0.50 (0.05, 5.26)	1.19 (0.83, 1.71)	1.13 (0.83, 1.53)	0.54 (0.21, 1.40)	**1.62 (1.27, 2.07)**
0.74 (0.51, 1.08)	1.29 (0.54, 3.07)	0.82 (0.39, 1.75)	0.89 (0.58, 1.36)	1.46 (0.81, 2.64)	0.96 (0.62, 1.48)	Paliperidone LAI (1-month)	0.86 (0.64, 1.15)	0.45 (0.04, 4.58)	1.05 (0.77, 1.43)	0.99 (0.76, 1.30)	0.48 (0.19, 1.20)	**1.43 (1.18, 1.74)**
1.07 (0.63, 1.81)	1.86 (0.71, 4.83)	1.18 (0.51, 2.77)	1.28 (0.73, 2.25)	**2.11 (1.05, 4.24)**	1.38 (0.79, 2.43)	1.44 (0.95, 2.19)	Paliperidone LAI (3-month)	0.52 (0.05, 5.41)	1.22 (0.81, 1.83)	1.16 (0.80, 1.68)	0.55 (0.21, 1.44)	**1.66 (1.20, 2.31)**
—	—	—	—	—	—	—	—	Perphenazine LAI	2.35 (0.23, 24.33)	2.23 (0.22, 23.10)	1.07 (0.09, 12.70)	3.21 (0.31, 33.07)
0.82 (0.43, 1.55)	1.42 (0.57, 3.57)	0.91 (0.41, 2.03)	0.98 (0.59, 1.63)	1.62 (0.82, 3.19)	1.06 (0.54, 2.06)	1.10 (0.59, 2.05)	0.77 (0.37, 1.58)	—	Pipothiazine LAI	0.95 (0.69, 1.31)	0.45 (0.18, 1.16)	**1.36 (1.05, 1.78)**
0.83 (0.54, 1.27)	1.44 (0.58, 3.61)	0.92 (0.41, 2.07)	0.99 (0.59, 1.67)	1.64 (0.87, 3.10)	1.08 (0.63, 1.83)	1.12 (0.70, 1.79)	0.78 (0.42, 1.43)	—	1.02 (0.51, 2.01)	Risperidone LAI	0.48 (0.19, 1.22)	**1.44 (1.18, 1.75)**
0.69 (0.21, 2.28)	1.21 (0.31, 4.65)	0.77 (0.22, 2.76)	0.83 (0.27, 2.56)	1.37 (0.46, 4.14)	0.90 (0.27, 3.01)	0.94 (0.29, 3.05)	0.65 (0.19, 2.24)	—	0.85 (0.25, 2.89)	0.84 (0.25, 2.80)	(Zu)clopenthixol LAI	**3.00 (1.20, 7.53)**
0.29 (0.21, 0.39)	0.50 (0.22, 1.15)	**0.32 (0.16, 0.65)**	**0.34 (0.24, 0.48)**	**0.57 (0.33, 0.97)**	**0.37 (0.26, 0.53)**	**0.39 (0.30, 0.50)**	**0.27 (0.17, 0.42)**	—	**0.35 (0.20, 0.62)**	**0.34 (0.23, 0.52)**	0.41 (0.13, 1.31)	Placebo

Relapse Acceptability

[a] Relative risks and 95% confidence intervals are reported. For both relapse and acceptability, relative risks lower than 1 favor the column-defining treatment. Treatments are ordered alphabetically. Statistically significant results are in boldface.

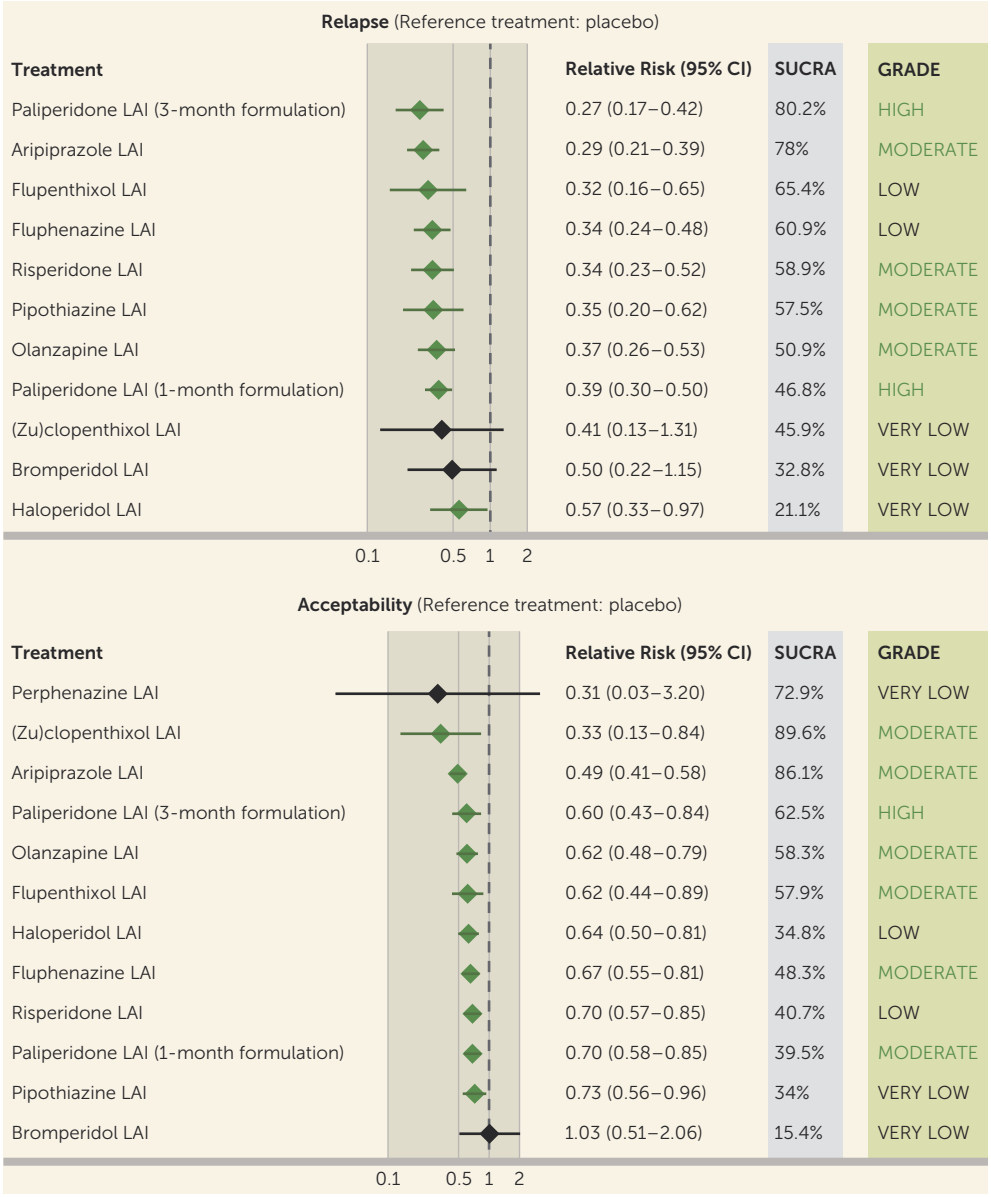
than paliperidone (1-month formulation), and no other significant differences emerged in head-to-head comparisons. No relevant overall heterogeneity and incoherence and no intraloop incoherence emerged for this network (see Supplement Q in the online supplement).

Regarding efficacy measured as the change in mean scores, the following LAIs, ordered from the largest to the smallest point estimate, were significantly superior to placebo: perphenazine, pipothiazine, risperidone, aripiprazole, haloperidol, fluphenazine, and paliperidone (1-month formulation). No significant differences emerged from head-to-head comparisons (Figure 4). Significant overall heterogeneity and incoherence emerged, related to relevant heterogeneity in some pairwise comparisons and intraloop incoherence, mostly involving placebo, haloperidol, aripiprazole, and fluphenazine. There was statistical agreement between direct and indirect estimates (see Supplement R in the online supplement).

Regarding quality of life, data were available for three LAIs only (aripiprazole, risperidone, and the 1-month formulation of paliperidone), and placebo was not included. The network had no triangular or quadratic loops. In head-to-head comparisons, aripiprazole was superior to paliperidone (1-month formulation). Significant overall heterogeneity and incoherence emerged for this network, related to the very high heterogeneity for the comparison between aripiprazole and paliperidone (1-month formulation). There was statistical agreement between direct and indirect estimates (see Supplement S in the online supplement).

For some of the additional secondary outcomes (namely, functioning, QTc prolongation, and sedation), the network meta-analysis could not be performed because one loop was formed of a three-arm trial and there were too few studies per comparison. For these outcomes, only pairwise meta-analyses were performed, but no significant differences between treatments emerged, with the exception that paliperidone (3-month formulation) showed better functioning than placebo and lower risk of QTc prolongation than paliperidone (1-month formulation), both based on results from one study only (see Supplements T–V in the online supplement). The other secondary analyses showed, with LAIs ordered from the largest to the smallest point estimate,

FIGURE 3. Forest plots comparing each long-acting injectable (LAI) antipsychotic with placebo for relapse and acceptability with the corresponding ranking probability and certainty of evidence, as assessed with the CINeMA appraisal, for each intervention in a meta-analysis of LAIs for nonaffective psychoses[a]



[a] Statistically significant results appear in green. Values below 1 favor LAI antipsychotics. The ranking probability was assessed by SUCRA (surface under the cumulative ranking curve), and the certainty of evidence was assessed by GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

significantly lower hospitalization rates for aripiprazole, paliperidone (3-month formulation), haloperidol, fluphenazine, and paliperidone (1-month formulation) compared with placebo (see Supplement W in the online supplement); significantly higher weight gain for paliperidone (1-month formulation), paliperidone (3-month formulation), and aripiprazole compared with placebo (see Supplement X in the online supplement); and significantly higher risk of hyperprolactinemia for paliperidone (1-month formulation), paliperidone (3-month formulation), and olanzapine compared with placebo (see Supplement Y in the online supplement). No LAIs showed a significantly higher risk of extrapyramidal symptoms relative to placebo (see Supplement Z in the online supplement).

DISCUSSION

In this network meta-analysis, most LAIs were superior to placebo in preventing relapse and were significantly more acceptable than placebo. For both of these primary outcomes, most LAIs had fairly similar effect sizes, and no relevant differences emerged when they were compared head to head, except for aripiprazole, which performed particularly well against other LAIs regarding acceptability. Importantly, the certainty of evidence was moderate or high for a number of LAIs, particularly second-generation LAIs. However, only the 3-month formulation of paliperidone, the 1-month formulation of paliperidone, aripiprazole, and olanzapine were supported by a moderate to high certainty of evidence in both primary outcomes and therefore can be regarded as reasonable first-line maintenance treatments in people with schizophrenia and related nonaffective psychosis. In general, these findings were confirmed by secondary analyses, such as efficacy measured via rating scales, hospitalization rates, and tolerability outcomes, although data on quality of life and functioning were lacking. The 3-month formulation of paliperidone and aripiprazole LAI were among the best performing treatments against placebo in many analyses and had very high SUCRA rankings in both primary outcomes.

The analysis of individual adverse events, although limited by relatively few and heterogeneous data, confirmed that weight gain and hyperprolactinemia may be relevant also for those LAIs with good overall acceptability and tolerability (i.e., paliperidone [1- and 3-month formulations], aripiprazole, and olanzapine).

FIGURE 4. Net league table of head-to-head comparisons for tolerability and efficacy in a meta-analysis of long-acting injectable (LAI) antipsychotics for nonaffective psychoses[a]

Aripiprazole LAI	−0.08 (−1.00, 0.84)	0.17 (−0.61, 0.95)	0.09 (−0.61, 0.79)	0.07 (−0.57, 0.70)	0.21 (−0.55, 0.98)	0.24 (−0.18, 0.67)	0.22 (−0.44, 0.87)	−0.60 (−1.89, 0.70)	−0.23 (−0.99, 0.53)	−0.08 (−0.64, 0.47)	0.07 (−0.79, 0.92)	**0.74 (0.33, 1.15)**
0.58 (0.08, 4.20)	Bromperidol LAI	0.25 (−0.61, 1.11)	0.17 (−0.61, 0.95)	0.15 (−0.64, 0.93)	0.29 (−0.77, 1.36)	0.32 (−0.56, 1.20)	0.30 (−0.71, 1.30)	−0.52 (−1.87, 0.83)	−0.15 (−0.98, 0.69)	−0.00 (−0.94, 0.94)	0.15 (−0.79, 1.09)	0.82 (−0.03, 1.67)
0.53 (0.06, 4.51)	0.92 (0.07, 12.78)	Flupenthixol LAI	−0.08 (−0.50, 0.34)	−0.10 (−0.61, 0.41)	0.05 (−0.91, 1.00)	0.07 (−0.65, 0.80)	0.05 (−0.83, 0.92)	−0.77 (−1.80, 0.27)	−0.40 (−0.89, 0.09)	−0.25 (−1.05, 0.55)	−0.10 (−0.71, 0.51)	0.57 (−0.14, 1.27)
0.36 (0.13, 1.03)	0.63 (0.10, 3.92)	0.68 (0.10, 4.60)	Fluphenazine LAI	−0.02 (−0.43, 0.38)	0.12 (−0.77, 1.02)	0.15 (−0.49, 0.79)	0.13 (−0.68, 0.94)	−0.69 (−1.81, 0.43)	−0.32 (−0.66, 0.02)	−0.17 (−0.90, 0.55)	−0.02 (−0.61, 0.56)	**0.65 (0.03, 1.27)**
0.49 (0.22, 1.06)	0.85 (0.12, 5.79)	0.92 (0.11, 7.68)	1.35 (0.49, 3.75)	Haloperidol LAI	0.15 (−0.69, 0.99)	0.18 (−0.38, 0.73)	0.15 (−0.60, 0.90)	−0.67 (−1.82, 0.49)	−0.30 (−0.78, 0.18)	−0.15 (−0.80, 0.50)	−0.00 (−0.60, 0.60)	**0.67 (0.12, 1.22)**
1.22 (0.46, 3.24)	2.12 (0.26, 17.58)	2.32 (0.24, 22.01)	3.40 (0.98, 11.83)	2.51 (0.82, 7.70)	Olanzapine LAI	0.03 (−0.71, 0.77)	0.00 (−0.87, 0.87)	−0.81 (−2.22, 0.60)	−0.44 (−1.38, 0.49)	−0.30 (−1.04, 0.44)	−0.15 (−1.16, 0.87)	0.52 (−0.14, 1.18)
0.50 (0.30, 0.83)	0.87 (0.12, 6.18)	0.95 (0.11, 7.98)	1.39 (0.50, 3.87)	1.03 (0.55, 1.94)	0.41 (0.15, 1.11)	Paliperidone LAI (1-month)	−0.03 (−0.60, 0.54)	−0.84 (−2.10, 0.42)	−0.47 (−1.17, 0.23)	−0.33 (−0.86, 0.21)	−0.18 (−0.98, 0.62)	**0.49 (0.12, 0.86)**
0.47 (0.20, 1.12)	0.82 (0.10, 6.58)	0.90 (0.10, 8.41)	1.31 (0.38, 4.53)	0.97 (0.37, 2.51)	0.39 (0.12, 1.29)	0.94 (0.46, 1.92)	Paliperidone LAI (3-month)	−0.82 (−2.17, 0.54)	−0.45 (−1.30, 0.41)	−0.30 (−1.02, 0.42)	−0.15 (−1.09, 0.79)	0.52 (−0.05, 1.09)
—	—	—	—	—	—	—	—	Perphenazine LAI	0.37 (−0.78, 1.52)	0.52 (−0.79, 1.82)	0.67 (−0.54, 1.87)	**1.34 (0.08, 2.59)**
0.45 (0.14, 1.46)	0.78 (0.11, 5.35)	0.85 (0.12, 6.03)	1.25 (0.68, 2.30)	0.92 (0.30, 2.89)	0.37 (0.10, 1.43)	0.90 (0.29, 2.83)	0.95 (0.25, 3.65)	—	Pipothiazine LAI	0.15 (−0.63, 0.92)	0.30 (−0.36, 0.95)	**0.97 (0.29, 1.65)**
1.05 (0.48, 2.30)	1.83 (0.24, 13.99)	2.00 (0.23, 17.61)	2.93 (0.97, 8.87)	2.16 (0.83, 5.63)	0.86 (0.35, 2.14)	2.10 (0.94, 4.67)	2.23 (0.78, 6.41)	—	2.34 (0.69, 7.98)	Risperidone LAI	0.15 (−0.72, 1.02)	**0.82 (0.34, 1.30)**
0.48 (0.04, 5.66)	0.83 (0.04, 15.79)	0.91 (0.07, 12.10)	1.33 (0.13, 14.04)	0.98 (0.09, 11.01)	0.39 (0.03, 5.14)	0.95 (0.08, 11.03)	1.01 (0.08, 12.93)	—	1.06 (0.09, 11.89)	0.45 (0.04, 5.58)	(Zu)clopenthixol LAI	0.67 (−0.12, 1.46)
0.94 (0.53, 1.66)	1.63 (0.23, 11.54)	1.77 (0.22, 14.58)	2.60 (0.99, 6.81)	1.92 (0.87, 4.25)	0.77 (0.35, 1.70)	**1.87 (1.02, 3.40)**	1.98 (0.79, 4.94)	—	2.08 (0.69, 6.23)	0.89 (0.51, 1.56)	1.96 (0.17, 22.70)	Placebo

Tolerability Efficacy (continuous)

[a] For tolerability, relative risks and 95% confidence intervals are reported. Relative risks lower than 1 favor the column-defining treatment. For efficacy, standardized mean differences and 95% confidence intervals are reported. Standardized mean differences lower than 0 favor the column-defining treatment. Treatments are ordered alphabetically. Statistically significant results are in boldface.

The findings of this network meta-analysis are consistent with those from the largest randomized trials comparing LAIs head to head (106, 112, 118) and with large observational studies that analyzed the efficacy of individual LAIs in preventing rehospitalization (11, 135).

To our knowledge, this is the first comparison of individual LAIs using a network meta-analysis methodology. This approach allowed comparisons of LAIs for which no direct evidence was available while avoiding questionable pooled subgroups (i.e., first- or second-generation LAIs) and obtaining more precise estimates. The primary analyses included more than 11,000 participants, making this the largest meta-analysis conducted on LAIs to date. Furthermore, estimates for dichotomous outcomes are conservative, as they were calculated considering the total number of patients who underwent randomized assignment in the denominator.

Despite these strengths, several limitations should be considered when interpreting the results. First, although we aimed to evaluate the ability of LAIs in preventing relapse in patients already stabilized, for some randomized controlled trials, stabilization was not clearly described. Therefore, several factors were considered as proxy measures of stabilization (e.g., the PANSS score at recruitment), which may lack precision. Second, included randomized controlled trials were published across a long time span and therefore are heterogeneous in terms of methodology, diagnostic criteria, follow-up periods, and outcomes. Despite that, overall coherence appeared to be well preserved for most analyses. Third, for a relevant number of studies, important information was lacking, and imputation methods had to be employed. Although this is an acceptable approximation in most cases (32), some degree of imprecision cannot be excluded. Fourth, placebo-controlled studies may suffer from intrinsic limitations (20, 136), in particular, the selection of relatively well-stabilized patients. The sensitivity analyses that removed these studies confirmed that placebo-controlled studies may have introduced some overall heterogeneity and incoherence, although overall results did

not change substantially. Placebo-controlled studies of paliperidone (3-month formulation) may be of particular concern, considering that patients in these studies underwent a stabilization phase with paliperidone (1-month formulation) before randomization to the 3-month formulation or placebo. This study design may have inflated the effect size of the 3-month formulation of paliperidone by using a particularly enriched sample for benefit and tolerability in patients ultimately randomized to the placebo discontinuation phase of the study. Fifth, risk of bias was relatively high for many studies, particularly regarding attrition, reporting, and sponsorship biases. However, a sensitivity analysis showed that primary outcomes did not relevantly change after removing these studies. Sixth, some secondary outcomes, such as quality of life, functioning, and common adverse events, which might play a relevant role in helping clinicians to tailor LAIs to individual patients, were poorly reported by the original studies, leading to poorly populated and connected networks, high imprecision, and heterogeneity. These outcomes were not originally included in the protocol and were regarded as merely exploratory. Nevertheless, a meta-analysis found that LAIs and their corresponding oral antipsychotics did not differ significantly in 97% of the 119 analyzed adverse effects (137). Seventh, as no comparison included ≥10 studies, the risk of publication bias could not be ruled out. Considering that we included only one unpublished trial (87) and that many data from old studies were included, publication bias cannot be completely excluded, although it is expected to be less relevant compared with studies of other classes of psychotropic drugs (138). Lastly, the network meta-analytic approach is not free from technical and theoretical shortcomings, including the risk related to multiple statistical assumptions and the challenges in addressing the problem of intransitivity and incoherence (139).

The findings of this network meta-analysis have relevant implications for policy and research. Current guidelines emphasize the importance of considering LAIs for maintenance treatment of patients who might prefer this formulation for practical reasons, that is, those in the earliest illness phases and those with adherence problems (7–10). However, no clear indication is provided on which LAIs should be considered the first-choice options. Guidelines from the U.K. National Institute for Health and Care Excellence suggest following the same criteria used for oral antipsychotics, but it is unclear whether the efficacy and tolerability of the two formulations are identical (4, 11, 135, 137, 140), and results from this network meta-analysis suggest that LAI characteristics, such as the time between administrations, might play a relevant role. Results from this study can help clinicians in tailoring the choice of LAI even from the first episode of psychosis, considering the impact of a successful maintenance treatment on long-term outcomes (141). From a global health standpoint, it is relevant to consider that the WHO Model List of Essential Medicines (142) includes only fluphenazine as an LAI formulation, although this medication is no longer regularly supplied globally, causing a disservice for the most vulnerable populations (i.e., those in low- and middle-income countries and humanitarian settings). Therefore, we argue that results from this network meta-analysis should rapidly inform the update of guidelines from the WHO and other organizations, with the aim of informing and improving psychiatric care worldwide.

Large, pragmatic, and high-quality head-to-head studies comparing LAIs are needed to overcome the methodological limitations mentioned above, including the lack of information on functioning, quality of life, common adverse events, and cost-effectiveness. Further, studies recruiting patients after the first episode of psychosis are needed to confirm the clinical utility of LAIs when utilized from the earliest phases of the disease, reversing the paradigm of LAIs as treatments reserved for patients with the most severe and chronic forms of illness.

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Examination Questions: Ostuzzi et al.

1. **Which long-acting antipsychotic showed a particularly favorable profile relative to placebo in terms of acceptability?**
   a. Bromperidol.
   b. The 3-month formulation of paliperidone.
   c. The 1-month formulation of paliperidone.
   d. Aripiprazole.
2. **What are the most common sources of bias across the included randomized controlled trials on long-acting antipsychotics?**
   a. Sponsorship bias, reporting bias, and attrition bias (high dropout rates).
   b. Selection bias.
   c. Indirectness of the included population.
   d. Lack of blindness.
3. **The authors defined the outcome of "acceptability" in their study as:**
   a. The number of patients whose quality of life improved at the end of the study.
   b. The number of patients willing to take the therapy until the end of the study.
   c. The number of patients dropping out by the end of the trial for any cause, as a proportion of the total number of randomized patients.
   d. The number of patients dropping out by the end of the trial because of severe adverse events, as a proportion of the number of patients included in the primary analysis.